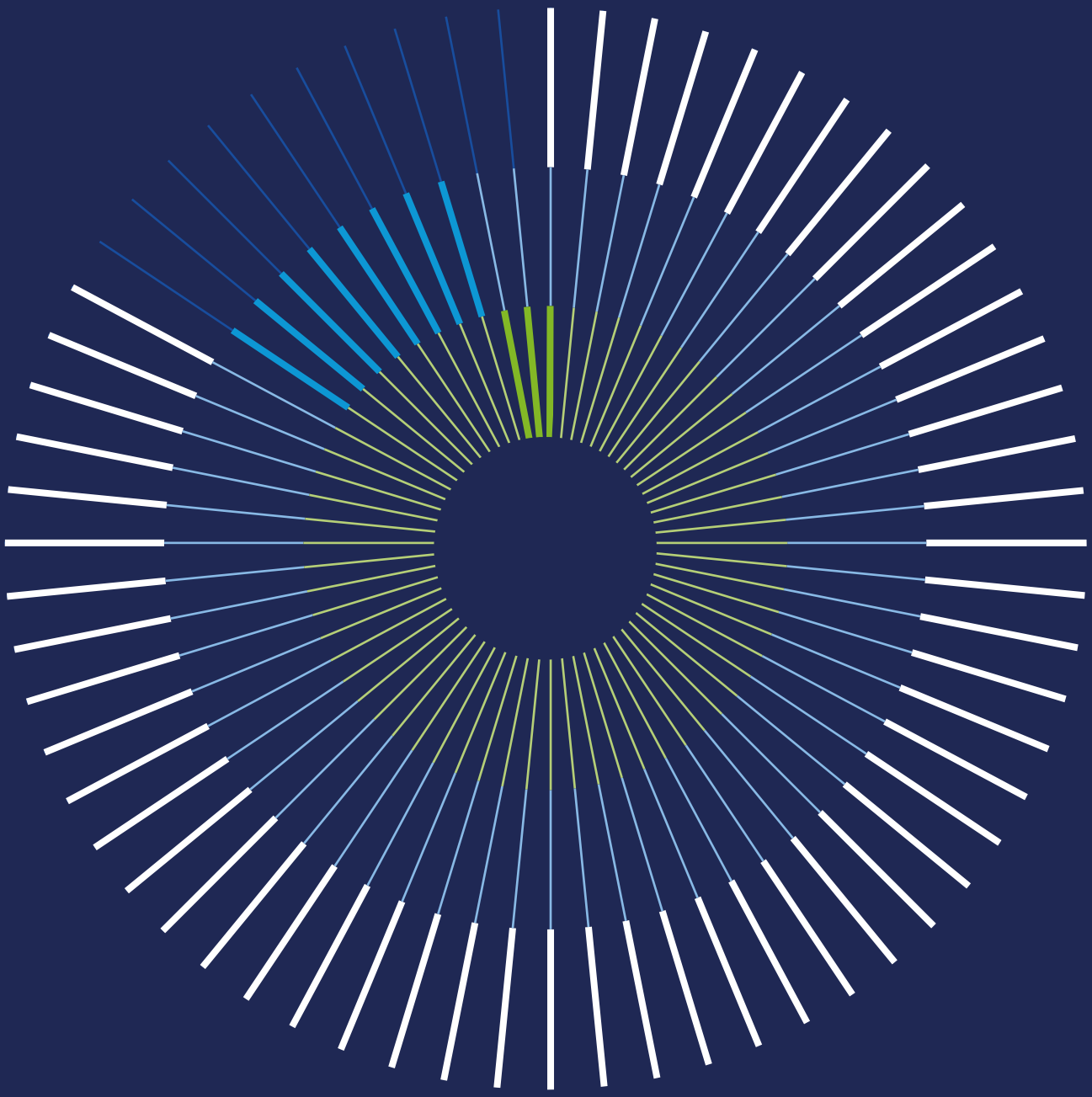

2023 Antibacterial agents in clinical and preclinical development

an overview and analysis

World Health Organization

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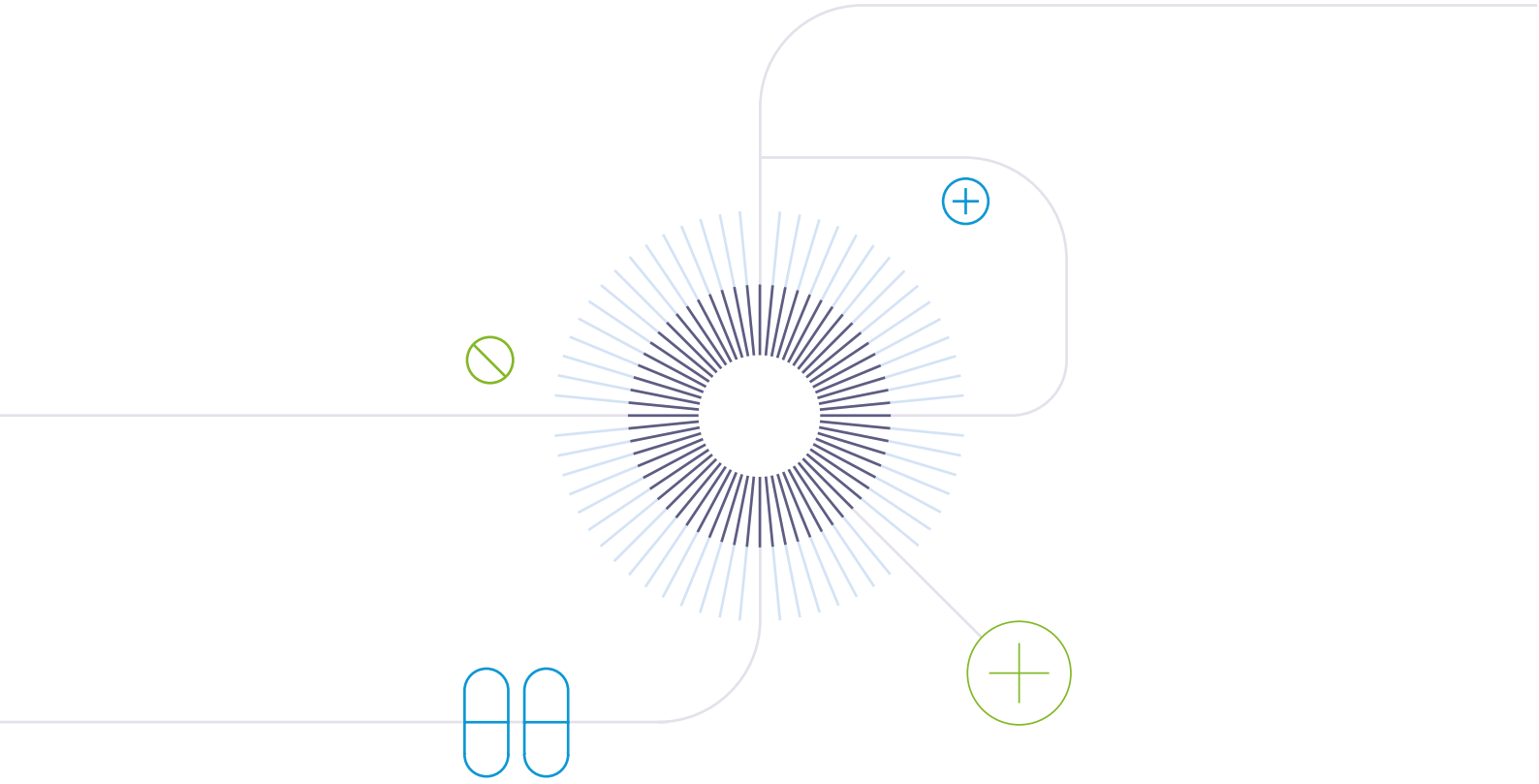


Abbreviations & Acronyms

3GCRE	third-generation cephalosporin-resistant Enterobacterales
ABSSSI	acute bacterial skin and skin structure infection
ADMET	absorption, distribution, metabolism, excretion and toxicity
AE	adverse event
AFB	acid-fast bacilli
AGE	acute gastroenteritis
AIEC	adherent-invasive *Escherichia coli*
AKI	acute kidney injury
Allo-HCT	allogeneic haematopoietic cell transplantation
ALT	alanine aminotransferase
AMR	antimicrobial resistance
ANZCTR	Australian New Zealand Clinical Trials Registry
AP	acute pyelonephritis
ARDS	acute respiratory distress syndrome
AST	aspartate transaminase
ATM-AVI	aztreonam + avibactam
AUC	area under the concentration–time curve
AWaRe	Access, Watch, and Reserve (WHO classification)
BARDA	Biomedical Advanced Research and Development Authority
BEAM	Anti-Microbial resistance research
bid	twice a day
BIO	Biotechnology Innovation Organization
BLI	β-lactamase inhibitor
BPaL	bedaquiline, pretomanid and linezolid
BPP	WHO bacterial priority pathogen
BPPL	WHO bacterial priority pathogen list
BSI	bloodstream infection
CABP	community-acquired bacterial pneumonia
CAP	community-associated pneumonia

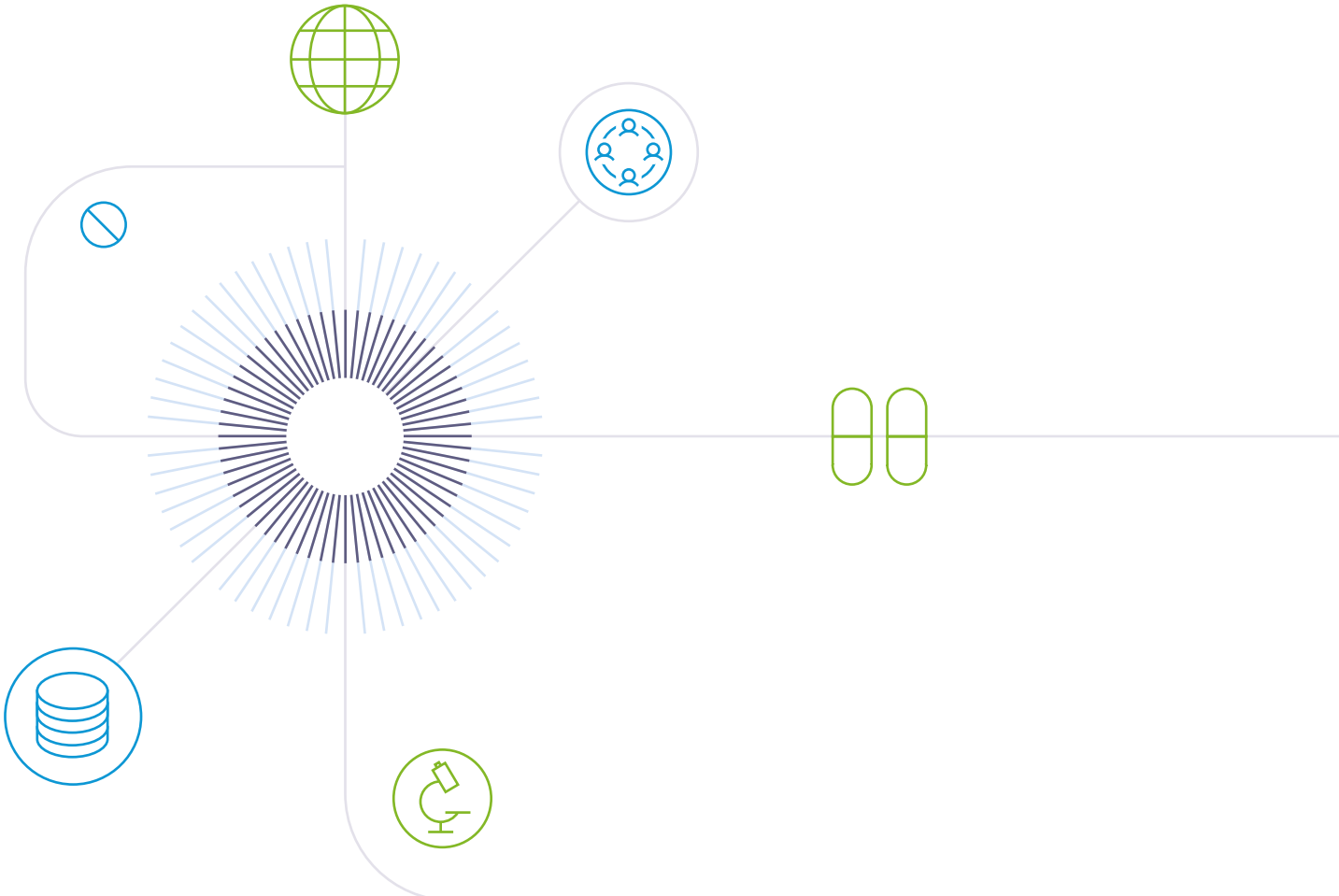
CDAD	*Clostridioides difficile*-associated diarrhoea
CDC	United States Centers for Disease Control and Prevention
CDI	*Clostridioides difficile* infection
CF	cystic fibrosis
CFU	colony-forming unit
cIAI	complicated intra-abdominal infection
CLSI	Clinical and Laboratory Standards Institutes
Cmax	maximum concentration
CoNS	coagulase-negative staphylococci
CPE	carbapenemase-producing Enterobacterales
CPP	critical priority pathogens on the WHO bacterial priority pathogens list
CR-EC	carbapenem-resistant *Escherichia coli*
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CRE	carbapenem-resistant Enterobacterales
CRISPR	clustered regularly interspaced short palindromic repeats
CRKP	carbapenem-resistant *Klebsiella pneumoniae*
CRPA	carbapenem-resistant *Pseudomonas aeruginosa*
cSSTI	complicated skin and soft tissue infection
CT	clinical trial
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
cUTI	complicated urinary tract infection
DAIR	debridement, antibiotics and implant retention
DBO	diazabicyclooctane
DFO	diabetic foot osteomyelitis
DHFR	dihydrofolate reductase inhibitor
DMID	Division of Microbiology and Infectious Diseases
DOI	declaration of interest
DprE1	decaprenylphosphoryl-β-D-ribose 2-epimerase
DS-TB	drug-susceptible tuberculosis
EBA	early bactericidal activity
eCAPs	engineered cationic antimicrobial peptides
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EML	WHO Essential Medicines List
EOT	end of treatment

ESBL	extended-spectrum β-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FabI	enoyl-acyl carrier protein reductase
fAUC	free drug area under the concentration–time curve
FDA	Food and Drug Administration
FimH	type 1 fimbrin D-mannose specific adhesin
FMT	faecal microbiome transplant
FPFV	first patient first visit
FTIH	first time in humans
FtsZ	filamenting temperature-sensitive Z
GARDP	Global Antibiotic Research and Development Partnership
GI	gastrointestinal
GIT	gastrointestinal tract
GLASS	Global Antimicrobial Resistance and Use Surveillance System
GvHD	graft vs host disease
HABP	hospital-acquired bacterial pneumonia
HBsAg	hepatitis B surface antigen
HDPs	host defence peptides
HDT	host-directed therapy
HERA	Health Emergency Preparedness and Response Authority
HSCT	haematopoietic stem cell transplant
IAI	intra-abdominal infection
ICTRP	WHO International Clinical Trials Registry Platform
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IM	intramuscular
IMI	imitable 1b penem-hydrolysing β-lactamase
IMP	active-on-imipenem type β-lactamase
iMPV	inhaled murepavadin
INCATE	INCubator for Antibacterial Therapies in Europe
IND	Investigational New Drug
INN	international nonproprietary name
ITT	intent-to-treat

iv	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
KPC-Kp	*Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*
LeuRS	leucyl-tRNA synthetase
LptD	lipopolysaccharide transport protein D
MAA	Marketing Authorization Application
mAb	monoclonal antibody
MBL	metallo-β-lactamase
MDR	multidrug-resistant
MDR-TB	multidrug-resistant tuberculosis
MIC	minimum inhibitory concentration
micro-ITT	microbiologic intent-to-treat
micro-MITT	microbiologic-modified intent-to-treat
micro-MITTR	microbiologic-modified intent-to-treat resistant
micro-MITTS	microbiologic-modified intent-to-treat susceptible
MITT	modified intent-to-treat
MoA	mode of action
MRSA	methicillin-resistant *Staphylococcus aureus*
mSOFA	modified sequential organ failure assessment
MSSA	methicillin-susceptible *Staphylococcus aureus*
NAAT	nucleic acid amplification test
NBTI	novel bacterial type II topoisomerase inhibitor
NCFB	non-cystic fibrosis bronchiectasis
NDA	New Drug Application
NDM	New Delhi metallo-β-lactamase
NIAID	National Institute of Allergy and Infectious Diseases
NOAEL	no observed adverse effect level
NTF-S	susceptible to nitrofurantoin
NTM	non-TB mycobacteria
OMIP	other medically important pathogens
OPP	other priority pathogens on the WHO bacterial priority pathogens list (“high” and “medium” priority)
OUCRU	Oxford University Clinical Research Unit
OXA	oxacillinase
PA	*Pseudomonas aeruginosa*
PBP	penicillin-binding protein

PCR	polymerase chain reaction
PIP	paediatric investigational plan
PJI	prosthetic joint infection
PK	pharmacokinetics
PK/PD	pharmacokinetics/pharmacodynamics
PMB	polymyxin B
PO	per os (oral)
PPL	priority pathogen list
qid	four times a day
R&D	research and development
rCDI	recurrent *Clostridioides difficile* infection
RCT	randomized control trial
Rhu-pGSN	rhu-plasma gelsolin
RIF	rifabutin
RR-TB	rifampicin-resistant tuberculosis
SAT	suppressive antibiotic therapy
SBI	serious bacterial infection
SBL	serine-β-lactamase
SLE	systemic lupus erythematous
SME	Serratia marcescens enzyme
SOC	standard of care
SRA	stringent regulatory authority
T3SS	type III secretion system
TB	tuberculosis
TB Alliance	Global Alliance for TB Drug Development
TBP-PI	tebipenem pivoxil
TEAEs	treatment emergent adverse events
tet	tetracycline resistance encoding gene
TGA	Australian Therapeutic Goods Administration
TKA	total knee arthroplasty
Tmax	maximum plasma concentration
TMP/SMX	trimethoprim/sulfamethoxazole
TNF-α	tumour necrosis factor α
TOC	test-of-cure
tRNA	transfer RNA
UTI	urinary tract infection

uUTI	uncomplicated urinary tract infection
VABP	ventilator-associated bacterial pneumonia
VIM	Verona integron-encoded metallo-β-lactamase
VRE	vancomycin-resistant enterococci
WBA	whole blood activity
WBC	white blood cell
WHO	World Health Organization
WLA	WHO Listed Authorities
XDR	extensively drug-resistant



Executive summary

This report presents an analysis of antibacterial agents in preclinical (fourth annual review) and clinical (sixth annual review) development. The analysis covers traditional (direct-acting small molecules) and non-traditional antibacterial agents in development worldwide.

The report evaluates to what extent the present pipeline addresses infections caused by drug-resistant bacterial priority pathogens (BPPs) according to the updated 2024 WHO bacterial priority pathogen list (BPPL)[1] to provide an overview of the current R&D landscape and steer development towards the most urgent unmet medical needs. The report also assesses traditional agents with respect to whether they meet a set of predefined criteria for innovation, namely no cross-resistance; new target, mode of action (MoA) and/or class; and a new analysis on trends. For the purpose of this review, agents targeting drug-resistant *Mycobacterium tuberculosis* are discussed separately from drugs targeting the other WHO BPPs. The review also includes products intended against *Clostridioides difficile* and *Helicobacter pylori*, given the clinical importance of these pathogens and associated resistance.

The WHO Secretariat's pipeline team, along with an advisory group of experts, rigorously evaluated antibacterial agents in clinical and preclinical development. The process involved pre-consultation surveys, in-depth discussions during a 2-day virtual meeting and use of a newly developed assessment matrix. The 2023 pipeline report was circulated among all members and observers of the advisory group for feedback before publication. The full methodology is described in section 7 on methods.

Key facts about the clinical pipeline

The current clinical antibacterial pipeline contains 97 antibacterial agents and/or combinations that include at least one new therapeutic entity. Of these, 57 are traditional antibacterial agents and 40 are non-traditional. There are four products in New Drug Application /Marketing Authorization Application (NDA/MAA) stages: three traditional agents and one non-traditional agent.

Of the 57 traditional antibacterials, 12 new products entered the clinical pipeline since the last report. In addition, three agents were either discontinued or no recent information was available since the last report (see Table 8).

Of the 57 traditional antibacterials, 32 (56%) are intended against the WHO BPPs and 19 (33%) against drug-resistant *M. tuberculosis*. Additionally, five (9%) traditional agents are being developed against *C. difficile*, and one (2%) against *H. pylori*.

Analysis of the 32 traditional antibacterials under development against WHO BPPs other than *M. tuberculosis*, found that:

- Twelve fulfil at least one of the WHO innovation criteria; however, of these 12, only four are active against at least one WHO "critical" pathogen.[2] Six innovative agents are active against high and medium priority pathogens[2] (i.e., other priority pathogens – OPPs), including two against carbapenem-resistant *Pseudomonas aeruginosa* (CRPA).
- Several agents have insufficient evidence of activity[3] and are assessed as possibly active towards critical pathogens ($n = 9$) and/or OPPs[2] ($n = 5$).
- Forty-seven per cent of traditional antibiotics (15/32) are β-lactam or β-lactam/β-lactamase-inhibitor (β-lactam/BLI) combinations with a major gap in activity against metallo-β-lactamase (MBL) producers.

[1] To guide readers, especially those in drug discovery and development, in interpreting priority for R&D, please refer to section 5.7 on the BPPL update and recommendations for R&D.
[2] Critical, high and medium BPPs are presented in the WHO 2024 BPPL in Box 1.
[3] See activity assessment in section 7 on methods.

Key facts about the clinical pipeline (continued)

Analysis of the 19 antibiotics developed against drug-resistant *M. tuberculosis* found that 10 (53%) are assessed as innovative according to the WHO criteria.

Of the 40 non-traditional antibacterials, 30 are intended against WHO BPPs, nine agents are directed against *C. difficile*, and one addresses *H. pylori*. Analysis of the 30 non-traditional antibacterials against WHO BPPs shows that:

- Most are bacteriophages or phage-derived enzymes (*n* = 13), seven are antibodies, three are anti-virulence agents, two are immune-modulating agents, one is a microbiome-modulating agent, and four are grouped as miscellaneous agents.
- Three new non-traditional products entered the clinical pipeline since the last report; all are microbiome-modulating agents.
- Of the 30 non-traditional antibacterials against WHO BPPs, 13 target WHO critical bacteria (five target *Escherichia coli* – including one against adherent-invasive *E. coli* (AIEC) strains, and one against *E. coli/Campylobacter jejuni* – and seven are extended-spectrum agents with activity against Gram-positive and Gram-negative bacteria, including three against biofilm-producing pathogens (two monoclonal antibodies and one engineered cationic antimicrobial peptide).

Key facts about newly approved antibacterials

- Since 1 July 2017, 16 new antibacterials have been approved by the FDA, the EMA or any stringent regulatory authority (SRA)/WHO Listed Authority (WLA), [4] of which there has been only one since the last report *(1)*.
- Only two antimicrobial agents with activity against carbapenem-resistant *Acinetobacter baumannii* (CRAB) – cefiderocol and sulbactam-durlobactam – have been approved since July 2017.
- The first microbiome-modulating agents (three products against *C. difficile*) were authorized[5] in 2022 and 2023.

Approximately 77% (10/13) of the traditional agents approved since July 2017 belong to existing antibiotic classes for which resistance mechanisms are well known.

Key facts about clinical pipeline trends

Since the first release of the WHO antibacterial pipeline analysis report in 2017 and up to 31 December 2023, the following trends were observed in the pipeline:

- The number of both traditional and non-traditional agents addressing the WHO BPPs has increased, with Gram-negative broad-spectrum agents being far more numerous in the 2023 pipeline report compared to 2017.[6]
- Extended-spectrum (both Gram-positive and Gram-negative) traditional and non-traditional agents in clinical development increased from 0 in 2017 to 9 (14%) in 2023.
- Oral traditional antibacterial formulations decreased from 47% in 2017 to 37.5% in 2023. The same negative trend is observed in the number of antibacterials with both iv and oral formulations. In general, oral formulations in the 2023 pipeline are limited and represent a significant unmet medical need. Other routes of administration (intra-articular, intraurethral/irrigation and inhalation) were not a feature of the 2017 pipeline but collectively represented 15% in 2023.
- The range of indications addressed by traditional agents expanded in 2023 compared to 2017; however, indications in complex and more severe pathologies, including hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP) or bloodstream infections (BSIs), have decreased or are insufficiently represented.
- There is an imbalance in the availability of antibacterial agents with paediatric indications and/or formulations against the WHO BPPs when compared to those for adults.

Overall, antibacterial agents in the clinical pipeline combined with those approved in the last six years are still insufficient to tackle the ever growing threat of the emergence and spread of drug-resistant infections.

[4] For more information, see WHO's health topic on WLAs *(19)*.
[5] All medicines must be authorized before they can be marketed and made available to patients. In this report the terms *authorized* and *approved* are both used to indicate that a marketing authorization has been issued.
[6] Broad-spectrum agents target two or more pathogens from the WHO BPPL.

Key facts about the preclinical pipeline

Overall 244 products in preclinical development targeting WHO 2023 BPPs and *C. difficile* are being progressed by 141 individual developers/groups.

The preclinical pipeline is dynamic and innovative, with agents being developed in many parts of the world to prevent and treat drug-resistant bacterial infections.

Preclinical research projects are captured across all WHO regions, with most programmes (54.9%) being developed in the European Region followed by the Region of the Americas (34.8%). For the first time, one programme was captured from the Eastern Mediterranean Region in addition to one programme from the African Region.

- One hundred and fifty-three products are broad-spectrum agents that have claimed activity against more than one pathogen from the BPPL.
- Ninety-one agents (37.3%) are narrow spectrum and target a single pathogen. A total of 43 products target one of the WHO critical priority pathogens (CPPs), including 26 products intended against *M. tuberculosis*. When considering the high priority group, a total of 20 programmes are directed against *Pseudomonas aeruginosa*, along with 12 directed against *Staphylococcus aureus* and eight against *Neisseria gonorrhoeae*.
- Ninety-three products (38.1%) are classified as non-traditional. These include bacteriophages, virulence inhibitors, immunomodulatory compounds and potentiator agents, among others.

Results from the pre-clinical and clinical antibacterial pipeline are based on publicly available data and are available to download from the WHO Global R&D Health Observatory (link below). WHO will continue to collect and make available this data on a regular basis to promote innovation, collaboration and transparency in the scientifically and economically challenging field of early antibacterial discovery and development to collectively move forward in developing the needed products to prevent and treat drug-resistant bacterial infections.

Editorial note: In this report, the terms *antibacterial agents* and *antibiotics* are used somewhat interchangeably when referring to small molecules, whereas for non-traditional agents the term *antibacterial agents* is most appropriate. In this context, the antibiotics under analysis are those that kill or prevent bacterial growth. Also, in this report the order Enterobacterales was used instead of the family Enterobacteriaceae; the same applies to *Clostridioides difficile*, which replaces the former nomenclature *Clostridium difficile*.

All data contained in this report can be downloaded from the WHO Global Observatory on Health R&D.

1

Introduction

1. Introduction

Antimicrobial resistance (AMR) continues to pose a significant global public health threat, ranking among the top 10 challenges faced by humanity *(2)*. In 2019 alone, AMR was associated with the deaths of 4.95 million individuals *(3)*. One out of every five deaths related to AMR occurred in children under the age of 5, underscoring the urgent need for a global, coordinated action.

Beyond its devastating impact on human lives, AMR also jeopardizes the global economy, with implications for international trade, health care expenditures and overall productivity. If left unaddressed, by 2050 the economic toll of AMR could reach a staggering US$ 100 trillion *(4)*.

The link between AMR and use of antibiotics is well established. Additionally, the misuse of medically important antibiotics in farms, aquaculture and in agriculture *(5)* is a significant contributor to the rising prevalence of AMR. Moreover, AMR is influenced by a wide array of additional risk factors, encompassing environmental, governance and socioeconomic elements. To effectively address AMR, adoption of a multifaceted approach is crucial. This includes implementation of surveillance and tracking systems, antibiotic stewardship, and infection prevention and control measures. At the same time, it is imperative to bolster laboratory capabilities, monitor drug use while enhancing access and invest in the development of innovative and effective antibacterial agents as well as novel diagnostic approaches and vaccines.

This report by WHO sheds light on the progress made in combating AMR through R&D on new therapeutic options. The report highlights the innovation potential of traditional antibiotics and emphasizes the remaining challenges to ensuring a robust pipeline of effective antibiotic treatments. The report emphasizes the urgent need to address the rising prevalence of AMR by developing effective solutions to combat bacteria causing life-threatening bloodstream infections. Although beyond the scope of this report, equally important is a comprehensive AMR action plan which includes stewardship of new and existing antibiotics, regulation of agricultural antibiotic use and R&D advancement of vaccines and diagnostics.

Global trends in drug resistance

The urgent need for effective antibacterial drugs is further highlighted by increasing resistance trends. The 2022 WHO report on the Global Antimicrobial Resistance and Use Surveillance System (GLASS) *(6)* report revealed alarming levels of resistance. The resistance rate towards cephalosporin exceeds 50% in *Klebsiella pneumoniae*, which typically necessitate the use of carbapenems (i.e., “Reserve” antibiotics), while over 50% resistance towards carbapenems in *Acinetobacter* spp. Leaves patients with very few options. Over 60% of *N. gonorrhoeae* isolates showed resistance to ciprofloxacin, one of the most frequently prescribed oral antibacterials. Similarly, more than 20% of isolates of *E. coli*, the primary pathogen responsible for urinary tract infection (UTI), demonstrated resistance to both first-line (ampicillin and co-trimoxazole) and second-line (fluoroquinolone) treatment.

While some resistance trends have remained stable over the past 4 years, the rates of BSI caused by resistant *E. coli*, *Salmonella* spp., and resistant *N. gonorrhoeae* infections have increased by at least 15% compared to 2017 figures.

Updating the WHO BPPL

Recognizing the ever-evolving nature of the antibiotic resistance crisis, the 2017 WHO BPPL *(7)* has been updated to reflect changing trends in resistance, the distribution of bacterial infections, their burden and the emergence of new resistance mechanisms. This analysis evaluates the current pipeline of antibacterial agents against the new WHO 2024 BPPL (see also section 5.7. WHO 2024 BPPL changes and implications for R&D for novel antibacterial agents).

Box 1. List of WHO BPPs of public health importance, 2024 update (7)

BPPs: bacterial priority pathogens; OPPs: other priority pathogens.
[a] High and medium BPPs are also referred to as OPPs.

2

Agents that obtained market authorization since 1 July 2017

2. Agents that obtained market authorization since 1 July 2017

Since the first WHO analysis of the clinical antibacterial pipeline in 2017, 13 new antibiotics and three new non-traditional antibacterial agents have been approved for marketing by the FDA, the EMA or other SRA or WLA.[4]

2.1 Innovation assessment

Antibiotics either authorized or in the pipeline are evaluated against four WHO innovation criteria: new chemical class, new target, new MoA and absence of cross-resistance. The WHO innovation criteria are poorly addressed by newly authorized agents. Only two of the newly approved agents, vaborbactam (approved in combination with meropenem) and lefamulin,[7] represent new chemical classes and therefore meet one of the four innovation criteria. Most recently approved agents are derivatives of known classes, including combination of the penicillin analogue sulbactam with the diazabicyclooctane (DBO) BLI durlobactam; the siderophore cephalosporin cefiderocol; the fluoroquinolone derivatives delafloxacin, lascufloxacin and levonadifloxacin (developed as the prodrug alalevonadifloxacin); and the tetracycline derivatives eravacycline and omadacycline. Currently, data to evaluate the potential for cross-resistance are inconclusive for two compounds: vaborbactam in combination with meropenem and lefamulin. No newly approved agents show any new mechanism of action or new molecular target.

2.2 Evaluation against the WHO priority pathogens list

In terms of activity, most newly approved agents have an indication for classic syndrome-based indications, for example treatment of complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI), community-associated bacterial pneumonia (CABP), HABP and/or acute bacterial skin and skin structure infection (ABSSSI). Only two agents target CRAB, one of which, cefiderocol, is also active against both CRPA and carbapenem-resistant Enterobacterales (CRE), while sulbactam/durlobactam is not active against other priority bacteria. Five of the 13 approved antibiotics target one or more types of CRE (most data available are for *E. coli* and *K. pneumoniae*), and seven are active against other high or medium priory pathogens from the WHO 2024 BPPL, including one product for extremely resistant or multidrug-resistant tuberculosis (XDR/MDR-TB). CRPA is also targeted by the combination of imipenem with cilastatin and the BLI relebactam, but with limited evidence of efficacy from randomized control trials (RCTs) at present *(8)*.

[7] Pleuromutilins were discovered in the 1950s and were used in veterinary medicine. Lefamulin is a pleuromutilin antibiotic that has been developed for human use; chemical properties have been modified to offer an iv/oral form.

2.3 Product descriptions

2.3.1 Traditional agents

A new antibiotic, the sulbactam + durlobactam combination (Xacduro), was approved by the FDA in 2023 for HABP and VABP caused by susceptible strains of *A. baumannii*, for patients 18 years of age and older *(9)*.

Sulbactam + durlobactam: Sulbactam is a penicillin analogue BLI with intrinsic activity against *A. baumannii*, while durlobactam is a diazabicyclooctane class of BLIs with activity against A, C and D serine β-lactamases *(10)*. The combination is intended for the parenteral route. The efficacy of sulbactam + durlobactam was established in a multicentre, active-controlled, open-label, non-inferiority clinical trial in 177 hospitalized adults with pneumonia mostly caused by CRAB. Patients were randomized into two arms and received either sulbactam + durlobactam or colistin for up to 14 days, both combined with imipenem and cilastatin. The primary end-point was mortality from all causes within 28 days. A total of 19% of patients (12 of 63 patients) in the sulbactam + durlobactam arm died, compared to 32% of patients (20 of 62 patients) in the colistin arm, showing non-inferiority of sulbactam + durlobactam to colistin. Acute kidney injury (AKI) was less frequent with sulbactam + durlobactam (0/91) compared to colistin (8/86) *(11)*.

Sulbactam + durlobactam is one of only two authorized agents (after cefiderocol) to address CRAB (but not MBL-producing strains), a CPP, and possesses the potential to significantly impact the successful treatment of CRAB-induced infections despite meeting none of the WHO innovation criteria. Mortality rates due to CRAB are extremely high, ranging between 40% and 60%, with some studies showing even higher rates in critically ill patients *(12)*.

2.3.2 Non-traditional agents

The three new non-traditional agents are live biotherapeutic products and have all been approved for preventing recurrence of *C. difficile* infection (CDI) following antibiotic treatment in adults (Table 1b). SER-109 (VOWST) was approved by the FDA in 2023, BB128 (Biomictra) by Australia's Therapeutic Goods Administration (TGA) in 2022 and RBX2660 (Rebyota) by the FDA in 2022.

SER-109 (VOWST) contains a collection of pathogen-free, purified bacterial spores of multiple firmicutes, derived from healthy human donor stools. The FDA has approved SER-109 for preventing recurrence of CDI following antibiotic treatment in adults. SER-109 acts by restoring the gut microbiota and can be administered by the oral route. The clinical development programme included two Phase 3 studies, SERES-012 and SERES-013. After 8 weeks of treatment in the SERES-012 study, statistically significantly fewer SER-109 recipients (11 of 89) showed CDI recurrence than did placebo recipients (37 of 93) (12.4% vs 39.8%; RR 0.32 (95% CI: 0.18–0.58). The most common adverse events included abdominal distension, constipation, chills and diarrhoea *(15)*.

RBX2660 (Rebyota) is a faecal microbiota product authorized by the FDA to prevent recurrent CDI in adults. RBX2660 is administered rectally in one dose. The safety and efficacy of the treatment were evaluated by the FDA in two randomized, double-blind, placebo-controlled trials and in open-label studies. Recurrent CDI was prevented in 70.6% of patients administered RBX2660 vs a 57.5% reduction observed in the placebo group. The most common adverse events were abdominal pain, bloating, diarrhoea, gas and nausea *(16)*.

BB128 (Biomictra) is a faecal transplant therapy authorized by the Australia's TGA. This biotherapeutic product is intended to restore the gut microbiota in treating recurrent CDI. It is formulated as a frozen syringe for colonic and enema delivery. Capsules to improve patient access could be made available in the future *(17)*.

Table 1a. Traditional antibacterial agents that gained market authorization between 1 July 2017 and 31 December 2023

Name (trade name USA/ EU)	Marketing authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication(s)	WHO EML and AWaRe classification[a]	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Sulbactam + durlobactam (Xacduro)	Innoviva (formerly Entasis Therapeutics)	FDA (05/2023)	BLI/PBP1,3 binder + DBO-PBP2 binder	iv	HABP/VABP	WHO EML: not yet evaluated; AWaRe: not yet classified	●	X	X	/	–	–	–	–
Delafloxacin (Baxdela/ Quofenix)	Melinta Therapeutics (USA) (Menarini, EU)	FDA (6/2017 ABSSSI, 10/2019 CAP), EMA (12/2019 ABSSSI, 02/2021 CAP)	Fluoroquinolone	iv	ABSSSI, CABP	WHO EML: no; AWaRe: Watch	X	X	X	●	–	–	–	–
Meropenem + vaborbactam (Vabomere)	Melinta Therapeutics (USA) (Menarini, EU)	FDA (8/2017) EMA (11/2018)	β-lactam (carbapenem) + boronate BLI	iv	cUTI (cUTI, cIAI, HABP/VABP in EU)	WHO EML: yes; AWaRe: Reserve	X	X	●[b]	/	?[c]	✓	–	–
Plazomicin (Zemdri)	Achaogen (Cipla USA / QiLu Antibiotics, China)	FDA (8/2018)	Aminoglycoside	iv	cUTI	WHO EML: yes; AWaRe: Reserve	X	X	●	/	–	–	–	–
Eravacycline (Xerava)	Tetraphase Pharmaceuticals (La Jolla Pharmaceutical Company, Everest Medicines)	FDA (8/2018) EMA (9/2018)	Tetracycline	iv	cIAI	WHO EML: no; AWaRe: Reserve	?	X	●	/	–	✓	–	✓
Omadacycline (Nuzyra)	Gurnet Point Capital and Novo Holdings	FDA (10/2018)	Tetracycline	iv and PO	CABP (iv), ABSSSI (iv, PO)	WHO EML: no; AWaRe: Reserve	X	X	X	●	?	✓	–	✓

Table 1a (continued). Traditional antibacterial agents that gained market authorization between 1 July 2017 and 31 December 2023

Name (trade name USA/ EU)	Marketing authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication(s)	WHO EML and AWaRe classification[a]	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Imipenem/ cilastatin (Recarbrio) + Relebactam	Merck Sharp & Dohme	FDA (7/2019 cUTI/cIAI, 7/2020 HAP/VAP), EMA (2/2020 G-ve)	β-Lactam (carbapenem) / degradation inhibitor + DBO-BLI	iv	cUTI, cIAI, HABP/ VABP	WHO EML: no; AWaRe: Reserve	X	?	●[b]	/	–	–	–	–
Lefamulin (Xenleta)	Nabriva (Sunovion Pharmaceuticals Canada)	FDA (8/2019) EMA (7/2020)	Pleuromutilin	iv and PO	CABP	WHO EML: not yet evaluated; AWaRe: Reserve	/	/	/	●	?	✓[d]		
Pretomanid (Dovprela)	TB Alliance (Viatris)	FDA (8/2019) EMA (8/2020) CDSCO (7/2020)	Nitroimidazole	PO	XDR-TB	WHO EML: yes; AWaRe: not yet classified	/	/	/	●[e]	–	–	–	–
Lascufloxacin (Lasvic)	Kyorin Pharmaceutical	PDMA (8/2019)	Fluoroquinolone	iv and PO	CABP, otorhinolaryngological	WHO EML: not yet evaluated; AWaRe: Watch	X	X	X	●	–	–	–	–
Cefiderocol (Fetroja)	Shionogi	FDA (11/2019 cUTI, 9/21 HAP/ VAP), EMA (4/2020)	Siderophore β-lactam (cephalosporin)	iv	cUTI, HABP/ VABP, aerobic G-negative[f]	WHO EML: yes; AWaRe: Reserve	●	●	●	/	–	–	–	–
Levonadifloxacin (Emrok); alalevonadifloxacin (Emrok-O)	Wockhardt	CDSCO (1/2020)	Fluoroquinolone	iv and PO	ABSSSI	WHO EML: not yet evaluated; AWaRe: Watch amd not yet classified, respectively[g]	X	X	X	●	–	–	–	–

Table 1a (continued). Traditional antibacterial agents that gained market authorization between 1 July 2017 and 31 December 2023

Name (trade name USA/ EU)	Marketing authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication(s)	WHO EML and AWaRe classification[a]	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Contezolid (Youxitai); contezolid acefosamil	MicuRx	NMPA (6/2021)	Oxazolidinone	iv and PO	cSSTI	WHO EML: not yet evaluated; AWaRe: not yet classified	/	/	/	●	–	–	–	–

Activity Assessment:

● Active
? Possibly Active
X Not Active
/ Not Tested

Innovation Assessment:

✓ Criterion fulfilled
? Inconclusive data
– Criterion not fulfilled

ABSSSI: acute bacterial skin and skin structure infection; AWaRe: Access, Watch, Reserve; BLI: β-lactamase inhibitor; CAP: community-acquired pneumonia; CABP: community-acquired bacterial pneumonia; CC: new chemical class; CDSCO: Central Drugs Standard Control Organization of the Government of India; cIAI: complicated intra-abdominal infection; CRAB: carbapenem-resistant *A. baumannii*; CRE: carbapenem-resistant Enterobacterales; CRPA: carbapenem-resistant *P. aeruginosa*; cSSTI: complicated skin and soft tissue infection; cUTI: complicated urinary tract infection; EMA: European Medicines Agency; EML: WHO Essential Medicines List; FDA: United States Food and Drug Administration; HABP: hospital-acquired bacterial pneumonia; HAP: hospital-acquired pneumonia; iv: intravenous; KPC: *K. pneumoniae* carbapenemase; MBL: metallo-β-lactamase; MDR: multidrug-resistant; MoA: new mode of action; N/A: not applicable; NCR: no cross-resistance to other antibiotic classes; NMPA: China National Medical Products Administration; OPP: other priority pathogens; PBP: penicillin-binding protein; PDMA: Pharmaceuticals and Medical Devices Agency (Japan); PO: per os (oral); T: new target; TB: tuberculosis; VABP: ventilator-associated bacterial pneumonia; VAP: ventilator-associated pneumonia; XDR-TB: extensively drug-resistant TB.

Pathogen activity: ● active; ? possibly active; X not or insufficiently active; / activity not assessed, as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods. Agents not active against CPPs were assessed for activity against OPP, which includes the WHO high and medium priority pathogens.

Innovation assessment: ✓ criterion fulfilled; ? inconclusive data; - criterion not fulfilled.

[a] For inclusion in the WHO EML: no = evaluated and not recommended and yes = evaluated and included on list.

[b] Active against KPC, but not MBL-producing Enterobacterales.

[c] New reports suggest that cross-resistance can be obtained when the porin OmpK35-36 level is varied (13) and for overproduction of KPC-3 associated with increased gene dosage (14).

[d] First systemic formulation of this class, which was previously used in animals and topically in humans.

[e] Approved for the treatment of XDR-TB or treatment-intolerant/non-responsive MDR-TB, in combination with bedaquiline and linezolid.

[f] The EMA approved cefiderocol for treatment of infections due to aerobic Gram-negative bacteria in adults with limited treatment options, which is broader than the FDA approval.

[g] Only levonadifloxacin has been classified under AWaRe (Watch). Alalevonadifloxacin has yet to be classified under AWaRe.

Table 1b. Non-traditional antibacterial agents that gained market authorization between 1 July 2017 and 31 December 2023

Name (trade name)	Marketing authorization Holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication/s	Pathogen	Reference (product information)
SER-109 (VOWST (faecal microbiota spores, live-brpk))	Seres Therapeutics	FDA 04/2023	Live biotherapeutic product	PO	Recurrent/ refractory diarrhoea prevention[a]	*C. difficile*	Vowst
BB128 (Biomictra faecal microbiota)	BiomeBank	TGA (Aus) 11/2022	Live biotherapeutic product	Endoscopic delivery or enema	Recurrent/ refractory diarrhoea prevention[a]	*C. difficile*	Biomictra
RBX2660 (Rebyota (faecal microbiota, live-jslm))	Ferring Pharmaceuticals	FDA 11/2022	Live biotherapeutic product	Enema	Recurrent/ refractory diarrhoea prevention[a]	*C. difficile*	Rebyota

CDI: *C. difficile* infection; FDA: United States Food and Drug Administration; PO: per os (oral); rCDI: recurrent *C. difficile* infection; TGA: Australian Therapeutic Goods Administration.

[a] Prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

3

Agents in clinical development

3. Agents in clinical development

The following sections describe the current clinical antibacterial development pipeline with activity against WHO 2024 BPPL. In this report agents intended against *M. tuberculosis* are discussed in a dedicated section. Although not included in the 2024 BPPL, agents against CDI and *H. pylori* have also been reviewed, given their clinical importance and the limited therapeutic options.

The report is organized as follows:

- **Sections 3.1–3.2** provide an overview and analysis of traditional, direct-acting small molecules in clinical development and at the NDA/MAA stage:
  - **3.1** Antibacterial agents targeting WHO priority pathogens (excluding *M. tuberculosis*).
  - **3.2** Antibacterial agents targeting *M. tuberculosis*.
- **Section 3.3** provides an overview of non-traditional antibacterial agents targeting WHO priority pathogens in clinical development and at the NDA/MAA stage.
- **Section 3.4** provides an overview of traditional and non-traditional antibacterial agents targeting *C. difficile* and *H. pylori*.
- **Section 3.5** includes agents that are not under active development and/or are no longer listed in a company's pipeline or for which there is no recent information.

Potential for clinical utility and clinical differentiation of antibacterials under development

The potential for clinical utility and clinical differentiation for each of the Phase 1–3 traditional and non-traditional antibacterials is described in detail in the annexes. The data are based on pharmacology, spectrum of activity, sought therapeutic indications, pharmaceutical formulation, route of administration and proposed posology, and clinical trial design and results, and are drawn from published information. The scope is to highlight certain drug attributes that would be relevant for potential clinical use, including information on clinical trial study, design and results. As products advance in their development, a more comprehensive profile can be drawn in terms of dose-response, safety and expected efficacy.

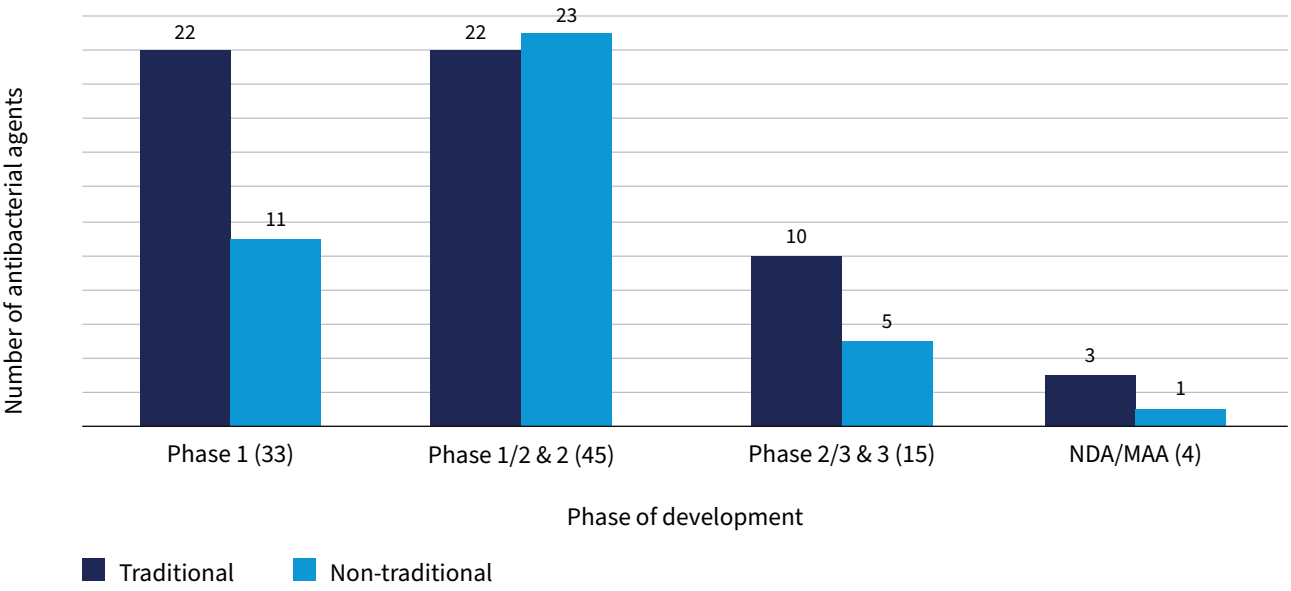
Since the last report, published in 2022 (*1*), product profiles have been developed for both traditional and non-traditional agents intended against drug-resistant infections, including drug-resistant TB, CDI and *H. pylori*. The product profiles contain direct links to their respective trials registered under clinical trial registries.

Overview

As of 31 December 2023, there are 97 antibacterial agents with new therapeutic entities targeting WHO BPPs, *M. tuberculosis*, *C. difficile* and *H. pylori* in different phases of clinical development (Phases 1–3 and NDA/MAA) (Fig. 1). A new therapeutic entity is defined as any antibacterial agent that represents a new substance, a new chemical entity, a new biological entity and/or a new molecular entity (*18*).

Most of the traditional and non-traditional agents are in early stage of clinical development. Only 15 agents are in Phase 2/3 or Phase 3, and four agents are at the NDA/MAA stage.

Fig. 1. Number of traditional and non-traditional antibacterials by clinical development phase (Phases 1–3 and NDAs/MAAs)



MAA: Marketing Authorization Application; NDA: New Drug Application.

Of the 57 traditional agents in clinical development, 32 target WHO bacterial priorities excluding *M. tuberculosis*, 19 target drug-resistant *M. tuberculosis*, five target *C. difficile* and one targets *H. pylori* (Fig. 2). Of the 32 products intended for BPPs, 56 % (*n* = 18) have conclusive evidence of activity against at least one of the Gram-negative pathogens listed as critical in the BPPL: eight target CRAB (five of which also target CRE and/or third-generation CRE (3GCRE)), and 15 target CRE and/or 3GCRE.

Of the 32 antibiotics in development for BPPs, six show conclusive evidence of activity against CRPA, an important pathogen for R&D, and another seven are active against OPPs that are high or medium priority on the WHO BPPL.

As Fig. 2 shows, among traditional agents, 12 are active and three possibly active on **critical pathogens only**, while seven are active only on OPPs. In addition, six traditional agents are active *(note: when sufficiently active against one critical pathogen/order for CRE and 3GCRE out of three plus active against one OPP)* and seven possibly active *(note: when possibly active against one critical pathogen/order for CRE and 3GCRE out of three plus one OPP)* against **both CPPs and OPPs**.

Of the 40 non-traditional antibacterials, 30 are intended against BPPs, mostly against high and medium priority pathogens, whereas nine agents are directed against *C. difficile*, and one against *H. pylori*. No non-traditional agents target *M. tuberculosis*.

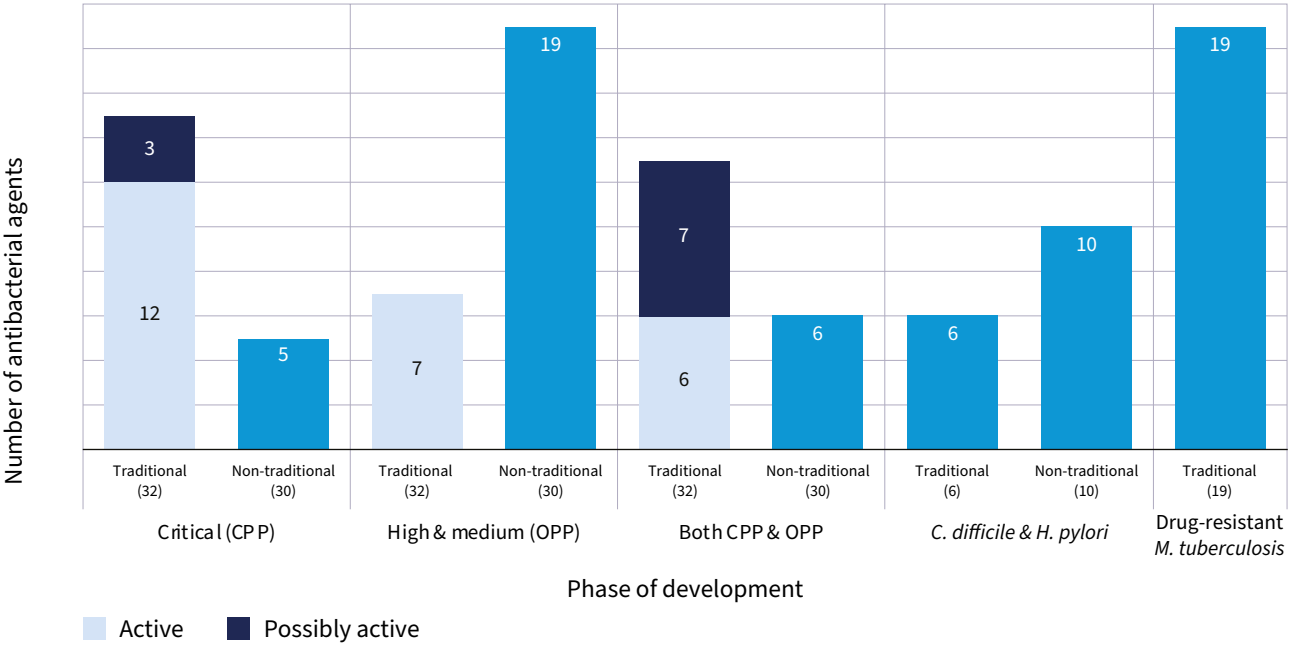
Progression or discontinuation of the antibacterial pipeline since the 2021 report to 31 December 2023

Fig. 3 presents the trend of progression or discontinuation of antibacterial agents under development since the last WHO report *(1)*, published in June 2022. The 2023 analysis provides significant findings such as the increase from 80 products in 2021 to 97 in 2023, the approval of an additional four agents against WHO BPPs since 2017 and the discontinuation of four agents.

For the purpose of this analysis, the following definitions were used:

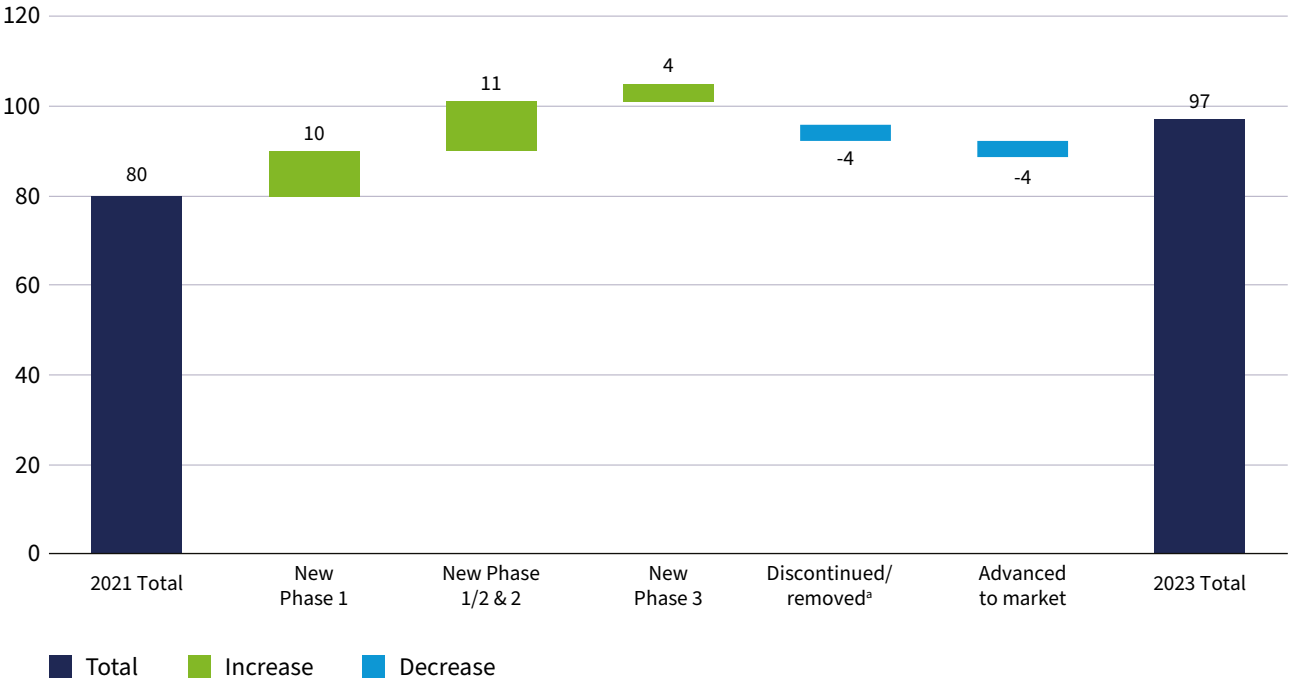
- new entry: any new antibacterial agent and/or combination that includes at least one new therapeutic entity that entered the pipeline in Phases 1–3, including products that were not captured in the report for 2021. The analysis also covers discontinued products that were revived;
- discontinued: products that are not under active development and/or are no longer listed in a company's pipeline;
- advanced to market: any product that has received marketing authorization from an SRA or WLA *(19)*; and
- NDA/MAA: any product that is under regulatory review by an SRA or a WLA *(19)*.

Fig 2. Number of traditional and non-traditional antibacterials in clinical development (Phases 1–3 and NDAs/MAAs) by intended target



CPP: critical priority pathogen; OPP: other priority pathogen.
Note: The category "BOTH CPP & OPP" refers to agents active against pathogens in both critical and other priority groups (high and medium).
Agents that are considered possibly active (see section 7.1.3 on assessment of activity against priority pathogens and innovation) and indicated with a question mark (?) in Table 2 are included in this count

Fig. 3. Number of products entering and exiting the pipeline since the 2021 report to 31 December 2023



[a] QPX7728+2015 and QPX7728+2014, previously reported as two separate programmes, are now assessed as one in this pipeline analysis.

Analysis, including trends on products in clinical development

The WHO BPPL, released in 2017, identified 12 priority pathogens posing a significant threat to public health and for which R&D should be prioritized *(20)*. The pivotal WHO antibacterial pipeline analysis report, published in the same year, revealed that only 46 antibiotics under development demonstrated promising activity against BPPs *(21)*. Almost 7 years have passed since the first WHO BPPL. During this time WHO has been monitoring the pipeline on an annual basis, which now gives us an opportunity to consider the evolution of the pipeline since the list was published.

A series of targeted trend analyses have been performed for this pipeline review, examining product formulations, activity and desired clinical indications data from 2017 to 31 December 2023, the cut-off date of the present analysis. The results of the trend analyses emphasize improvements and gaps in the current 2023 pipeline compared to the start of the observation period in 2017. The results highlight the ongoing urgent need for the development of highly effective antibiotics in a robust and sustainable pipeline. The geographic distribution of research facilities contributing to the clinical pipeline is also examined, to provide insight into the global landscape of antibiotic research and development endeavours. Additionally, evaluation of the presence or absence of paediatric investigation plans sheds light on the extent to which the specific needs of the paediatric population are being addressed in the antibiotic development process.

Antibacterial agents by spectrum of activity

The total number of products addressing WHO BPPs increased from 43 in 2017 to 62 in 2023. There has been a clear shift in antibacterials (traditional plus non-traditional drugs) with activity against Gram-positive bacteria, which decreased from 58% (18) in 2017 to 27% (17) in 2023, compared to agents with activity against Gram-negative bacteria, which increased from 35% (15) pathogens in 2017 to 50% (31) in 2023. Of note, the total number of extended-spectrum agents, with activity against both Gram-positive and Gram-negative WHO BPPs, increased from only 2.3% (1) in 2017 to 15% (8) in 2023 (Fig. 4).

In particular, when comparing broad spectrum Gram-negative agents, their proportion increased from 5% (2) to 24% (15) (Fig. 5).

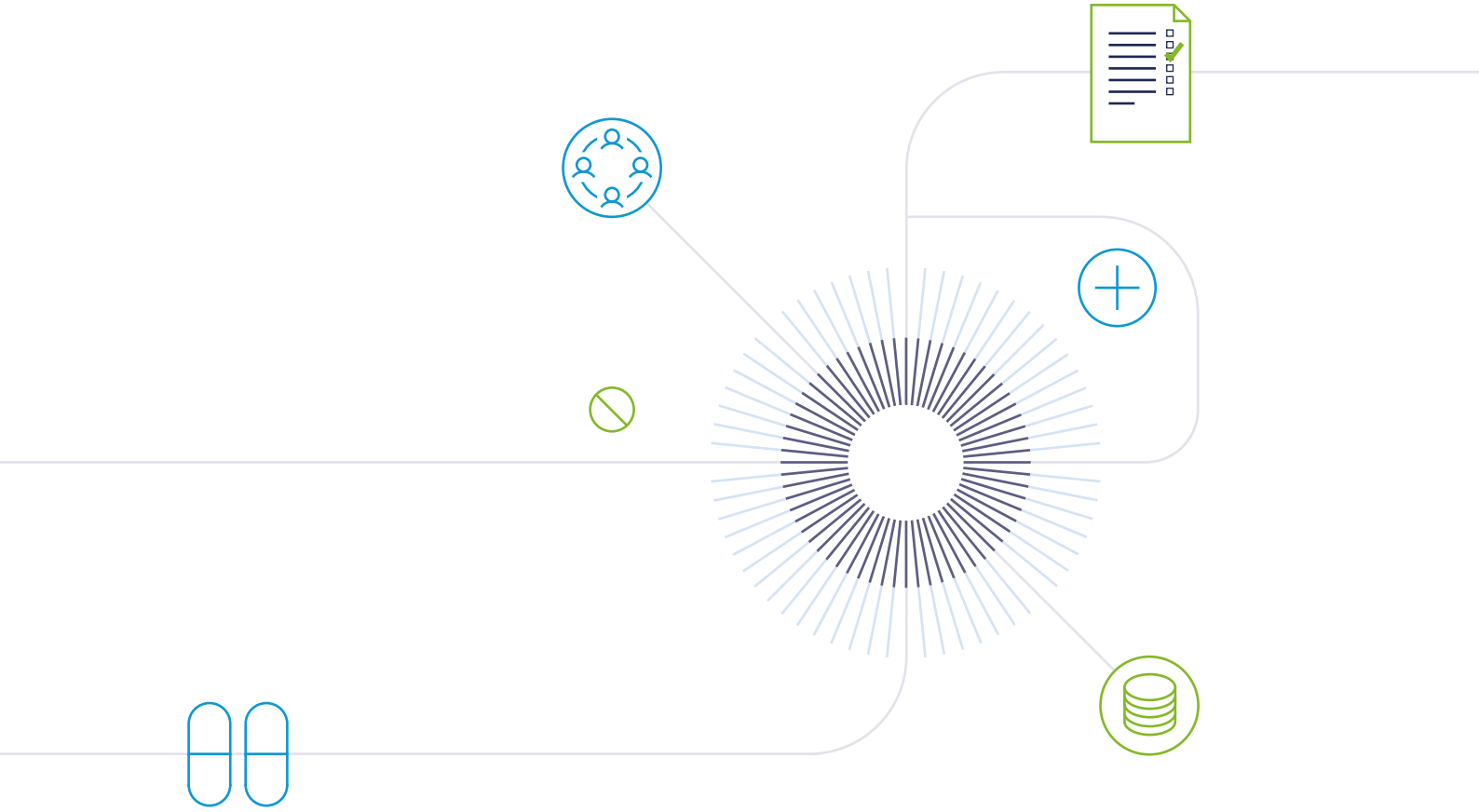
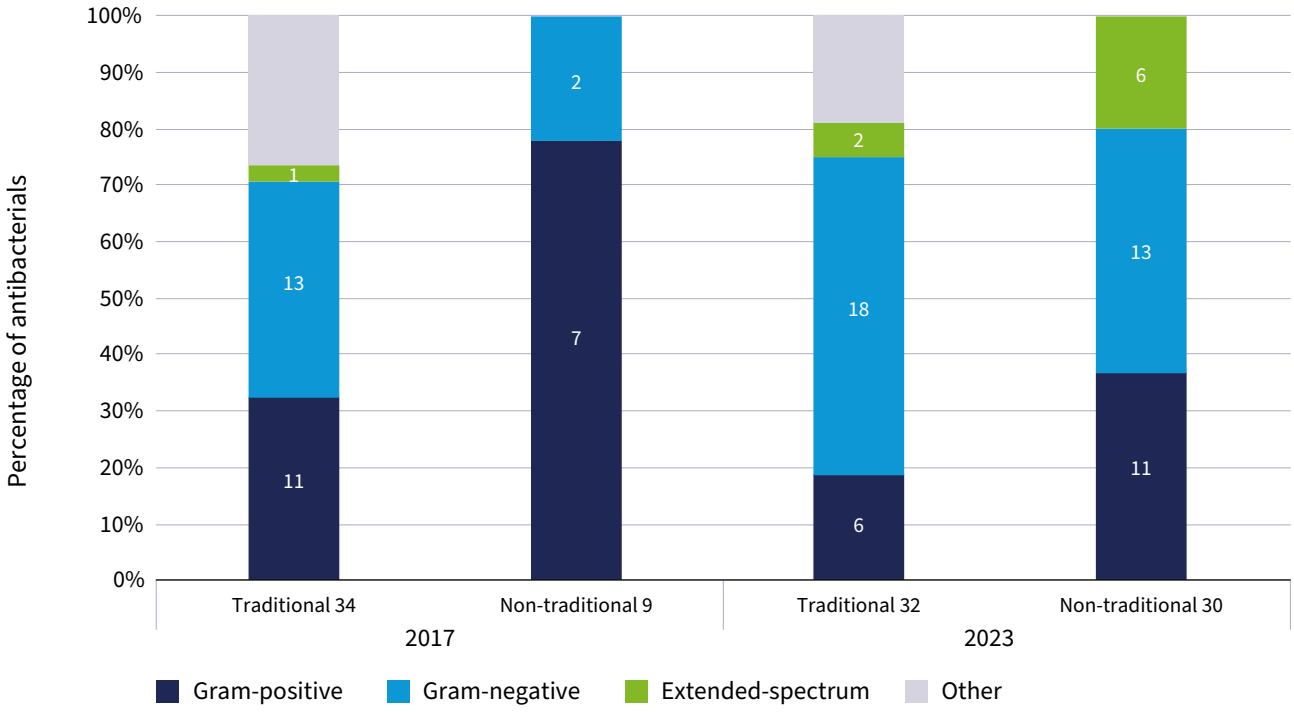


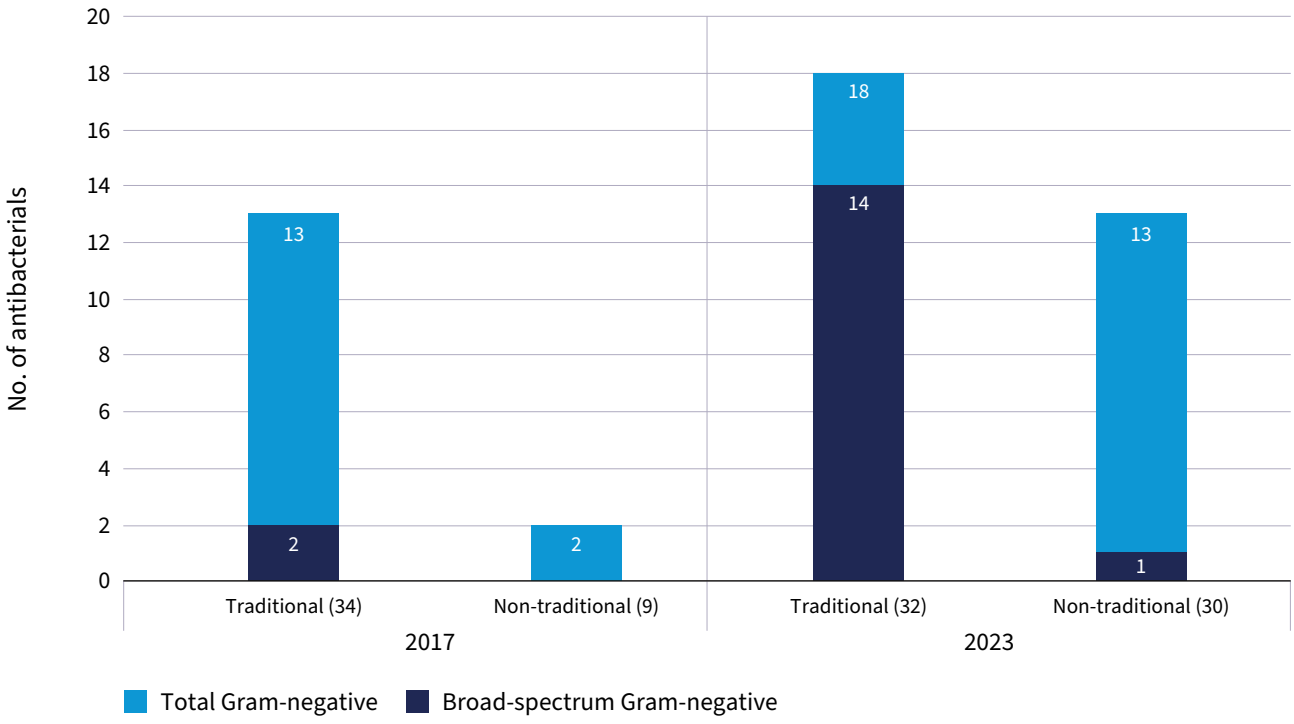
Fig. 4. Spectrum of activity of traditional and non-traditional antibacterial agents against BPPs in the 2017 vs 2023 clinical pipeline



Note: Only traditional antibacterials with sufficient data supporting activity (full dot in Table 2) are considered for the analysis. Traditional agents with at present insufficient data to support activity are included in the "other" group. In referring to the spectrum of activity of clinically exploited agents, extended spectrum denotes agents that target both Gram-positive and Gram-negative pathogens.

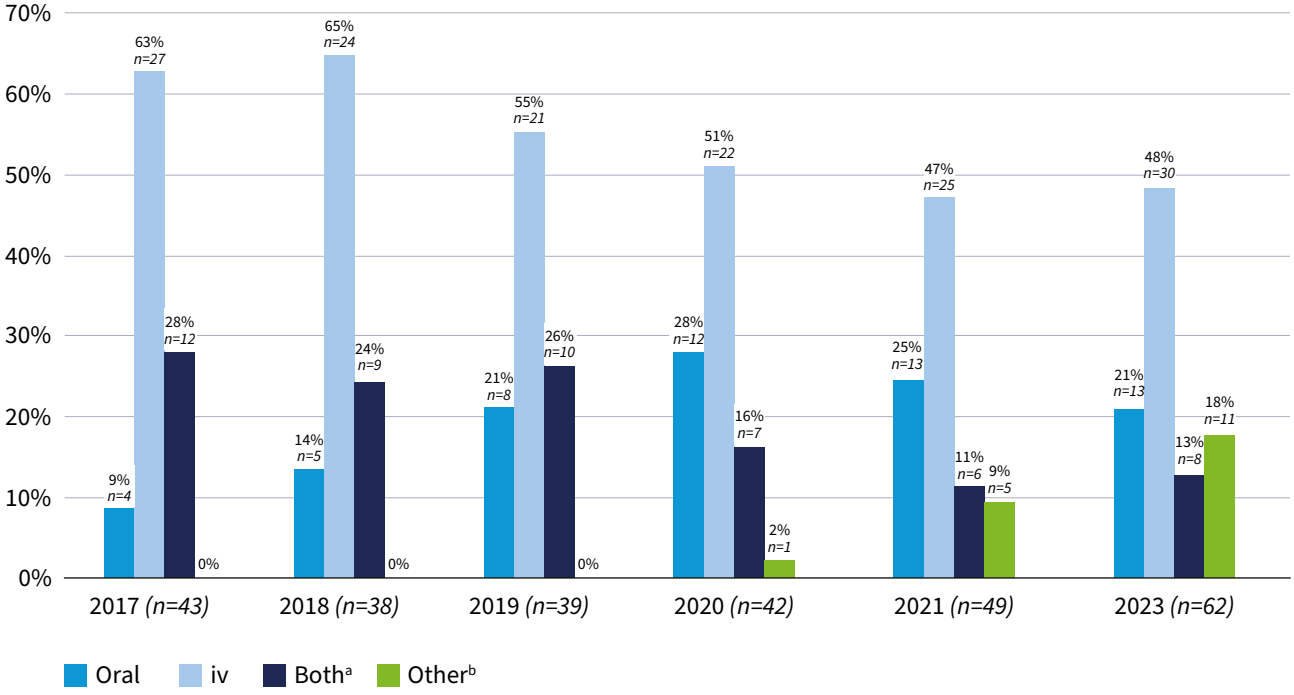
Agents with activity against drug-resistant TB, *C. difficile* and *H. pylori* (limited to 2023) are not included in this analysis.

Fig. 5. Traditional and non-traditional agents active against Gram-negative bacteria in the 2017 vs 2023 clinical pipeline



Note: Only traditional antibacterials with sufficient data supporting activity (full dot in Table 2) are considered for the analysis.
In referring to the spectrum of activity of clinically exploited agents, broad-spectrum Gram-negative denotes agents that target two or more Gram-negative pathogens/orders for CRE and 3GCRE.

Fig. 6. Percentage of antibacterials (traditional and non-traditional) in the clinical pipeline against BPPs by formulation, 2017–2023



[a] Both iv and oral formulations in clinical trials.
[b] Other formulations include intra-articular, irrigation and inhaled.
Note: Agents with activity against drug-resistant TB and *C. difficile* are not included in this analysis; agents with activity against *H. pylori* were removed from the 2023 analysis.

Analysis of clinical formulations for the period 2017–2023

In clinical practice, it is important to have a diverse array of options for treating severe drug-resistant bacterial infections. When applied correctly, parenteral formulations are essential for eliciting a rapid response and are also valuable for optimized therapy, as they are typically administered directly by health care providers. At the same time, the availability of oral formulations for antibiotics plays a pivotal role in stepping down patients and facilitating outpatient treatment.

Fig. 6 shows the trend in the development of agents from 1 May 2017 to 31 December 2023. Intravenous formulations predominate annually. Disappointingly, the proportion of oral medications has decreased from 47% (n = 16) in 2017 to 34% (n = 21) in 2023. Since 2020, there has been a noteworthy increase in the number of other formulations, such as intraurethral/irrigation, intra-articular and inhalation, from 2% (n = 1) in 2020 to 15% (n = 11) in 2023.

Paediatric investigation plans/study plans for antibiotics in late-stage development

Bacterial infections, particularly pneumonia, neonatal sepsis and gastrointestinal (GI) infection, continue to be leading causes of infectious mortality among children under the age of 5 worldwide *(22)*. Antibiotics are the most prescribed medications for children. However, many antibiotics authorized for use in adults lack authorized indications for paediatric use and often lack optimal formulations for administration to children, toddlers and neonates *(23)*. To assess the potential for traditional late-stage clinical candidates[8] to target severe drug-resistant infections in children and neonates, a survey and a search in the EMA paediatric investigational plan (PIP) repository were conducted. Our results show that of the 14 products in Phase 2 development or later, six have an approved/amended PIP, whereas nine have presented no PIP yet, including all three products in Phase 2. The agents with a PIP are: solithromycin (2016), cefepime + taniborbactam (2020), cefepime + enmetazobactam (2022), zoliflodacin (2022), gepotidacin (2022) and cefepime + zidebactam (2021). Three of these six products are in Phase 3 (zoliflodacin, gepotidacin, cefepime + zidebactam), and three are at the NDA/MAA stage (solithromycin, cefepime + taniborbactam, cefepime + enmetazobactam).

[8] For the purpose of this analysis, *late-stage* are products in Phase 2, Phase 3 and at the NDA/MAA stage.

For antibiotics with existing PIPs, registered clinical trials in paediatric subjects were searched in ClinicalTrials.gov:

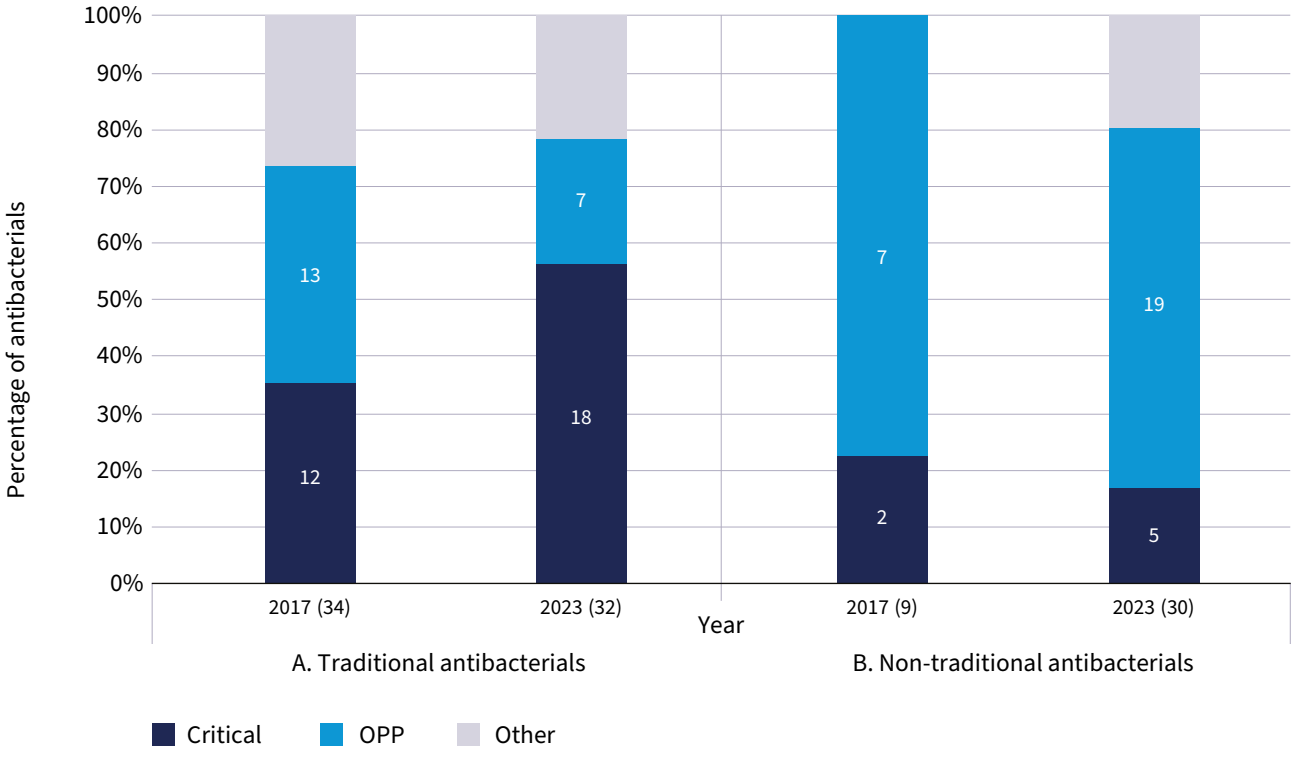
- For solithromycin, three paediatric studies were completed (see Annex 2), two Phase 1 studies (0–17 and 12–17) and a Phase 2/3 study in children and adolescents.
- For cefepime + enmetazobactam, a Phase 2 study is intended to evaluate the combination in paediatric participants to support extension of the indication to children with cUTI. The estimated completion date is 2025/2026.
- For gepotidacin, the date of the PIP deferral is March 2028. However, adolescents (12–18 years old) have been included as part of the adult pharmacokinetics (PK) and safety investigation.
- For cefepime + zidebactam, the estimated completion of the paediatric investigation plan is July 2029; no paediatric study is currently registered.
- For cefepime + taniborbactam, the date of the PIP completion is June 2027; no paediatric study is currently registered.
- For zoliflodacin, the date of PIP completion is June 2024; no paediatric study is currently registered.
- For sulopenem, despite the absence of a PIP, a Phase 1 study was found for hospitalized patients 12–18 years of age receiving background antibiotic treatment for uncomplicated UTI (uUTI), cUTI, acute pyelonephritis or complicated intra-abdominal infection.

This review underscores the limited number of clinical trials involving paediatric antibiotics on a global scale, and the time gap between approval of the adult indication and completion of a paediatric development plan. A noticeable imbalance is evident when comparing antibiotic drug development efforts for adults and children.

Analysis of antibacterial candidates in the clinical pipeline, 2017–2023, by target

The following analysis (Fig. 7) presents the distribution of antibacterial agents (traditional and non-traditional) according to their activity against CPPs or only OPPs. An increase in the proportion of agents targeting critical pathogens can be observed for both traditional and non-traditional products.

Fig. 7. Proportion of (A) traditional and (B) non-traditional antibacterial agents in clinical development for critical vs other priority pathogens, 2017–2023



CPP: critical priority pathogen; OPP: other priority pathogen.
Note: Only traditional agents with sufficient data showing activity against each group of pathogens (full dot in Table 2) were included. Traditional agents with at present insufficient data supporting activity are included in the "other" group. Agents with activity against drug-resistant TB and *C. difficile* are not included in this analysis; agents with activity against *H. pylori* were removed from the 2023 analysis. Each bar is labelled with the absolute number of CPP or OPP agents captured, while the y-axis displays the proportion of CPP and OPP products based on the annual total.

Limitations of this analysis include the fact that some agents display activity against multiple pathogens; for instance, products addressing both CPPs and OPPs have been counted as active against CPPs, while the OPP group includes agents active only against OPPs. In addition, for 2023, the updated classification of pathogens (2024 WHO BPPL, see Box 1) was taken into consideration as was a revised activity assessment (see section 7 on methods), which may have impacted the results.

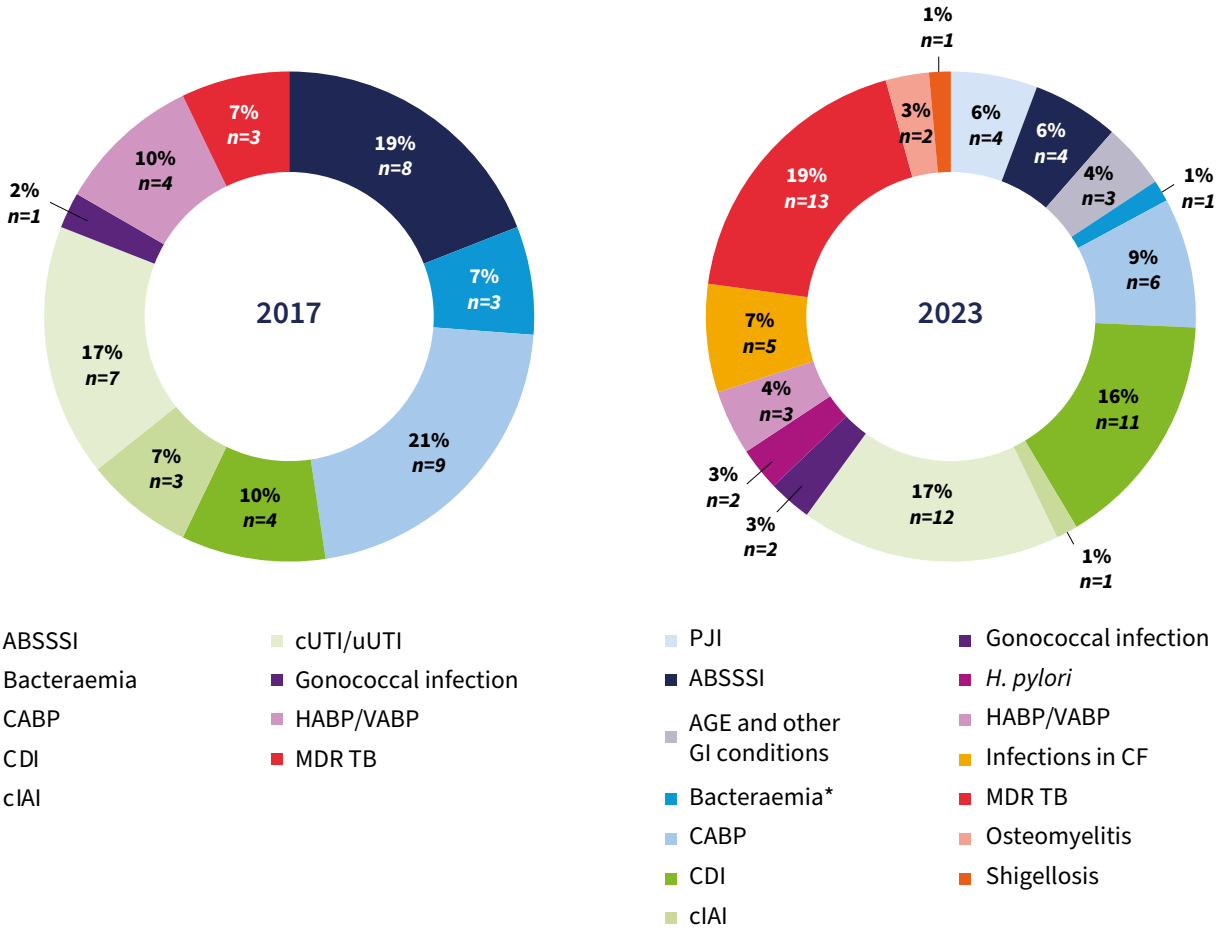
Analysis of antibacterial agents in late-stage development according to the indication(s) foreseen

To assess the progress in agents for treating severe, drug-resistant bacterial infections caused by BPPs from 2017 to 31 December 2023, late-stage antibacterial agents *(note: for the purpose of this analysis, those in Phase 2 and 3)* were analysed based on their intended therapeutic indications (Fig. 8).

Overall, agents that are intended against cUTI/uUTI and pulmonary infections represent the majority of Phase 2 and 3 antibacterials (43% (20/46) in 2017 and 34% (21/62) in 2023). Marketing authorizations between 2017 and 2023 tend to align with this trend, as nine of the 13 traditional agents have been approved for use in cUTI/uUTI, CABP and HABP/VABP (Table 1a).

The 2023 pipeline also shows an expansion of clinical indications, including prosthetic joint infections (PJIs), infections in cystic fibrosis (CF) patients, *H. pylori* infections and shigellosis, all of which were not addressed in the 2017 list. For infections in CF patients and PJIs, this is distinctly due to the increasing catalogue of non-traditional antibacterials intended against these clinical syndromes. A noteworthy decrease in ABSSSI indications under development from 2017 (n = 8, 19%) to 2023 (n = 4, 6%) may likely be due to the recent authorization of four antibacterials with this indication.

Fig. 8. Phase 2 and 3 antibacterial products in clinical development by intended therapeutic indication(s), 2017 and 2023



ABSSSI: acute bacterial skin and skin structure infection; AGE: acute gastroenteritis; CABP: community-associated bacterial pneumonia; CDI: *C. difficile* infection; CF: cystic fibrosis; cIAI: complicated intra-abdominal infection; cUTI: complicated urinary tract infection; GI: gastrointestinal; HABP: hospital-*acquired bacterial pneumonia; MDR-TB: multidrug-resistant tuberculosis; PJI: prosthetic joint infection; uUTI: uncomplicated urinary tract infection; VABP: ventilator-associated bacterial pneumonia.

Snapshot of geographical location of antibacterial research facilities

This analysis is intended to provide a snapshot of where antibacterial R&D happens (Fig. 9). It is based on the location of headquarters of research facilities, including academic groups/universities, biotechnology companies (large, medium, small and micro) and foundations. For this analysis, economies are divided into four income groups – low, lower-middle, upper-middle and high – according to the World Bank 2023 classification *(24)*. Income is measured using gross national income per capita, in US dollars *(25)*.

Over 90% of antibacterial product development takes place in high-income (84%) and upper-middle-income (12%) settings, which are likely closer to funding opportunities and R&D initiatives in other therapeutic areas. Only four products are being developed in a lower-middle-income economy. Of note, no antibacterial drugs were found to be under clinical development by research facilities in low-income economies.

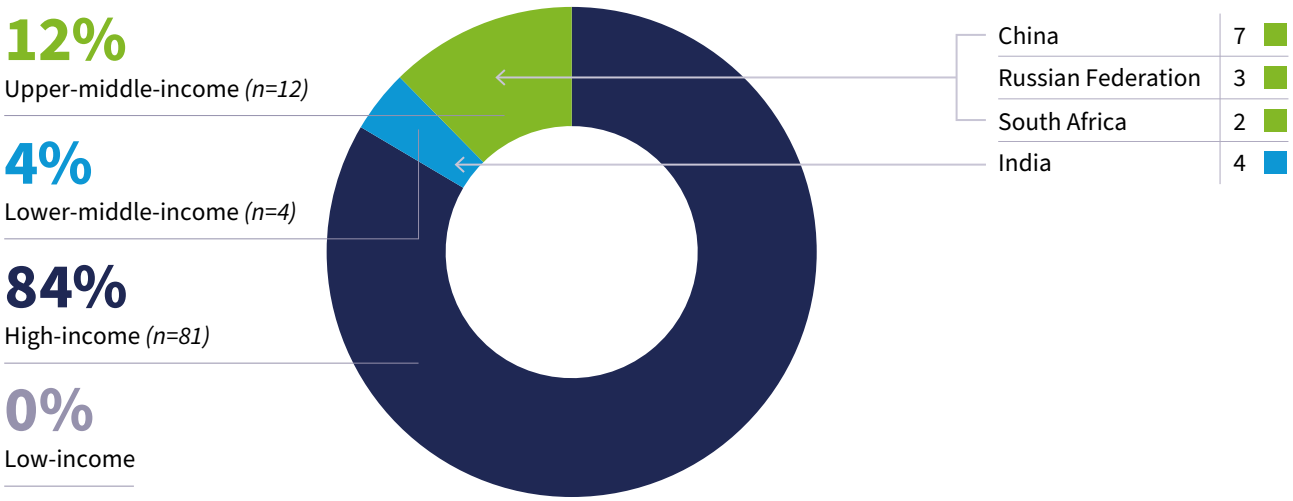
3.1 Antibacterial agents being developed against WHO priority pathogens

Activity assessment and changes since the last update

Overall, the pipeline contains 57 traditional agents in clinical development. Of these, currently 32 target WHO priority pathogens and 19 target drug-resistant TB (Fig. 2). More than half (*n* = 17, 53%) of the 32 products have confirmed activity against at least one of the critical Gram-negative bacterial pathogens, eight target CRAB, and 15 target CRE and/or 3GCRE. Furthermore, 13 compounds display activity against OPPs, including six that target CRPA (Table 2). An additional five traditional antibacterials are under development for treatment of CDI, along with one agent designed for *H. pylori* treatment (see section 3.4.1).

Since the last update, several advancements have been observed. The cefepime-taniborbactam combination advanced to NDA/MAA status. A Phase 3 trial with cefepime in combination with zidebactam (WCK 5222) vs meropenem started for cUTI or acute pyelonephritis. The combination showed activity against CRE, 3GCRE and CRPA, including MBL-producing *P. aeruginosa (26)*. Two DBO BLIs, namely, cefepime + nacubactam (OP0595) and aztreonam + nacubactam (OP0595), have entered the pipeline in Phase 3, both being a combination of an authorized agent and a new chemical entity. Two novel products, murepavadin (POL7080, iMPV) and RECCE 327 (R327), entered the pipeline in Phase 1/2.

Fig. 9. Percentage of antibacterial agents in clinical development, by location of research facilities



Murepavadin, a macrocyclic compound, demonstrated specific activity against *P. aeruginosa*, while RECCE 327, a synthetic polymer, targets several pathogens. In addition, four new products entered the pipeline in Phase 1: OMN6, zidebactam in combination with ertapenem, meropenem in combination with ANT3310 and KSP-1007 in combination with meropenem (MEROPEN). These new entries bring the total number of traditional agents currently in Phase 1 to 16.

> Up to 3 million newborns get serious infections that lead to sepsis every year; however, today neonatal sepsis caused by antibiotic-resistant bacteria is not or only poorly addressed by antimicrobials in the pipeline.

The current antibiotic clinical pipeline continues to be dominated by β-lactam/BLI combinations (*n* = 13, 41% of antibiotics targeting WHO priority pathogens). Out of nine new entries in the clinical development pipeline, only three agents are not β-lactam/BLI combinations (Fig. 10). These are murepavadin,[9] OMN6 and RECCE 327. Of note, RECCE 327 has still no peer-reviewed data available and as such is considered to have conclusive data neither for activity nor for innovation assessment.

Innovation assessment

Of the 32 traditional antibiotics under development against BPPs, excluding TB drugs, 12 meet at least one of the four WHO innovation criteria. Gepotidacin meets two innovation criteria for new chemical class and new MoA. Three products – zoliflodacin, murepavadin and OMN6 – meet three innovation criteria. Only two, afabicin and TXA709, meet all four innovation criteria.

When evaluating the absence of cross-resistance, inconclusive data are associated with 11 agents. Perhaps in the near future, as development progresses, new evidence will allow the inclusion of at least some of these 11 antibacterials among innovative drugs.

Of the 12 innovative agents, only four are active against at least one of the WHO critical Gram-negative bacteria: OMN6, cefepime + taniborbactam, ceftibuten + ledaborbactam and xeruborbactam. The latter three compounds are a combination of a boronate BLI with a β-lactam, and the functional class of BLIs is predicted to show some cross-resistance to other BLI classes when used clinically, despite having been classified as a new chemical class.

Among the 12 innovative agents:

- one β-lactam/boronate BLI is under regulatory evaluation by the FDA (cefepime + taniborbactam), and two topoisomerase inhibitors (zoliflodacin and gepotidacin) are in Phase 3;
- one NBTI (BWC0977) is in Phase 1;
- one novel pyrido-enamide (afabicin, a FabI inhibitor) is in Phase 2;
- two agents disruptive of cell membrane integrity, murepavadin and OMN6, are in Phase 1/2 and 1, respectively; and
- also in Phase 1 development are one filamenting temperature-sensitive Z (FtsZ) inhibitor (TXA709), one third-generation aminomethylcycline (zifanocycline) and two β-lactam/boronate BLI combination (meropenem + KSP-1007 and xeruborbactam + β-lactam).

Of the 12 innovative compounds, seven also target OPPs, although at present only four have sufficient data to be assessed as active. Among all seven innovative compounds developed against OPPs, two agents, zoliflodacin and gepotidacin, belong to a new class of topoisomerase II inhibitors. They are chemically distinct and target different binding sites on the same enzyme.

Little information exists on potential cross-resistance with other topoisomerase II inhibitors, although some cross-resistance has been reported for gepotidacin, and in vitro evolutionary resistance has been reported for zoliflodacin in *N. gonorrhoeae*. One additional novel bacterial topoisomerase II inhibitor (NBTI), BWC0977, is claimed to have a broader spectrum, including CRAB, CRE, CRPA and other OPPs, with reduced potential for cross-resistance. However, publicly available data are at present insufficient to thoroughly assess innovation.

When observing the distribution of traditional antibacterial agents according to their antibiotic class (Fig. 10), most antibiotics that target WHO priority pathogens are β-lactam or β-lactam/BLI combinations (*n* = 15, 47%), followed by polymyxins and NBTIs (*n* = 3, 9%), host defence peptides (*n* = 2, 6%) and macrolide/ketolides (*n* = 2, 6%).

[9] Murepavadin was previously tested as an iv formulation in HABP and VABP in two Phase 3 trials terminated in 2019 due to safety concerns. Currently it is being studied as inhaled formulation for *P. aeruginosa* infection, CF and NCFB.

Table 2. Antibacterial agents being developed against WHO priority pathogens

INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Nonclinical data supporting the activity assessment	Expected activity against priority pathogens					Innovation			
						CRAB	CRE	3GCRE	CRPA	OPP[a]	NCR	CC	T	MoA
Solithromycin (T-4288)	NDA	Macrolide/ketolide	iv/PO	Fujifilm Toyama Chemical		/	/	/	/	●	-	-	-	-
Cefepime + taniborbactam (VNRX-5133)	NDA	β-Lactam (cephalosporin) + boronate BLI	iv	Venatorx Pharmaceuticals/ GARDP/Everest Medicines		X	●	●	●	/	?	✓	-	-
Cefepime (EXBLIFEP) + enmetazobactam (AAI-101)	NDA and MAA	β-Lactam (cephalosporin) + BLI	iv	Allecra Therapeutics		X	X	●	X	/	-	-	-	-
Sulopenem; sulopenem etzadroxil/probenecid	3	β-Lactam (thiopenem)	iv/PO	Iterum Therapeutics		X	X	●	X	/	-	-	-	-
Zoliflodacin	3	Spiropyrimidenetrione (topoisomerase inhibitor)	PO	Innoviva (former Entasis Therapeutics)/ GARDP		/	/	/	/	●	✓[b]	✓	-	✓
Gepotidacin	3	Triazaacenaphthylene (topoisomerase inhibitor)	iv/PO	GSK		/	/	?[c]	/	?	?	✓	-	✓
Nafithromycin (WCK-4873)	3	Macrolide/ketolide	PO	Wockhardt/ Jemincare		/	/	/	/	●	-	-	-	-
Cefepime + zidebactam (WCK 5222)[d]	3	β-Lactam (cephalosporin) + DBO-BLI/PBP2 binder	iv	Wockhardt		?[e]	●	●	?[e]	/	-[f]	-	-	-
Cefepime + nacubactam (OP0595)[d]	3	β-Lactam (cephalosporin) + DBO-BLI/PBP2 binder	iv	Meiji Seika		/	●	●	?	/	-	-	-	-
Aztreonam + Nacubactam (OP0595)[d]	3	β-Lactam (monobactam) + DBO-BLI/PBP2 binder	iv	Meiji Seika		/	●	●	X	/	-	-	-	-

Table 2 (continued). Antibacterial agents being developed against WHO priority pathogens

INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Nonclinical data supporting the activity assessment	Expected activity against priority pathogens					Innovation			
						CRAB	CRE	3GCRE	CRPA	OPP[a]	NCR	CC	T	MoA
Funobactam (XNW4107) + imipenem + cilastatin	3	DBO-BLI + β-lactam (carbapenem) + degradation inhibitor	iv	Evopoint Bioscience		?[g]	?[h]	?[i]	X	/	-	-	-	-
Benapenem	2	β-Lactam (carbapenem)	iv	Xuanzhu Biopharm[j]		X	X	?	X	/	-	-	-	-
Afabicin (Debio-1450)	2	Pyrido-enamide (FabI inhibitor)	iv/PO	Debiopharm		/	/	/	/	●	✓	✓	✓	✓
TNP-2092	2	Rifamycin-quinolizinone hybrid	iv/PO[k]	TenNor Therapeutics		/	/	/	/	●	-	-	-	-
RECCE 327 (R327)	1, 2	Synthetic (acrolein) polymer	iv/topical	Recce Pharma-ceuticals		?	?	?	?	?	?	?	?	?
Murepavadin (POL7080, iMPV)	1, 2	Macrocyclic peptidomimetic compound	inhaled[l]	Spexis		X	X	X	●	/	?	✓	✓	✓
Meropenem + nacubactam (OP0595)[d]	1	β-Lactam (carbapenem) + DBO-BLI/PBP2 binder	iv	Meiji Seika		X	●	●	?	/	-	-	-	-
Cefpodoxime proxetil + ETX0282[d]	1	β-Lactam (cephalosporin) + DBO-BLI/PBP2 binder	PO	Entasis Therapeutics		X	●	●	X	/	-	-	-	-
Ceftibuten + ledaborbactam (VNRX-7145)	1	β-Lactam (cephalosporin) + boronate-BLI	PO	Venatorx Phar-maceuticals		X	●	●	X	/	?	✓	-	-
Xeruborbactam (QPX7728) + β-lactam (S-649228)	1	Boronate-BLI + undisclosed iv β-lactam	iv	Qpex Biopharma / Shionogi		●	●	●	●	/	?	✓	-	-

Table 2 (continued). Antibacterial agents being developed against WHO priority pathogens

INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Nonclinical data supporting the activity assessment	Expected activity against priority pathogens					Innovation			
						CRAB	CRE	3GCRE	CRPA	OPP[a]	NCR	CC	T	MoA
Upleganan (SPR-206)	1	Polymyxin	iv	Spero Therapeutics		●	●	●	●	/	-	-	-	-
MRX-8	1	Polymyxin	iv	MicuRx		●	●	●	●	/	-	-	-	-
QPX9003	1	Polymyxin	iv	Brii Biosciences		●	?	?	●	/	?[m]	-	-	-
Zifanocycline (KBP-7072)	1	Tetracycline (aminomethylcycline)	iv/PO	KBP BioSciences		●	?	?	X	●	✓	-	-	-
Apramycin (EBL-1003)[n]	1	Aminoglycoside	iv	Juvabis		●	●	?	?	/	-	-	-	-
TXA709	1	Difluorobenzamide (FtsZ inhibitor)	iv/PO	TAXIS Pharma-ceuticals		X	X	X	X	●	✓	✓	✓	✓
Zosurabalpin (RG6006)	1	Macrocyclic peptide	iv	Roche		?[o]	X	X	X	X	?[o]	?	?	?
BWC0977	1	Pyrazino-oxazinones; novel NBTI	iv/PO	Bugworks Research		?	?	?	?	?	?	?	?	✓
OMN6	1	Insect host defence peptide	iv	Omnix Medical		●	?	/	?	?	?	✓	✓	✓
Ertapenem + zidebactam[d]	1	β-Lactam (carbapenem) + DBO-BLI/PBP2 binder	iv	Wockhardt / NIAID		X	●	●	?	/	-	-	-	-
Meropenem + ANT3310	1	β-Lactam (carbapenem) + DBO-BLI/PBP2 binder	iv	Antabio SAS		●	●	●	?	/	-	-	-	-

Table 2 (continued). Antibacterial agents being developed against WHO priority pathogens

INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Nonclinical data supporting the activity assessment	Expected activity against priority pathogens					Innovation			
						CRAB	CRE	3GCRE	CRPA	OPP[a]	NCR	CC	T	MoA
Meropenem + KSP-1007 (MEROPEN)	1	β-Lactam (carbapenem) + boronate BLI	iv	Sumitomo Dainippon Pharma		?	?	?	?	/	?	✓	-	-

Table Key

Peer-reviewed data
Not-peer-reviewed data

In vivo data
In vitro data

Innovation Assessment:

✓ Criterion fulfilled
? Inconclusive data
– Criterion not fulfilled

BLI: β-lactamase inhibitor; CC: chemical class; CRAB: carbapenem-resistant *A. baumannii*; CRE: carbapenem-resistant Enterobacterales; CR-EC: carbapenem-resistant *E. coli*; CRKP: carbapenem-resistant *K. pneumoniae*; CRPA: carbapenem-resistant *P. aeruginosa*; DBO: diazabicyclooctane; ESBL: extended-spectrum β-lactamase; FabI: enoyl-acyl carrier protein reductase; FQR: fluoroquinolone-resistant; FtsZ: filamenting temperature-sensitive Z; GARDP: Global Antibiotic Research and Development Partnership; iv: intravenous; HAP: hospital-associated pneumonia; KPC: *K. pneumoniae* carbapenemase; MBL: metallo-β-lactamase; MIC: minimum inhibitory concentration; MoA: mode of action; MRSA: methicillin-resistant *Staphylococcus aureus*; NBTI: novel bacterial type II topoisomerase inhibitors; NCR: no cross-resistance; NDA: New Drug Application; NDM: New Delhi metallo-β-lactamase; NT: non-typhoidal; OPP: other priority pathogen; PBP2: penicillin-binding protein 2; POS: per os (oral); T: new target; TB: tuberculosis; 3GCR: third-generation cephalosporin-resistant Enterobacterales; uUTI: uncomplicated urinary tract infection; VAP: ventilator-associated pneumonia; VRE: vancomycin-resistant enterococci.

Activity assessment: ● active; ? possibly active; X not active; / not tested.

Innovation assessment: ✓ criterion fulfilled; ? Inconclusive data; - criterion not fulfilled.

[a] OPP targets – solithromycin: *S. pneumoniae*; afithromycin: *S. aureus* and *S. pneumoniae*; zoliflodacin and gepotidacin: *N. gonorrhoeae* and MRSA; afabicin, TNP-2092 and TXA709: MRSA; zifanocycline (KBP-7072): MRSA and VRE faecium; BWC0977: VRE faecium; MRSA, FQR *N. gonorrhoeae*, VRE faecium, macrolide-resistant pneumococcus, macrolide-resistant group A streptococci and FQR NT *Salmonella*.

[b] The GyrB D429N substitution reduces susceptibility to zoliflodacin. The GyrB D429N substitution can be acquired by *N. gonorrhoeae* in the presence of ciprofloxacin, resulting in increased ciprofloxacin MIC, at least in some backgrounds (Rubin et al. 2023).

[c] Non-clinical and a small Phase 2 clinical trial data available only against *E. coli*.

[d] The DBO-BLIs zidebactam, OP0595 (nacubactam) and ETX0282 also have some antibacterial activity and have been classified as β-lactam enhancers.

[e] Limited animal data obtained with human simulated regimens suggest possible activity. See product profile for details.

[f] Activity against aztreonam-avibactam resistant NDM-like producing *E. coli* shown in one paper (Terrier et al. 2023).

[g] Activity towards OXA-23, -27 and -51 -producing CRAB, but susceptibility rate 57.5%; No activity vs MLB (Li et al. 2022).

[h] Activity towards KPC-producing CRKP; NOT against CR-EC (Fratoni et al. 2023).

[i] Activity against 3GCR-*K. pneumoniae* but insufficient data against 3GCR-*E. coli* (Li et al. 2022, Fratoni et al. 2023).

[j] Xuanzhu Biopharm is a subsidiary of Sichuan Pharmaceutical Holdings but possesses fully independent intellectual property rights.

[k] No clinical data are available for the POS formulation.

[l] Previously tested as IV in HAP and VAP in 2 phase 3 trials terminated in 2019 due to safety concerns. https://www.biospace.com/article/polyphor-temporarily-halts-enrollment-in-the-phase-iii-studies-of-murepavadin-for-the-treatment-of-patients-with-nosocomial-pneumonia/

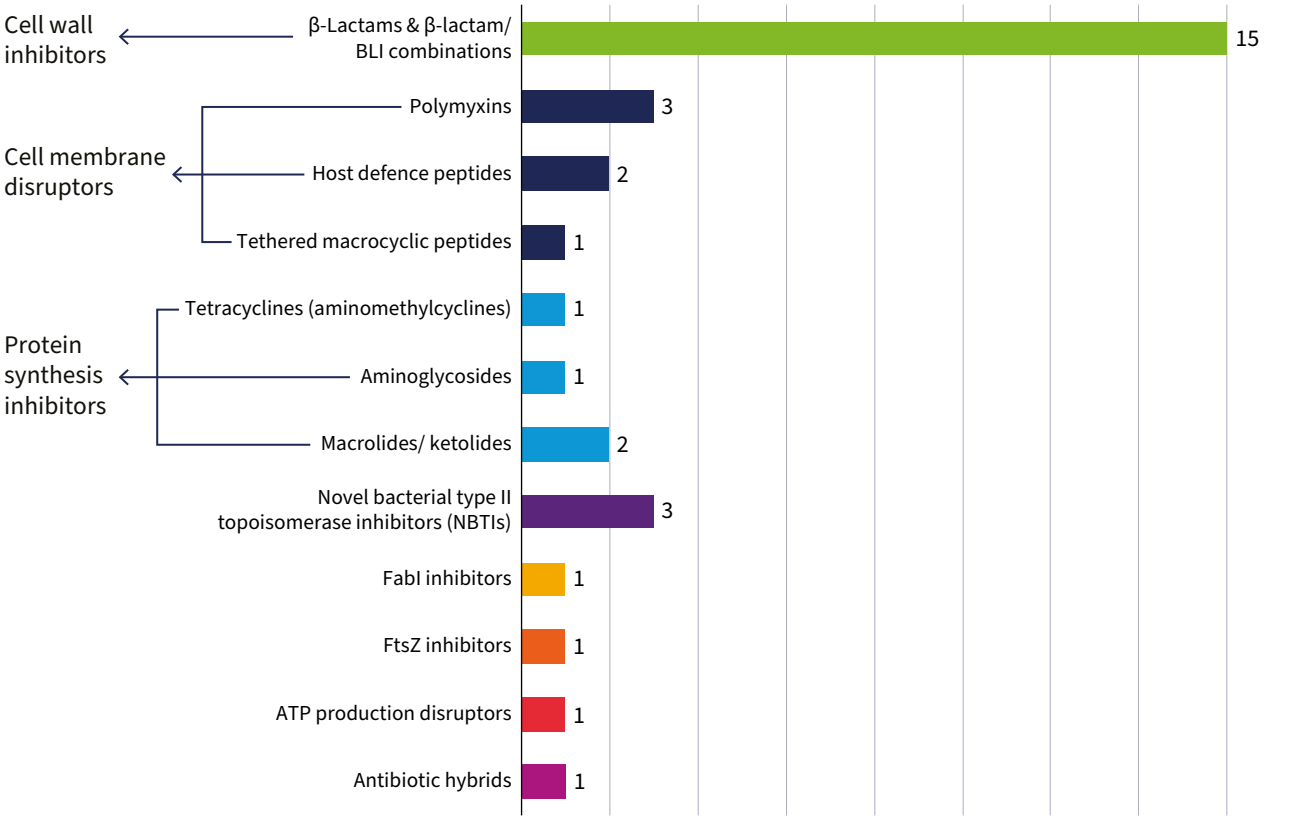
[m] Activity at higher doses against colistin-resistant strains (Zhuang et al. 2023).

[n] Previously used as an antibacterial treatment in animals. (Di Bonaventura et al. 2021).

[o] In January 2024, after the deadline for inclusion in the present pipeline, Zampaloni et al. published in vitro and in vivo data showing activity against CRAB (Zampaloni et al., 2024). Activity against Colistin resistant CRAB (Shortridge et al. 2023, Poster data).

Note: Agents intended against TB, *C. difficile* and *H. pylori* are not included in this analysis. These agents are presented in detail in Tables 6 and 7 and in the following sections.

Fig. 10. Distribution of traditional agents according to their antibiotic class



3.1.1 Cell wall inhibitors

3.1.1.1 β-Lactams and BLIs

β-Lactams are a well-established group of antibiotics that inhibit bacterial cell wall formation through covalent linking to penicillin-binding proteins (PBPs) and subsequent disruption of peptidoglycan biosynthesis. This class includes penicillins, cephalosporins, carbapenems and monobactams *(34)*.

Resistant bacteria produce enzymes (β-lactamases) that hydrolyse β-lactam antibiotics, making many of these agents ineffective. In addition, the spread of extended-spectrum β-lactamases (ESBLs) that confer resistance to broad-spectrum cephalosporins, and of carbapenemases that confer resistance to carbapenems, is a major threat *(34)*. Currently, resistance mediated by carbapenemases presents a significant public health challenge, sometimes causing even the most potent antibiotic class, carbapenems, to lose their effectiveness.

β-Lactamases comprise four structural classes, known as A, B, C and D *(35)*. Class B enzymes are MBLs that contain zinc in their active site. The zinc ion activates a water molecule which serves as the nucleophile that hydrolyses the β-lactam moiety. The remaining three classes (A, C and D) are serine-β-lactamases that use a serine nucleophile to hydrolyse β-lactams. ESBLs mostly belong to Class A. Enzymes with carbapenemase activity are found among Class A – *K. pneumoniae* carbapenemases (KPCs), imipenem-hydrolysing β-lactamases (IMIs) and *Serratia marcescens* enzymes (SMEs); Class B MBLs – active-on-imipenem-type β-lactamases (IMPs), New Delhi MBLs (NDMs) and Verona integron-encoded MBLs (VIMs); and Class D oxacillinases (OXAs) *(36)*.

The main strategy for circumventing hydrolysis of β-lactams is to combine a β-lactam antibiotic with a BLI to restore the bacterium sensitivity to the β-lactam. Traditional BLIs (such as clavulanic acid, tazobactam and sulbactam) inhibit some ESBLs to a certain degree but do not fully inhibit Class A carbapenemases.

Over the past years, some new BLI combinations with carbapenems or cephalosporins have entered the market (e.g., ceftolozane + tazobactam, ceftazidime + avibactam and meropenem + vaborbactam) *(37)* in addition to a siderophore cephalosporin, cefiderocol, which exhibits in vitro activity against isolates carrying all β-lactamase classes. The newest agent authorized, sulbactam + durlobactam (Xacduro), also inhibits OXA from CRAB.

Most of the BLIs in the clinical pipeline target Class A enzymes (ESBLs and KPCs), along with some D enzymes. However, only two agents – xeruborbactam and taniborbactam (broad-spectrum BLIs) – can also inhibit Class B enzymes, although heteroresistance to cefepime + taniborbactam has been described.

Table 3 shows the activity of different β-lactams and β-lactam/BLI combinations approved since 2017 and currently in development against the most clinically relevant β-lactamases, including carbapenemases.

Table 3. Activity of β-lactams and β-lactam/BLI combinations approved since 2017 and currently in development against the most clinically relevant β-lactamases, including carbapenemases

Reference	β-Lactams and β-lactam/ BLI combinations	CRE				CRAB OXA	CRPA
		A ESBL (CTX-M)	A KPC (KPC-2, -3)	D OXA (OXA-48)	B MBL (NDM)		
Approved	Vaborbactam + meropenem	●	●	●	X	X	X
Approved	Relebactam + imipenem + cilastatin	●	●	●	X	X	?
Approved	Cefiderocol	●	●	●	●	●	●
Approved	Sulbactam+ durlobactam (ETX-2514)	X	X	X	X	●	X
NCT05826990	Cefepime + enmetazobactam (AAI-101)	●	?	X	X	X	X
NCT05584657	Sulopenem	●	X	X	X	X	X
NCT03840148	Cefepime+ taniborbactam (VNRX-5133)	●	●	●	? [a]	-	●
NCT04505683	Benapenem	X	X	X	X	X	X
NCT04979806	Cefepime + zidebactam	●	●	●	?	? [b]	?
NCT03491748	Cefpodoxime proxetil + ETX0282	●	●	●	X	X	X
NCT02972255	Meropenem + nacubactam (OP0595)	●	●	●	? [c]	X	?
NCT05072444	Xeruborbactam (QPX7728) + b-lactam (S-649228)	●	●	●	●	●	●
NCT05204368	Funobactam (XNW4107) + imipenem + cilastatin	●	●	?	X	?	X
NCT05488678	Ceftibuten + ledaborbactam (VNRX-7145)	●	●	● [d]	X	X	X
NCT05645757	Ertapenem + zidebactam	●	●	● [e]	X	X	?
NCT05887908	Cefepime + nacubactam (OP0595)	●	●	X	? [b]	X	?
NCT05887908	Aztreonam + nacubactam (OP0595)	●	●	●	●	X	X
NCT05905913	Meropenem + ANT3310	●	●	●	/	●	X
NCT05226923	Meropenem + KSP-1007 (MEROPEN)	?	?	?	?	?	?

Pathogen activity: ● active; ? possibly active; X not active; / not tested.

Market authorized

[a] Heteroresistance described (38).

[b] MICs for CRAB isolates (183) expressing OXA23,24 and 58 clustered around 8–16 mg/L, compared with 64 mg/L for cefepime alone and >128 mg/L for zidebactam alone (39).

[c] Not active in vivo against IMP6 producing-KP (40,41) See product profile for details

[d] Loss of activity if co-production of class C and class D (OXA48-like) SBL (42).

[e] Active against MBL-producing E.coli, but not *K. pneumoniae*. Not active against Enterobacteriales with the combination of MBL+OXA48 (43).

With the exception of three agents (cefiderocol, xeruborbactam (formerly QPX7728) + β-lactam (S-649228) and aztreonam + nacubactam), and potentially three other β-lactam + BLI combinations (cefepime + taniborbactam, cefepime + zidebactam and cefepime + nacubactam), a notable development gap exists for agents that are active against β-lactamase producers, specifically Class B (MBLs) enzyme-producing bacteria.

Xeruborbactam is being developed for use in combination with S-649228, an oral β-lactam whose structure remains undisclosed (formerly QPX2014). In vitro and in animal studies showed that xeruborbactam restored the potency of multiple β-lactam antibiotics against β-lactamase-producing isolates of Gram-negative bacilli, including CRAB, KPC-producing *K. pneumoniae* and CRPA.

Finally, while some BLIs in the pipeline – such as ETX0282, nacubactam, zidebactam and ANT3310 – have intrinsic antibacterial activity, based on binding to penicillin-binding protein 2 (PBP2), and may result in synergistic antibacterial activity in some Enterobacterales *(44)*, other mechanisms may still confer resistance to β-lactam/BLI combinations, despite their inhibition of β-lactamases *(45,46,47)*. Similarly, *P. aeruginosa* and, to a certain extent, *A. baumannii* have developed resistance mechanisms beyond the production of β-lactamases, including decreased permeability of the outer membrane and upregulation of efflux pumps and modified PBPs. This situation further confirms the need for more innovative compounds/strategies to address critical antibacterial-resistant Gram-negative pathogens.

3.1.2 Cell membrane disruptors

3.1.2.1 Polymyxins

Polymyxins are cationic polypeptides that act to disrupt the phospholipid structure of the outer cell membrane and increase cell permeability. They were resurrected as a last-resort antibiotic against XDR Gram-negative bacteria, despite their well-documented side effects (nephro- and neurotoxicity) compared with newer Gram-negative antibiotics *(48)*. Colistin and polymyxin B (PMB) are increasingly used, but resistance has also emerged in response to increased use. Three polymyxin derivatives, MRX-8, QPX9003 and upleganan (SPR-206), with a possible better safety profile, are in early clinical development (Table 2).

3.1.2.2 Host defence peptides

Host defence peptides (HDPs), also termed antimicrobial peptides, are naturally occurring peptides produced by both invertebrate and vertebrate species that can combat infection through their direct microbicidal properties and/or by influencing the host's immune response. However, many HDPs cause lysis of erythrocytes and display cytotoxicity against a variety of cells *(49)*. In the last decade, efforts have been devoted to designing synthetic peptides from sequences of HDPs with optimized antimicrobial functions in vivo and improving the safety profile (i.e., avoiding haemolytic or cytotoxic effects on healthy vertebrate cells) *(50)*.

Currently, two agents from this group are under clinical development (Table 2). OMN6 is an engineered 40-amino-acid cyclic peptide based on a cecropin (i.e., insect peptide) derivative that binds to and penetrates bacterial membranes, causing loss of the membrane ionic gradient balance and bacterial death *(51)*. OMN6 was selected due to its improved stability and significant decrease in proteolytic degradation, together with a bactericidal effect on Gram-negative bacteria and a lack of cytotoxicity towards eukaryote cells *(51)*. It is currently under evaluation for treatment of CRAB infection.

Murepavadin is a synthetic lipidated HDP mimetic that selectively targets LptD, a *P. aeruginosa* outer membrane lipopolysaccharide protein transporter *(52)*. Although evaluation of iv administration of murepavadin in nosocomial pneumonia was halted due to reports of kidney injury, an inhaled formulation of the antibacterial is under investigation for its potential effectiveness in treating *Pseudomonas* infection in patients with CF *(53)*.

3.1.2.3 Tethered macrocyclic peptides

Zosurabalpin/RG6006 is in Phase 1 for treatment of HABP, VABP and bacteraemia caused by CRAB. Its newly elucidated mechanism of action involves blocking the transport of bacterial lipopolysaccharide from the inner membrane to its outer membrane destination, through inhibition of LptB2FGC complex *(54)*.

3.1.3 Protein synthesis inhibitors

3.1.3.1 Tetracyclines

Tetracyclines are broad-spectrum bacteriostatic antibiotics that in 1948 were discovered to have activity against Gram-positive and Gram-negative bacteria. Tetracyclines bind to the A-site of the 30S ribosomal subunit and inhibit binding of tRNA, preventing synthesis of polypeptides *(55)*. Following the discovery of tetracycline, chemical modifications enabled development of numerous semi-synthetic and, later, fully synthetic tetracyclines with improved activity against emerging MDR bacteria *(56)*. Since their introduction, more than a thousand tetracycline resistance genes have been reported. They are often associated with mobile genetic elements, including efflux pumps, ribosomal protection proteins, mosaic genes and mutations in ribosomal proteins.

The semi-synthetic parenteral glycylcycline tigecycline was approved in 2005. This agent overcomes certain class-specific resistance mechanisms. In 2018 the FDA approved both iv and oral formulations of omadacycline (a semi-synthetic aminomethylcycline analogue of minocycline) and an iv formulation for eravacycline (synthetic fluorocycline).

Currently, only one third-generation aminomethylcycline (zifanocycline/KBP-7072) is in Phase 1 clinical trial.

3.1.3.2 Aminoglycosides

Aminoglycosides are bactericidal and are active against Gram-negative bacteria such as *Pseudomonas* spp., *Acinetobacter* spp. and *Enterobacter* spp. They inhibit protein synthesis and are administered via the iv or intramuscular (IM) route. Commonly used aminoglycosides such as gentamicin, netilmicin, tobramycin and amikacin show different resistance rates globally. The most common resistance mechanism is production of aminoglycoside-modifying enzymes and, more recently, bacterial ribosome-modifying enzymes (16S rRNA methylases), which often occur in β-lactamase-producing Enterobacterales *(57)*. The most recently approved aminoglycoside, plazomicin, was optimized to address most aminoglycoside-modifying enzymes. But it is currently approved only in the USA; the EU marketing authorization application was withdrawn due to financial limitations *(58,59)*. Currently, only one aminoglycoside, apramycin (EBL-1003), is in Phase 1 clinical trial.

3.1.3.3 Macrolides and ketolides

Macrolides disrupt protein synthesis through binding to the 50S ribosomal subunit peptidyl transferase centre at the nascent peptide exit tunnel *(60,61)*. They are bacteriostatic, with activity against many Gram-positive bacteria and limited activity against Gram-negative bacteria. Second-generation semi-synthetic derivatives of the first natural product include clarithromycin and azithromycin *(62)*. Ketolides, a subclass of macrolides, are erythromycin derivatives that feature an additional cyclic carbamate and replacement of the cladinose sugar by a ketone. Ketolides have higher affinity than macrolides for domains II and V of the 23S rRNA and retain activity against the main resistance mechanisms of erythromycin (target-site modification by inducible methylation and efflux-pump-mediated resistance) *(63)*. Two ketolides are currently in clinical development: nafithromycin is in Phase 3 clinical trial, and solithromycin is at the NDA stage.

3.1.4 NBTIs

Topoisomerase inhibitors include quinolones, which are synthetic bactericidal antibiotics discovered in the 1960s. The drugs in use today are fluoroquinolones. They target two essential type IIA topoisomerases: DNA gyrase and topoisomerase IV. Fluoroquinolones bind preferentially to the DNA gyrase subunit GyrA and to the topoisomerase IV subunit ParC *(64)*. Three new non-fluoroquinolone NBTIs are currently in development. Zoliflodacin and gepotidacin, which are in Phase 3, have new chemical structures with distinct (but potentially overlapping) binding sites with fluoroquinolones *(65)*; BWC0977, which is at present in Phase 1 and has no peer-reviewed published data, is claimed to have distinct binding sites and similar activity against GyrA and topoisomerase IV. Gepotidacin targets 3GCRE responsible for UTI and *N. gonorrhoeae*. Zoliflofacin has been developed for *N. gonorrhoeae* infection but is also active against methicillin-resistant *S. aureus* (MRSA), while BWC0977 targets all critical Gram-negative pathogens and CRPA.

3.1.5 FabI inhibitors – pyrido-enamide

FabI (an NADH-dependent enoyl-acyl carrier protein reductase, encoded by *fabI*) is a critical enzyme for the final step in elongation of fatty acid biosynthesis in many bacteria. As such, it is an attractive target for drug development. FabI inhibitors have been known since the 1950s and are represented by isoniazid (in addition to inhibiting FabI, isoniazid also inhibits the InhA enzyme, an enoyl-acyl carrier protein reductase) for TB treatment, and the non-specific biocide and slow-binding FabI inhibitor triclosan. These agents have different binding characteristics *(66)*. It is not known whether they exert selection pressure on staphylococci, which could lead to cross-resistance *(67,68)*. One FabI inhibitor, afabicin, is currently in clinical development (Phase 2).

3.1.6 FtsZ inhibitors

Filamenting temperature-sensitive Z is a vital cell division protein that is conserved in most bacteria. It undergoes assembly at the mid-cell, forming a dynamic membrane-attached ring structure which then recruits other division proteins to the Z-ring to form the divisome. Inhibiting FtsZ blocks cell division, and thus it is an attractive antibacterial target *(69,70)*. One FtsZ inhibitor, TXA709, is currently in clinical development (Phase 1).

3.1.7 ATP production disruptors

Disruption of ATP production in bacterial cells when targeted as the main mechanism of action, not secondary to other cell perturbation mechanisms, carries the potential to confer activity against both Gram-positive and Gram-negative pathogens. Being a novel target, the potential for resistance is presumably low at present. Only one product, RECCE 327, is currently in clinical development (Phase 1). It is claimed to have broad-spectrum activity against MDR strains of Gram-positive and Gram-negative bacteria. However, no peer-reviewed data are yet available.

3.1.8 Antibiotic hybrids

Antibiotic hybrids have been researched in the last few decades, with a focus on antibiotics conjugated to a range of functional moieties to create dual-acting agents. The building of the heterodimer is aimed at achieving higher efficacy of the constituent pharmacophores by improved on-site targeting, halted bacterial efflux, and protection from enzymatic degradation with concomitant reduced toxicity *(71)*.

One conjugate, TNP-2092, a rifamycin-quinolizinone hybrid, is currently in Phase 2 development for ABSSSI. It received orphan drug designation for PJI. TNP-2092 is able to overcome fluoroquinolone efflux pumps, which may be explained by steric interference from the rifamycin pharmacophore *(72)*.

3.1.9 Noteworthy compounds in development that do not meet inclusion criteria

This analysis mostly focuses on new antibacterial treatments. It does not include already authorized compounds that are being repurposed, pharmaceutically optimized (e.g., new formulation, route of administration) or studied for new indications.

However, improvement of existing agents, including novel combinations of existing agents, as well as new paediatric or oral formulations, agents with improved safety features and reduced drug–drug interactions can have significant clinical utility in managing patients with serious bacterial infections due to Gram-negative bacteria, including MBL-producing MDR pathogens for which treatment options are limited or nonexistent. Thus, this section describes development projects that do not meet the inclusion criteria (see section 7 on methods) yet were identified by the analysis as noteworthy and with potential impact on clinical practice.

Aztreonam + avibactam. Aztreonam and avibactam were first approved by the FDA in 1986 and 2015, respectively. The aztreonam (monobactam-type β-lactam) and avibactam (DBO-type BLI inhibitor) combination (ATM-AVI) was evaluated in two Phase 3 trials (NCT03329092, NCT03580044) to treat serious infection due to MBL-producing Gram-negative bacteria in BSI, cUTI, cIAI, HABP and VABP *(73,74,75)*.

Topline results published online showed in the REVISIT study (NCT03329092), comparing ATM-AVI ± metronidazole with meropenem ± colistin, that clinical cure rates in the intent-to-treat (ITT) population were 76.4% (95% CI: 70.3–81.8) vs 74.0% (95% CI: 65.0–81.7) for HABP/VABP, respectively, and 41.7% (95% CI: 26.7–57.9) vs 45.9% (95% CI: 34.9–57.3) among patients with cIAI, respectively.

These findings were further supported by results from the ASSEMBLE study (NCT03580044), which included 15 adult patients and compared aztreonam-avibactam to the best-available therapy. At the test-of-cure (TOC) visit, 41.7% (5/12) patients with infections due to confirmed MBL-producing Gram-negative bacteria were cured compared with none (0/3) of the patients on best-available therapy. The treatment emergent adverse events (TEAEs) of the ATM-AVI arm were in line with those of those reported for aztreonam alone. No patient treated with ATM-AVI experienced a treatment-related serious adverse event.

BV100. BV100 is an iv formulation of rifabutin (RIF) being developed to treat hospital infections caused by CRAB. Rifabutin is a semi-synthetic rifamycin that was first approved in 1992 by the FDA as an oral formulation for treatment of disseminated *Mycobacterium avium* complex disease in patients with advanced HIV infection. The BV100 safety and pharmacokinetic profile were studied in three Phase 1 trials (NCT04636983, NCT05086107, NCT05087069) *(76,77,78)*. In 2023 a multicentre Phase 2 study (NCT05685615) started to investigate the PK, efficacy and safety of iv BV100 combined with PMB in VABP patients with suspected or confirmed CRAB infection.

The recently elucidated MoA shows active and selective uptake of RIF by the siderophore receptor FhuE into the Gram-negative bacterial species, such as CRAB, overcoming common rifampicin resistance mechanisms and leading to high intracellular concentrations. In preclinical studies, RIF showed in vitro activity on the 293 CRAB clinical isolates tested, with a MIC50/90 of 0.008/1 mg/L, and was more potent in vitro with respect to all other antibiotics tested, including colistin, tigecycline and cefiderocol (MIC90 of 8 mg/L). Rifabutin remained active on resistant subpopulations, including strains resistant to the siderophore-cephalosporin cefiderocol (MIC90 of 2 mg/L, $n = 23$). Rifabutin concentrations of 2 mg/L are required; therefore, an iv formulation is likely required *(79)*.

Tebipenem pivoxil hydrobromide (TBP-PI-HBr). Tebipenem pivoxil has been approved since 2009 in Japan, where it has been used for the treatment of ear, nose and throat infections, otitis media and bacterial pneumonia. The active ingredient is tebipenem, a carbapenem, and it has been modified (esterified) as an oral prodrug to provide oral bioavailability of 60%. The oral formulation may allow an early switch from iv administration during treatment in stable patients, opening the option of early discharge from the hospital or outpatient therapy. A Phase 3 trial (NCT03788967), which was completed in May 2020, showed TBP-PI was non-inferior to iv ertapenem in treatment of hospitalized adult patients with cUTI or AP *(80)*. TBP-PI targets uropathogenic Enterobacterales, including ESBL-producing and fluoroquinolone-resistant strains, but not carbapenem-resistant strains, with activity similar to other carbapenems. It is not active against *A. baumannii* or *P. aeruginosa*.

Ceftibuten + avibactam tomilopil (CTB + AVP) PF-07612577 is a combination of a β-lactam (cephalosporin) + DBO-BLI. Avibactam tomilopil is the orally available prodrug of the DBO-BLI avibactam. In vitro studies have shown that CTB + AVP is active against a large collection of contemporary Enterobacterales spp. isolated from patients with cUTI *(81)*. CTB + AVP demonstrated increased activity against ESBL-producing, KPC-producing, chromosomal AmpC-positive, OXA-48-like-producing and acquired AmpC-producing isolates compared to cefibuten alone *(82)*. CTB + AVP is currently being developed for oral treatment of cUTI, including pyelonephritis caused by resistant Enterobacterales. Recruiting is currently underway for a Phase 1 trial *(83,84)*.

3.2 Agents in development for treating drug-resistant TB

The vast majority of human TB is caused by *M. tuberculosis*. An estimated 10.6 million (95% UI: 9.9–11 million) people fell ill with TB in 2021, an increase of 4.5% from 2020. Among them, an estimated 450 000 people fell ill with multidrug- or rifampicin-resistant TB. In 2021, an estimated 1.6 million deaths were due to TB among HIV-negative and -positive people *(85)*. Member States assembled at the United Nations on 22 September 2023 and adopted a political declaration reaffirming their commitment to end TB by 2030. They also asked for innovative and more effective solutions, including vaccines, to address all forms of TB, including drug-resistant TB *(86)*. For deeper insights on TB burden, along with recommended combination regimens, please consult the WHO TB Programme research and innovation website *(87)*.

Between 1 November 2021 and 31 December 2023, one new traditional agent for the treatment of *M. tuberculosis* entered Phase 1. TBD09 (MK7762) belongs to the oxazolidinone class and was discovered by Merck as part of the TB Drug Accelerator *(88)*.

Three new TB drug entries are in Phase 2:

- **Alpibectir BVL-GSK098 + ethionamide** acts on bacterial transcriptional regulators via a new mechanism, stimulating novel bioactivation pathways for ethionamide and resulting in a potential increase of ethionamide efficacy, while simultaneously overcoming resistance to the drug.
- **Dovramilast (CC-11050, AMR-634)** is a selective inhibitor of the enzyme PDE4 that downregulates tumour necrosis α (TNF-α) and interleukin 10 (IL-10) production in macrophages, reducing excessive pathological activation of the immune system by *M. tuberculosis*. The compound recently completed Phase 2a clinical trials for TB (NCT02968927) and stage 1 of a two-stage trial for non-TB mycobacteria (NTM).
- **Sanfetrinem cilexetil** is an oral β-lactam (first-in-class tricyclic carbapenem) developed in the 1990s whose development was stopped prior to Phase 3, primarily based on commercial considerations. It is now being repurposed for treatment of drug-sensitive and drug-resistant TB.

Additionally, two TB drugs were captured in Phase 2/3 and 3, respectively:

- **SQ109** targets the mycolic acid transporter MmpL3 in *M. tuberculosis*. It completed three Phase 1 studies in the USA and two Phase 2 studies in drug-sensitive TB patients in Africa, in addition to a Phase 2b–3 study in Russia.
- **Sudapyridine (WX-081)** is a novel diarylpyridine which showed an improved PK and safety profile compared to bedaquiline. Currently patients are being enrolled in a Phase 3 study in Beijing, China.

In addition to the agents referenced above, there are also:

- four TB drugs under development that target DrpE1;
- one leucyl-tRNA synthetase (LeuRs) inhibitor;
- three oxazolidinones;
- one riminophenazine (a clofazimine analogue);
- two diarylquinolines;
- one adenylyl cyclase Rv1625c agonist; and
- an imidazopyridine amide.

Overall, 19 agents are being developed against drug-resistant *M. tuberculosis* (Table 4). Of these 19 agents, six meet the innovation criterion of absence of known cross-resistance. Almost half of these ($n = 9$) belong to a new class, and eight have a new MoA and intended target.

Of the 19 agents being developed against *M. tuberculosis*, more than half (11/19) meet at least one innovation criterium; six meet the innovation criterium “no cross-resistance”; nine represent a new chemical class; and eight have a new target and a new MoA. In the last decade the pipeline of TB medicines has advanced significantly, and several agents are promising candidates for potential new treatment strategies.

Table 4. Antibacterial agents for the treatment of mycobacteria TB in clinical development

Name (synonym)	Phase	Antibiotic class	Route of administration	Developer	Innovation			
					NCR	CC	T	MoA
Sudapyridine (WX-081)	3	Mycobacterial ATP synthase inhibition	PO	Shanghai Jiatan Biotech	-	-	-	-
BTZ-043	2	Benzothiazinone (DprE1 inhibitor)	PO	University of Munich / Hans Knöll Institute, Jena / German Center for Infection Research	✓	✓	✓	✓
Delpazolid (RMW2001, LCB01-0371)	2	Oxazolidinone	PO	LegoChem Biosciences / Haihe Biopharma	-	-	-	-
Ganfeborole, GSK3036656 (GSK070)	2	Oxaborole (LeuRs inhibitor)	PO	GSK	✓	✓	✓	✓
Sutezolid (PF-2341272, PNU-100480)	2	Oxazolidinone	PO	TB Alliance / Sequella / Gates MRI / Aurum Institute	-	-	-	-
TBA-7371	2	Azaindole (DprE1 inhibitor)	PO	TB Alliance / Gates MRI / Foundation for Neglected Diseases Research	✓	✓	✓	✓
Telacebec (Q203)	2	Imidazopyridine amide	PO	Qurient / Infectex / TB Alliance	✓	✓	✓	✓
Quabodepistat (OPC-167832)	2	3,4-Dihydrocarbostyril (DprE1 inhibitor)	PO	Otsuka / Gates MRI	✓	✓	✓	✓
TBAJ-876	2	Diarylquinoline (bedaquiline analogue)	PO	TB Alliance	-	-	-	-
Pyrifazimine (TBI-166) [a]	2	Riminophenazine (clofazimine analogue)	PO	Institute of Materia Medica / TB Alliance / Chinese Academy of Medical Sciences / Peking Union Medical College	-	-	-	-
Alpibectir (BVL-GSK098) + ethionamide	2	Amido piperidine (inactivation of TetR-like repressor EthR2) spiroisoxazoline	PO	BioVersys / GSK	-	✓	-	-
Dovramilast (CC-11050, AMR 634)	2	PDE4 inhibitor (host immune response)	PO	Medicines Development for Global Health	-	✓	-	-
SQ109	2	Ethylenediamine	PO	Sequella	?	-	✓	✓
Sanfetrinem cilexetil	2	Tricyclic β-lactam	PO	GSK / Gates MRI	-	-	-	-
TBI-223	1	Oxazolidinone	PO	TB Alliance / Institute of Materia Medica	-	-	-	-
GSK2556286 (GSK286)	1	Adenylyl cyclase Rv1625c agonist	PO	GSK / TB Drug Accelerator / Gates MRI	?	✓	✓	✓

Table 4 (continued). Antibacterial agents for the treatment of mycobacteria TB in clinical development

Name (synonym)	Phase	Antibiotic class	Route of administration	Developer	Innovation			
					NCR	CC	T	MoA
Macozinone (PBTZ-169)	1	Benzothiazinone (DprE1 inhibitor)	PO	Innovative Medicines for Tuberculosis / Nearmedic Plus	✓	✓	✓	✓
TBAJ-587	1	Diarylquinoline (bedaquiline analogue)	PO	TB Alliance	-	-	-	-
TBD09 (MK7762)	1	Oxazolidinone	PO	Gates MRI	-	-	-	-

Innovation assessment: ✓ criterion fulfilled; ? Inconclusive data; - criterion not fulfilled.

CC: chemical class; DprE1: decaprenylphosphoryl-β-D-ribose 2´-epimerase; LeuRS: leucyl-tRNA synthetase; MOA: new mode of action; NCR: no cross-resistance; T: new target; TB: tuberculosis.

[a]The lead drug clofazimine is approved to treat leprosy and has been used off-label for TB.

See Annex 15 for drug profiles.

3.3 Non-traditional antibacterials

Development of alternative strategies to direct-acting small molecule antibacterials and β-lactam/BLI combinations is drawing increased interest *(89)*.These alternatives are collectively known as non-traditional antibacterials. They aim to prevent or treat bacterial infections by directly or indirectly inhibiting bacterial growth, inhibiting virulence, ameliorating antibacterial resistance, boosting the human immune system and positively altering and/or restoring a healthy microbiome *(90)*.

This report classifies non-traditional antibacterials into six categories:

- **Antibodies** inactivate or neutralize a pathogen, a virulence factor or a toxin or binders.
- **Anti-virulence agents** interfere with bacterial virulence factors but are neither bacteriostatic nor bactericidal.
- **Bacteriophages and phage-derived enzymes** cause direct lysis of a target bacteria by phages or recombinant enzymes and/or phages that have been engineered as nanodelivery vehicles.
- **Immunomodulating agents** augment/stimulate or suppress host immune responses that modify the course of infection.
- **Microbiome-modulating agents** modify the microbiome to eliminate or prevent carriage of resistant or pathogenic bacteria.
- **Miscellaneous agents** inhibit the production or activity of virulence factors – toxin production and virulence factor secretion, impeding bacterial adhesion to host cells and biofilm formation, interrupting or inhibiting bacterial communication and downregulating virulence.

Thirty non-traditional antibacterials against WHO BPPs are under active clinical development: 13 of these are bacteriophages and phage-derived enzymes, seven are antibodies, three are anti-virulence agents, two are immunomodulating agents, one is a microbiome-modulating agent and four are miscellaneous agents (Table 5 and Fig. 11). Of the agents targeting CPPs, four target *E. coli,* one is directed against vancomycin-resistant enterococcus (VRE) and one agent targets *Shigella.* Moreover, 36% (*n* = 11) are against *S. aureus* and 30% (*n* = 9) target *P. aeruginosa*. Seven agents, all intended for use with antibiotics, have an extended spectrum of activity against Gram-positive and Gram-negative organisms.

In addition, nine non-traditional agents target *C. difficile* and one agent targets *H. pylori* infections, bringing the total number of non-traditional agents under clinical development to 40.

3.3.1 Non-traditional antibacterials targeting BPPs

Of the 30 non-traditional antibacterials against WHO BPPs, 13 target WHO critical bacteria (five are against *E. coli,* including one against AIEC strains, and one against *E. coli/C. jejuni,* and seven are extended-spectrum agents with activity against Gram-positive and Gram-negative bacteria, including three against biofilm-producing pathogens (two monoclonal antibodies and one engineered cationic antimicrobial peptide). One product is intended for *Shigella,* a high priority species in the WHO BPPL, whereas 21 products target WHO high and medium priority Gram-negative bacteria (nine target *P. aeruginosa,* 10 target *S. aureus,* one is against *S. pneumoniae,* and one is directed against VRE).

Only one non-traditional agent, reltecimod (AB103), is at the NDA/MAA stage, whereas the majority are in early clinical stages. Some of these agents are designed to be given with existing therapy and thus face the additional challenge of needing to be shown to produce a superior outcome when added to best standard of care (SOC).

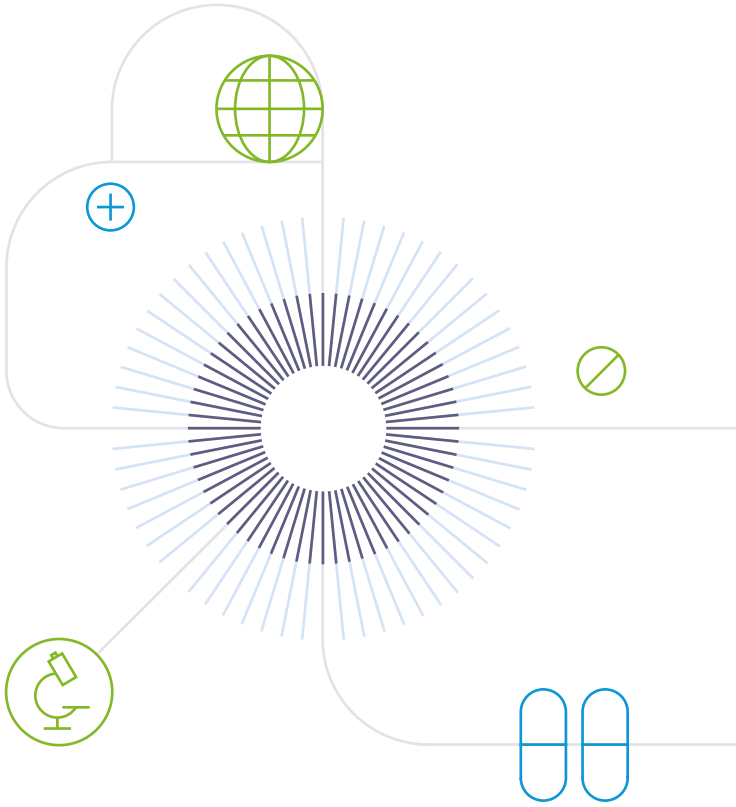


Table 5. Non-traditional antibacterial agents in clinical development

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Priority pathogen(s)
Antibodies	NCT03816956	Tosatoxumab (AR-301)	3	mAb anti-*S. aureus*	iv	Aridis Pharmaceuticals	VABP	*S. aureus*
	NCT05331885	Suvratoxumab (AR-320)	3	mAb anti-*S. aureus* (α-toxin)	iv	Aridis Pharmaceuticals [a]	Prevention of pneumonia in high-risk patients	*S. aureus*
	NCT05339802	9MW1411	2	mAb anti-*S. aureus* (α-toxin)	iv	Mabwell (Shanghai) Bioscience	ABSSSI	*S. aureus*
	NCT04763759	TRL1068 (calpurbatug)	1	mAb biofilm disruption	iv	Trellis Bioscience	PJI	Gram-positive and Gram-negative pathogens
	NCT05629741	CMTX-101	1b/2	mAb biofilm disruption	iv	Clarametyx Biosciences	CABP of moderate severity	Gram-positive and Gram-negative pathogens
	NCT04182490	LMN-101	2	mAb-like recombinant protein (anti-filament A)	PO	Lumen Bioscience	Traveller's diarrhoea	*E. coli*, *C. jejuni*
	ISRCTN17978477	RESP-X (INFEX702)	1	mAb, antivirulence activity	iv	Infex Therapeutics	Chronic *P. aeruginosa* lung infection in non-CF bronchiectasis patients (NCFB)	*P. aeruginosa*
Antiviulence	NCT03638830	Ftortiazinon (fluorothyazinone) + cefepime	2	Anti-virulence (thyazinone T3SS) + cephalosporin	PO	Gamaleya Research Institute of Epidemiology and Microbiology	cUTI caused by *P. aeruginosa*	*P. aeruginosa*
	NCT05138822	GSK3882347	1b	Anti-virulence (type 1 fimbrin D-mannose-specific adhesin, FimH inhibitor)	PO	GSK	uUTI	*E. coli*
	NCT05274802	ALS-4	1	Anti-virulence (staphyloxanthin biosynthesis inhibition)	PO	Aptorum Group	MRSA ABSSSI	*S. aureus*

Table 5 (continued). Non-traditional antibacterial agents in clinical development

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Priority pathogen(s)
Bacteriophages and phage-derived enzymes	NCT04160468	Exebacase (CF-301)	1b/2	Phage endolysin	intra-articular	ContraFect	PJI	*S. aureus*
	NCT03089697 (terminated b), NCT05329168 (withdrawn c)	LSVT-1701, N-Rephasin (SAL200, Tonabacase)	2	Phage endolysin	iv	Roivant Sciences [d]	MRSA bacteraemia	*S. aureus*
	NCT05616221	AP-PA02	2	Bacteriophage	inhalation	Armata Pharmaceuticals	Chronic *P. aeruginosa* lung infection in non-CF	*P. aeruginosa*
	NCT04596319 (SWARM-Pa)		1/2	Bacteriophage	inhalation	Armata Pharmaceuticals	Chronic *P. aeruginosa* lung infection in CF	*P. aeruginosa*
	NCT04684641	YPT-01	1/2	Bacteriophage	inhalation	Felix Biotechnology / Yale University	Chronic *P. aeruginosa* lung infection in CF	*P. aeruginosa*
	NCT05010577	BX004-A	1/2	Bacteriophage	Inhalation	BiomX	Chronic *P. aeruginosa* lung infections in CF	*P. aeruginosa*
	NCT05488340	LBP-EC01	2/3	CRISPR-Cas3 enhanced phage	irrigation/iv	Locus Biosciences	Recurrent uUTI caused by MDR *E. coli*	*E. coli*
	NCT05277350	SNIPR001	1	CRISPR-Cas3 enhanced phage	PO	SNIPR Biome	Prevention of BSI in patients with haematologic malignancy	*E. coli*
	NCT05177107 (DFO)	APT Phagebank	2b	Bacteriophage	iv	Adaptive Phage Therapeutics	DFO	*S. aureus*
	NCT05269121 (ACTIVE1)		1/2	Bacteriophage	intra-articular	Adaptive Phage Therapeutics	Chronic PJI	Gram-positive and Gram-negative pathogens
	NCT05269134 (ACTIVE2)		2	Bacteriophage	intra-articular	Adaptive Phage Therapeutics	Chronic PJI	Gram-positive and Gram-negative pathogens
	NCT05453578 (WRAIR-PAM-CF1)		1b/2	Bacteriophage	iv	Adaptive Phage Therapeutics / WRAIR	Chronic *P. aeruginosa* lung infection in CF	*P. aeruginosa*

Table 5 (continued). Non-traditional antibacterial agents in clinical development

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Priority pathogen(s)
Bacteriophages and phage-derived enzymes (continued)	NCT05369104	Phages: PP1493 and PP1815	2	Bacteriophage	intra-articular	PHAXIAM	Knee/hip PJI with the indication of DAIR and SAT	*S. aureus*
	NCT03808103	EcoActive	1/2a	Bacteriophage	PO	Intralytix	Crohn's disease	*E. coli*, AIEC
	NCT05182749	ShigActive	1/2a	Bacteriophage	PO	Intralytix	Shigellosis	*Shigella*
	NCT05715619	VRELysin	1/2a	Bacteriophage	PO	Intralytix	VRE colonization and associated bacteraemia	VRE
	NCT05184764	AP-SA02	1b/2a	Bacteriophage	iv	Armata Pharmaceuticals	Bacteraemia	*S. aureus*
Immune-modulating agents	NCT04995653	Reltecimod (AB103)	NDA	Synthetic peptide antagonist of both superantigen exotoxins and the CD28 T-cell receptor	iv	Atox Bio	Necrotizing soft tissue infection	*S. aureus*
	NCT03466073	Rhu-pGSN	1b/2a	Rhu-pGSN protein	iv	BioAegis Therapeutics	Hospitalized patients with acute CABP	Gram-positive and Gram-negative pathogens
Microbiome-modulating agents	NCT04995653	SER-155	1b	Microbiome modulator (fermented microbiome, commensal bacteria)	PO	Seres Therapeutics	Reduce GvHD in patients undergoing HSCT	Gram-positive and Gram-negative pathogens

Table 5 (continued). Non-traditional antibacterial agents in clinical development

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Priority pathogen(s)
Miscellaneous	NCT03822455	OligoG (CF-5/20)	2	Anti-biofilm (alginate oligosaccharide, G-block fragment)	inhalation	AlgiPharma	Chronic *P. aeruginosa* lung infection in CF	*P. aeruginosa*
	NCT05453578	PLG0206	1b/2	Anti-biofilm (eCAPs)	irrigation	Peptilogics	PJI	Gram-positive and Gram-negative pathogens
	NCT05776004 (SCABP)	CAL02	2	Broad-spectrum anti-toxin liposomal agent and nanoparticle	iv	Eagle Pharmaceuticals [e]	CABP	*S. pneumoniae*
	NCT03027609	AR501 (Panaecin)	1/2a	Anti-iron (gallium citrate solution)	inhalation	Aridis Pharmaceuticals	*P. aeruginosa* pneumonia	*P. aeruginosa*

ABSSSI: acute bacterial skin and skin structure infection; AIEC: adherent-invasive *E. coli*; BSI: bloodstream infection; CABP: community-acquired bacterial pneumonia; CF: cystic fibrosis; CRISPR: clustered regularly interspaced short palindromic repeats; cUTI: complicated urinary tract infection; DAIR: debridement, antibiotics and implant retention; DFO: diabetic foot osteomyelitis; eCAPs: engineered cationic antimicrobial peptides; FimH: type 1 fimbrin D-mannose-specific adhesin; FPFV: first patient first visit; GvHD: graft vs host disease; HSCT: haematopoietic stem cell transplant; iv: intravenous; mAb: monoclonal antibody; MDR: multidrug-resistant; MRSA: methicillin-resistant *S. aureus*; NFCB: non-cystic fibrosis bronchiectasis; PA: *P. aeruginosa*; PJI: prosthetic joint infection; PO: per os (oral); Rhu-pGSN: rhu-plasma gelsolin; SAT: suppressive antibiotic therapy; T3SS: type III secretion system; uUTI: uncomplicated urinary tract infection; VABP: ventilator-associated bacterial pneumonia; VRE: vancomycin-resistant enterococci.

[a] Licensed from AstraZeneca

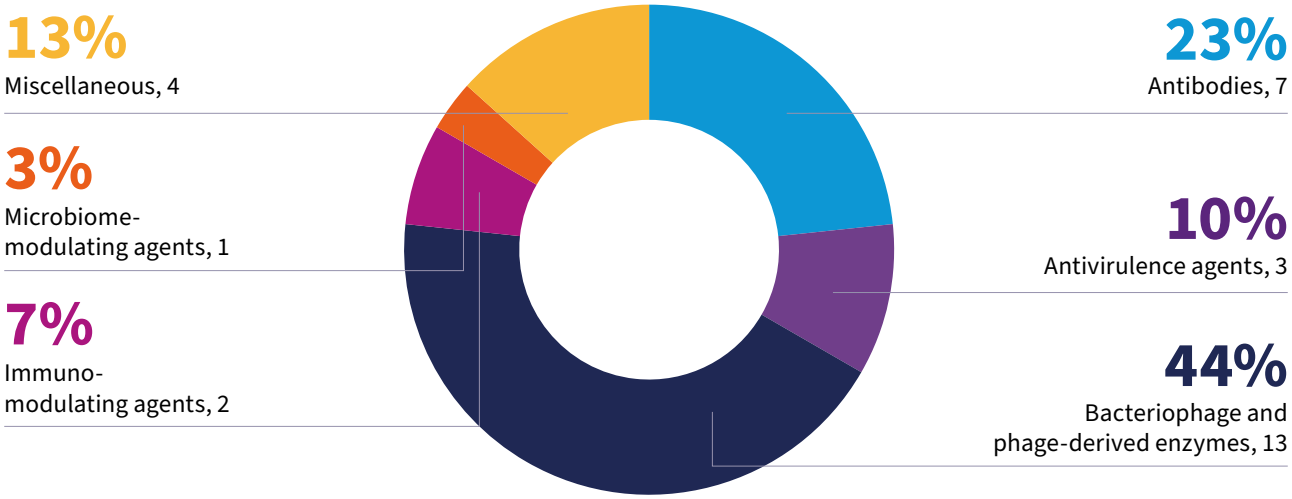
[b] Terminated: Enrollment into this study was terminated by the Sponsor prior to completion for strategic reasons.

[c] Withdrawn: business decision before FPFV; not related to any safety concerns

[d] Licensed from iNtRON

[e] Licensed from Combioxin

Fig. 11. Non-traditional antibacterials in the clinical pipeline



Note: Agents with activity against *C. difficile*, drug-resistant TB and *H. pylori* are not included in these figures.

3.3.1.1 Antibodies

When potentially harmful or foreign substances (antigens) such as pathogens or toxic chemicals are detected by the immune system, antibodies are produced that bind to the antigen (at the epitope) and facilitate their removal. Monoclonal antibodies are excreted as homogeneous groups of antibodies by a single clone of plasma B cells and interact with one specific epitope on the antigen. In contrast, polyclonal antibodies are a heterogeneous group produced by different clones of plasma B cells that interact with multiple epitopes of the antigen.

Due to multiple factors, including their homogeneity, selectivity and lower potential for cross-reactivity, monoclonal antibodies have emerged as an important treatment modality for several therapeutic areas in recent years. These areas include oncology, multiple sclerosis, systemic lupus erythematous, respiratory syncytial virus and, most recently, COVID-19. In addition, monoclonal antibodies are receiving increasing attention for treatment of bacterial infections *(91)*.

Historically, antibodies have been used as antitoxins (toxin-neutralizing antibodies), as they are able to bind directly to a toxin, either causing its removal or blocking its active site. The diphtheria antitoxins discovered in 1891 provide an example. Only recently have antibodies been studied against bacteria themselves. Antibody therapies can target numerous bacterial epitopes and virulence factors, including surface proteins, bacterial toxins and polysaccharides. However, development challenges remain, including identifying optimal bacterial targets and clinical trial design *(92)*.

Currently, seven antibodies are in clinical development against BPP (Table 5), with five targeting selected bacteria, albeit with different mechanisms and antibody compositions. Three of these are being developed against *S. aureus* (tosatoxumab (AR-301), suvratoxumab (AR-302) and 9MW1411, one against *P. aeruginosa* (RESP-X), one against *C. jejuni* and *E. coli* (LMN-101) and two (CMTX-101 and TRL1068) against the biofilms caused by various Gram-positive and Gram-negative bacteria.

3.3.1.2 Anti-virulence agents

Virulence factors enable bacterial colonization, immunoevasion and immunosuppression. They also play a role in obtaining nutriments and in damaging host cells. Anti-virulence agents interfere with adhesins, toxins and bacterial communication and, as a result, block bacterial pathogenicity *(93)*.

Three non-traditional anti-virulence agents are in the clinical pipeline: ftortiazinon, a bacterial type III secretion system (T3SS) inhibitor; GSK3882347, an adhesion protein inhibitor, and ALS-4 (target undisclosed).

3.3.1.3 Bacteriophages and phage-derived enzymes

Bacteriophages (also known as phages) are viruses that infect and replicate in bacteria. Since their discovery in 1915, phages have been used to treat infections in the former Soviet Union, France and central Europe *(94)*. In recent years, evaluating phages as new antibacterial agents has attracted renewed interest, including in the food animal industry. One option is to use the enzymes produced by phages, called lysins, which degrade bacterial cell walls. Another option is to use phages (or combinations of phages) selected from phage banks as specific therapy to treat specific individual patients with drug-resistant bacterial infections. A third option is to employ predefined phage cocktails selected to overcome the specificity of single phages and to sufficiently broaden the host range to allow empirical use. Some developers are also exploring synthetic biology techniques to engineer phages with more potent and broader activity spectra as vehicles to deliver lysins and bactericidal payloads.

In this review, only bacteriophage and phage-based therapeutics in clinical trials have been considered; a total of 13 phage cocktails were used under an Emergency Investigational New Drug application. Expanded access/compassionate use, national magistral frameworks *(95)* or the equivalent are not included in the present analysis.

3.3.1.4 Immunomodulating agents

The human immune system is highly effective at identifying and eliminating pathogens from the body. However, it can become overwhelmed or blocked, resulting in severe infection caused by bacteria, fungi, viruses or parasites. Host-directed immunomodulatory therapies seek to enhance protective immunity while minimizing tissue damage. Two non-traditional agents, reltecimod (AB103) and Rhu-pGSN (rhu-plasma gelsolin), are currently undergoing clinical trials to evaluate their immunomodulating effects.

3.3.1.5 Microbiome-modulating agents

Antibacterial agents have the potential to alter the delicate balance of the human microbiome, a critical component in maintaining human overall health by aiding in digestion, immune function and protection against harmful pathogens like *C. difficile*. Additionally, the use of these agents can create selective pressure on bacteria, leading to survival and proliferation of resistant bacterial pathogens *(96,97)*. As of the last WHO report in 2021, three microbiome-modulating products for the treatment of recurrent CDI had received marketing authorization (SER-109, BB128 and RBX2660).

Currently nine microbiome-modulating agents are in clinical trials. Eight of these agents are live biotherapeutic products under investigation to treat CDI or *H. pylori* and are described in section 3.4.1 – VE303, RBX-7455, NTCM-M3 (VP20621), MET-2, ADS024 (formerly ART24) and MBK-01 – one is an antibiotic inactivator (SYN-004), and SVT-1C469 targets *H. pylori*. An additional agent, SER-155, is aimed at reducing breakthrough bacteraemia in certain high-risk populations, such as haematopoietic stem-cell transplant (HSCT) patients.

3.3.1.6 Miscellaneous

Four antibacterial non-traditional agents in the pipeline fall under the miscellaneous category. Two inhibit biofilm formation: OligoG, an alginate oligosaccharide fragment derived from seaweed being investigated in the treatment of *P. aeruginosa* lung infection in patients with CF, and PLG0206, an engineered cationic antibiotic peptide as adjunct treatment for PJI after total knee arthroplasty (TKA).

CAL02 is a mixture of liposomes that binds and neutralizes bacterial toxins, to be used in association with antibiotics. This MoA confers to CAL02 a potential broad spectrum of activity. It is currently being investigated in severe CABP in a Phase 2 trial.

AR-501 is an inhalable form of gallium citrate which acts as an iron analogue to starve bacteria of iron. The agent is currently under investigation for bacterial lung infection in patients with CF.

3.4 Agents in development for treating CDI and *H. pylori*

Infection with *C. difficile* can cause serious bacterial infections, such as severe enterocolitis and life-threatening damage to the colon, that are a serious public health threat. CDI is primarily managed by prevention, control and antimicrobial stewardship activities. CDI is associated with antibiotic use and mostly affects frail patients or immune-compromised patients. CDI infection is the most prevalent health-care-associated infection *(98)*.

Candidates in development are included in this report for completeness, as extensive of antimicrobials is linked to CDI, and rising resistance is a cause for concern *(99)*.

H. pylori is a common bacterium that infects the stomach, potentially leading to inflammation and peptic ulcers in the upper digestive tract. It weakens the stomach lining by producing urease, an enzyme which neutralizes stomach acids, making the stomach more susceptible to damage from digestive fluids. Additionally, the bacteria can adhere to stomach cells, causing inflammation. Although many people carry *H. pylori* without symptoms, it is a primary cause of ulcers. Moreover, its mechanism for increasing stomach acid production remains not fully understood. Although *H. pylori* is no longer included in the WHO BPPL, *H. pylori* strains resistant to antimicrobials are evolving. Eradication of the bacterium is becoming more and more complex, involving an increasing number of antimicrobials, with reduced therapeutic compliance and a higher rate of treatment-related adverse events. In the attempt to drive developer attention regarding this issue, drugs under development against *H. pylori* are also included in this report.

3.4.1 Agents in development against CDI

3.4.1.1 Traditional agents against CDI

Five traditional antibacterials for the treatment of CDI are currently in clinical development, one in Phase 3 and four in Phase 2. Four of these five agents against CDI are considered innovative, with two agents – ridinilazole and CRS3123 – addressing all four innovation criteria. However, the Ri-CoDIFy Phase 3 trial of ridinilazole did not meet its primary end-point. In addition, the ongoing trial in the paediatric population was terminated in alignment with a corporate decision to pursue further development of the drug candidate with a partner.

Table 6. Traditional antibacterials in clinical development for the treatment of *C. difficile* and *H. pylori*

Name (synonym)	Phase	Antibiotic class	Route of administration	Developer	Pathogen	Innovation			
						NCR	CC	T	MoA
Ridinilazole	**3**[a]	Bis-benzimidazole	oral, not absorbed	Summit Therapeutics	*C. difficile*	✓	✓	✓	✓
CRS3123	**2**	Diaryldiamine	oral	Crestone/NIAID	*C. difficile*	✓	✓	✓	✓
Oxaquin (DNV3837, MCB-3837)	**2**	Oxazolidinone-quinolone hybrid	iv	Deinove	*C. difficile*	?	-	-	-
Ibezapolstat (ACX-362E)	**2**	DNA polymerase IIIC inhibitor	oral, not absorbed	Acurx Pharmaceuticals	*C. difficile*	?	✓	✓	✓
MGB-BP-3	**2**	Distamycin (DNA minor groove binder)	oral, not absorbed	MGB Biopharma	*C. difficile*	?	✓	✓	✓
Rifasutenizol (TNP-2198)	**3**	Rifamycin-nitroimidazole conjugate	oral	TenNor Therapeutics	*H. pylori*	-	-	-	-

Innovation assessment: ✓ criterion fulfilled; ? Inconclusive data; - criterion not fulfilled.

CC: chemical class; CDIs: *C. difficile* infections; iv: intravenous; MoA: new mode of action; NCR: no cross-resistance; NIAID: National Institute of Allergy and Infectious Diseases; T: new target.

[a] following negative results from the phase 3 study, the ongoing study in adolescent study was terminated in alignment with corporate decision to pursue further development of drug candidate with a partner.

3.4.1.2 Non-traditional agents against CDI

Nine non-traditional antibacterials are being developed against CDI (Table 7).

Table 7. Non-traditional antibacterials in clinical development for the treatment of *C. difficile* and *H. pylori*

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Pathogen
Antibodies	NCT04121169	IM-01	2	*Chicken egg-derived anti-C. difficile polyclonal antibody*	PO	ImmuniMed	CDI	*C. difficile*
Microbiome-modulating agents	ACTRN12620000923965	SVT-1C469	1	Live biotherapeutic product	PO	Servatus	*H. pylori* gastritis	*H. pylori*
	NCT03788434	VE303	2	Live biotherapeutic product	PO	Vedanta Biosciences	rCDI	*C. difficile*
	NCT02865616	MET-2	1	Live biotherapeutic product	PO	NuBiyota/Takeda	rCDI	*C. difficile*
	NCT02981316	RBX7455	1	Live biotherapeutic product	PO	Ferring Pharmaceuticals (Rebiotix)	rCDI	*C. difficile*
	NCT04692181	SYN-004 (ribaxamase)	2	Antibiotic inactivator	PO	Theriva Biologics [a]	Prevention of CDI in allogeneic HCST	*C. difficile*
	NCT04891965	ADS024 (formerly ART24)	1	Live biotherapeutic product	PO	Adiso Therapeutics [b]	rCDI	*C. difficile*
	Not yet registered	MBK-01	3	Live biotherapeutic product	PO	Mikrobiomik Healthcare Company	rCDI	*C. difficile*
	NCT01259726	NTCM-M3 (VP20621)	2	Live biotherapeutic product	PO	Destiny Pharma, Sebela Pharmaceuticals	rCDI	*C. difficile*
Bacteriophages and phage-derived enzymes	NCT05330182	LMN-201	2/3	Phage endolysin and three toxin-binding proteins (5D, E3 and 7F)	PO	Lumen Bioscience	rCDI	*C. difficile*

CDI: *C. difficile* infection; HCST: haematopoietic cell transplant; PO: per os (oral); rCDI: recurrent CDI.

[a] Formerly Synthetic Biologics

[b] Formerly Artugen Therapeutics and Bacainn Therapeutics

3.4.2 Agents in development against *H. pylori*

Currently one traditional and one non-traditional agent are under clinical investigation for *H. pylori* infection. The traditional agent, rifasutenizol (TNP-2198), a rifamycin-nitroimidazole conjugate, is currently in Phase 3. It does not address any of the WHO innovation criteria, but it is the first traditional product developed specifically for *H. pylori* infection (Table 6).

The non-traditional agent SVT-1C469 is a mix of bacterial strains claimed to inhibit growth of *H. pylori* and modulate immune and inflammatory responses (Table 7).

3.5 Agents not under active development or for which there is no recent information

In the antibacterial field it is not uncommon for companies to suspend product development for several years, in the hope that they may find the necessary financing to continue development at a later stage or that the product may be bought by another company. In addition, some developmental programmes were substantially curtailed by the COVID-19 outbreak.

Some of these compounds are still listed in the (online) clinical development pipelines of the sponsoring developers, but typically do not move through the clinical development pathway. If such products do not show any activity for at least 3 years, they are listed in Table 8 as agents that are not under active development. Agents that were discontinued/terminated on or after 2017 are also listed in Table 8.

Three antibacterial agents have been added to this table since the last review: two agents against *C. difficile* (DAV132 and CP101) and one monoclonal antibody – AR101 (Aerumab, KPBA-101) – for the *P. aeruginosa* lipopolysaccharide serotype O11 (Table 8).

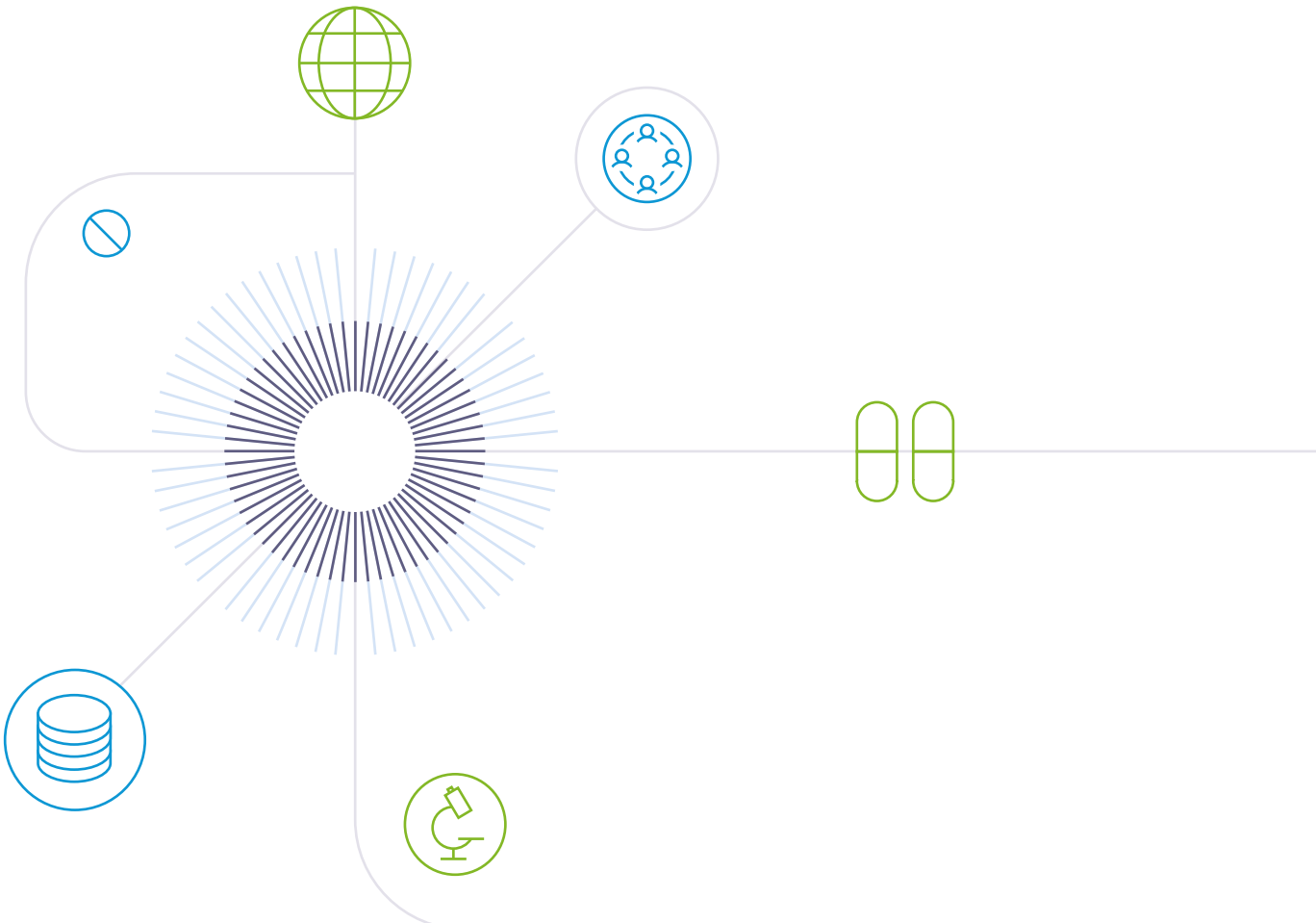


Table 8. Agents not under active development by year of activity last reported

Name (synonym)	Phase	Antibiotic class	Pathogen activity	Developer	Year activity last reported
GSK-3342830	1	Siderophore-cephalosporin	Gram-negative	GSK	2017
AIC-499 + unknown BLI	1	β-Lactam + BLI	Gram-negative	AiCuris	2017
DS-2969	1	New class (GyrB inhibitor)	*C. difficile*	Daiichi Sankyo	2017
514G3 (omodenbamab)	1/2	Anti-*S. aureus* IgG mAb	*S. aureus*	Xbiotech	2017
SPR-741 + β-lactam	1	Polymyxin (potentiator) + β-lactam	Gram-negative	Spero Therapeutics / Everest Medicines	2018
Cefilavancin (TD-1792, RD-1792)	3	Glycopeptide-cephalosporin hybrid	*S. aureus*	R-Pharm / Theravance Biopharma	2018
Ramoplanin	2	Lipodepsipeptide	*C. difficile*	Nanotherapeutics	2018
Ancremonam (BOS-228, LYS-228)	2	Monobactam	CRE	Boston Pharmaceuticals	2018
Cadazolid	3	Oxazolidinone-quinolone hybrid	*C. difficile*	Actelion Pharmaceuticals	2019
RC-01 (T 1228)	1	New class (LpxC inhibitor)	Gram-negative	Recida Therapeutics / Fujifilm Toyama Chemical	2019
GT-1	1	Siderophore-cephalosporin	Gram-negative	Geom Therapeutics	2019
MK-3866	1	BLI	Gram-negative	Merck Sharp & Dohme	2019
AR-105 (Aerucin)	2	Anti-*P. aeruginosa* fully human IgG1 mAb	*P. aeruginosa*	Aridis Pharmaceuticals (Serum Institute of India)	2019
BCM-0184	1	Undisclosed (likely peptide)	*S. aureus*	Biocidium Pharmaceuticals	2019
Iclaprim	3	DHFR inhibitor	*S. aureus*	Motif Bio	2020

Table 8 (continued). Agents not under active development by year of activity last reported

Name (synonym)	Phase	Antibiotic class	Pathogen activity	Developer	Year activity last reported
MEDI-3902 (gremubamab)	2	Anti-*P. aeruginosa* IgG mAb	*S. aureus*	AstraZeneca (MedImmune)	2020
OPS-2071	2	Quinolone	*C. difficile*	Otsuka	2020
AR-101 (Aerumab, KPBA-101)	2	mAb	*P. aeruginosa* LPS serotype O11	Aridis Pharmaceuticals / Kenta Biotech	2020
DSTA4637S	1	Anti-*S. aureus* IgG mAb / rifamycin conjugate	*S. aureus*	Genentech (Roche)	2021
KB109	N/A	Synthetic glycan	Gram-positive and Gram- negative	Kaleido Biosciences	2021
KB109	N/A	Synthetic glycan	Gram-positive and Gram- negative	Kaleido Biosciences	2021
TP-271	1	Tetracycline	*S. aureus* and *S. pneumoniae*	La Jolla Pharmaceutical Company (Tetraphase Pharmaceuticals)	2021
TP-6076	1	Tetracycline	*A. baumannii*	La Jolla Pharmaceutical Company (Tetraphase Pharmaceuticals)	2021
DAV132[a]	2	Antibiotic inactivator and protective colon-targeted adsorbent	*C. difficile*	Da Volterra	2022
CP101[a]	2	Live biotherapeutic product	*C. difficile*	Finch Therapeutics	2023
Bacteriophage[a]	3	Phage	Gram-positive and Gram-negative	Tashkent Pediatric Medical Institute	2023

BLI: β-lactamase inhibitor; CRE: carbapenem-resistant Enterobacterales; DHFR: dihydrofolate reductase inhibitor; GyrB: DNA gyrase subunit B; IgG: immunoglobulin G; LPS: lipopolysaccharide; mAb: monoclonal antibody; MoA: mode of action; N/A: not applicable.

Underlined: New chemical class.

[a] These antibacterials were previously listed as "in development" in the 2021 WHO pipeline report.

4

Agents in preclinical development

4. Agents in preclinical development

The first WHO analysis of antibacterial agents against priority pathogens in preclinical development was published in 2019 to guide the R&D of new antibacterial agents. Since 2019, WHO has continued to review the preclinical pipeline on an annual basis to identify how the early-stage R&D ecosystem is responding to the priority pathogens list.

This snapshot review of the preclinical pipeline identifies promising innovative products that may move forward to the clinical pipeline and eventually to market. While it is more difficult to fully analyse the preclinical pipeline, as not all programmes are disclosed and there is far greater turnover in the programmes due to both scientific progress and available resources, the snapshot helps identify trends in the broader antibacterial R&D ecosystem.

4.1 Preclinical pipeline overview

The total number of preclinical programmes and unique groups developing the products across the four pipeline analyses performed since 2019 has been very similar.

Overall, 244 preclinical projects are affiliated with 141 institutions, which is consistent with the three previous preclinical pipeline reviews performed since 2019 (Fig. 12). The 2023 preclinical pipeline analysis show a wide geographical distribution of developers across all six WHO regions (Fig. 13A) originating from 29 different countries (Fig. 13B). Most data in the 2023 survey were collected from groups in the European Region (*n* = 73, 51.8%) and the Region of the Americas (*n* = 50, 35.5%).

Fig. 12. Total number of preclinical programmes and unique groups developing the products across the four pipeline analyses performed since 2019

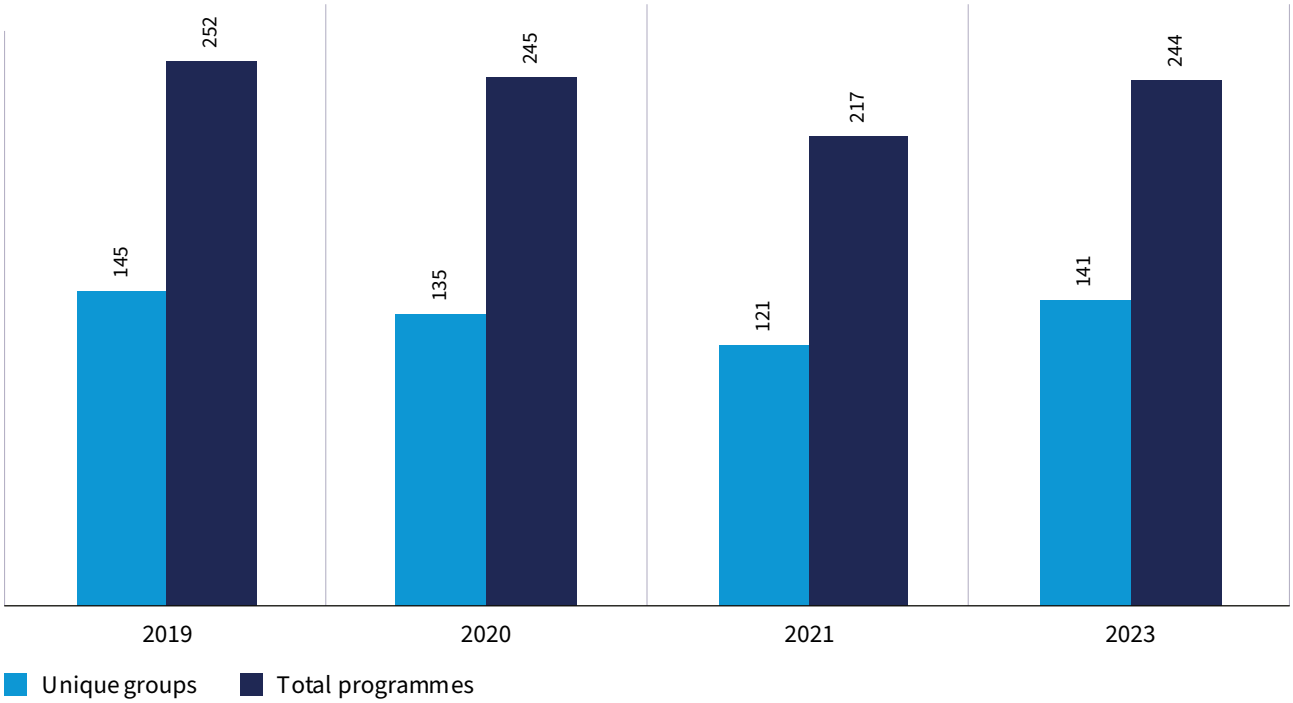
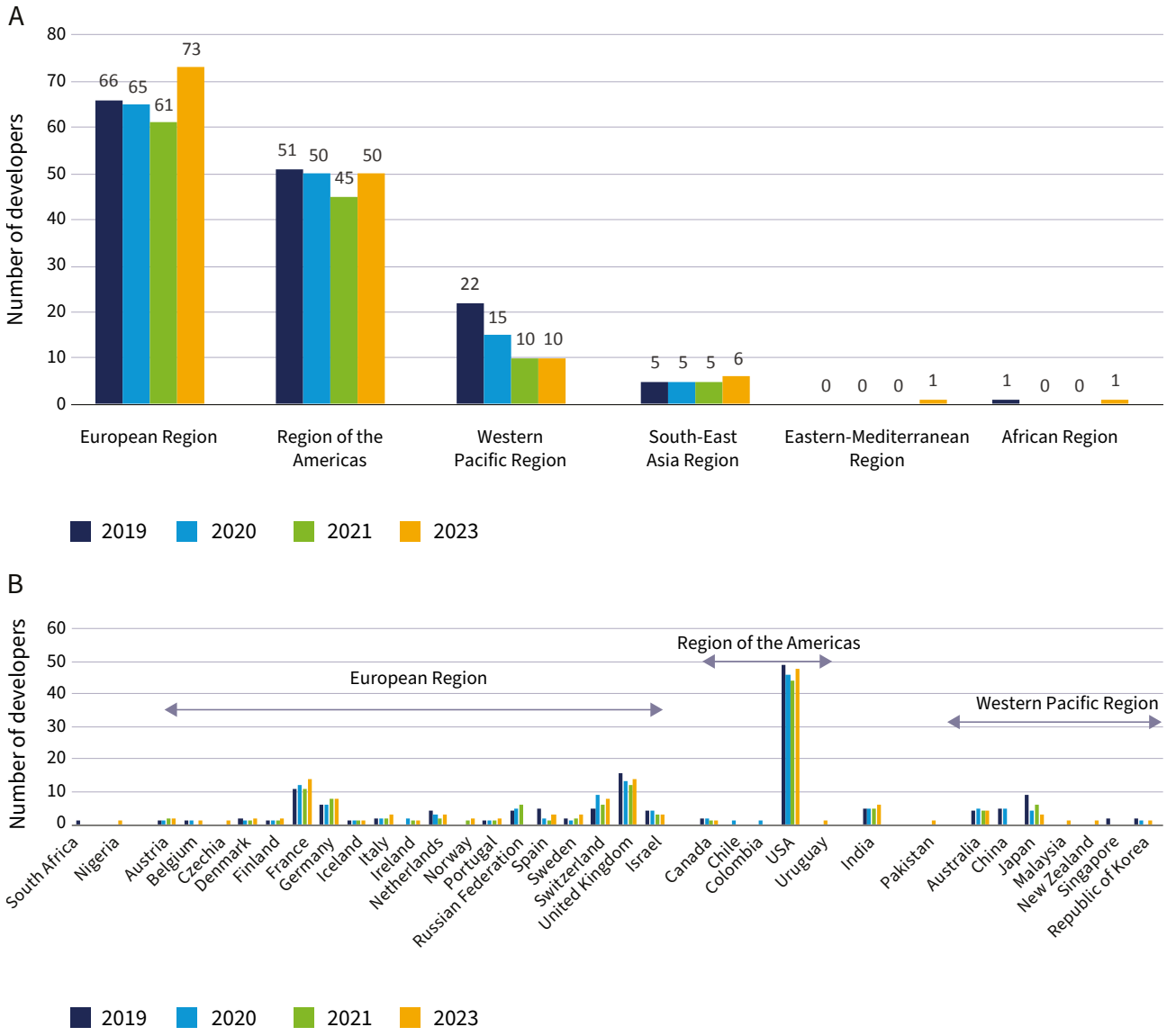


Fig. 13. Geographical distribution of the 141 institutions with preclinical pipeline projects across the 2019–2023 analysis shown by WHO geographical regions (panel A) or by country (panel B)



The 141 institutions were classified either as academic universities, companies or foundations. Most institutions in the 2023 analysis are commercial companies (*n* = 112, 79.4%), followed by academic institutions (*n* = 25, 17.7%) and foundations (*n* = 4, 2.8%). The dominance of commercial companies performing antimicrobial product development has remained stable over four consecutive years of analysis (Fig. 14). The 112 commercial institutions were further analysed by company size as well as whether they are publicly traded or privately owned. Most of the companies are privately owned (*n* = 95, 84.8%), and a significant proportion (*n* = 97, 86.7%) of all companies contain < 50 employees, with over half (*n* = 62, 55.4%) having < 10 employees (Fig. 15). This trend confirms what has been observed in prior years, which is that a significant majority of the preclinical pipeline developers are very small, privately funded organizations. This is also indicative of the number of large pharmaceuticals firms that have exited the antibacterial discovery area. A certain bias can also be expected, since large pharmaceutical companies remaining active in the area did not disclose their preclinical pipeline.

Fig. 14. Categorization of groups with preclinical pipeline projects by type

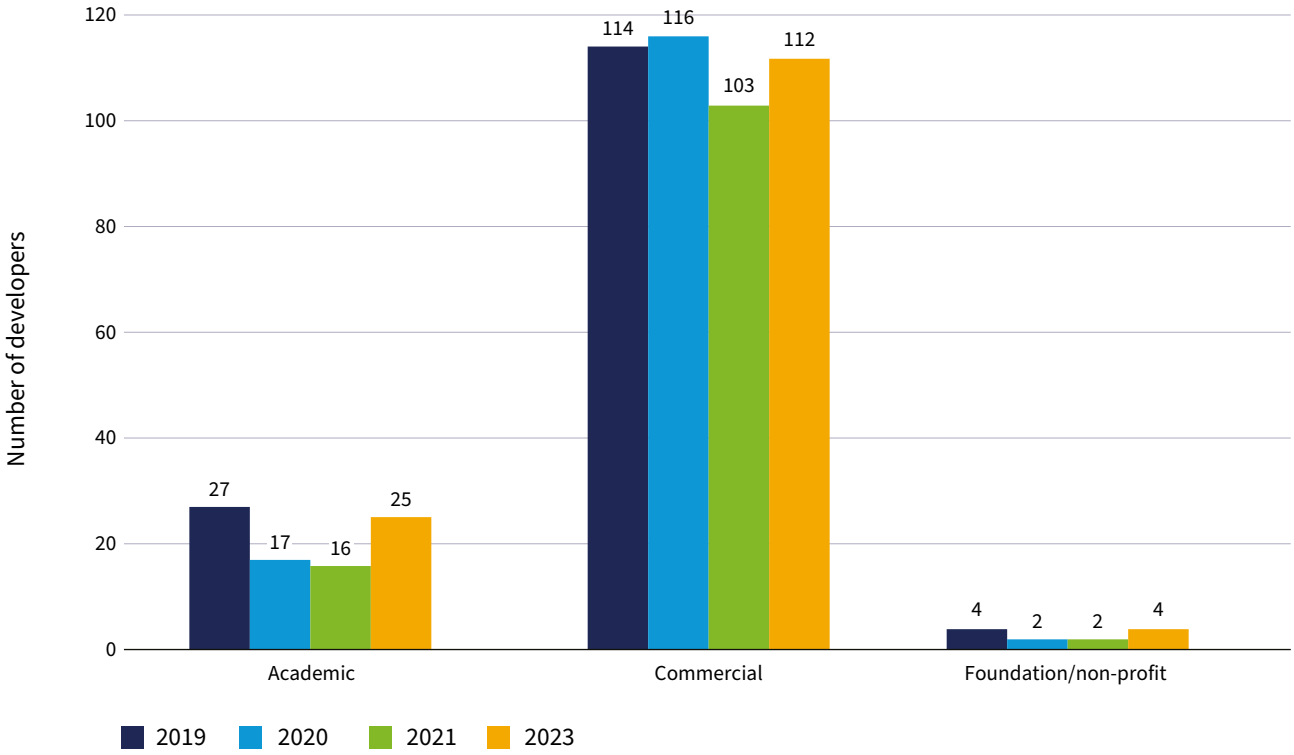
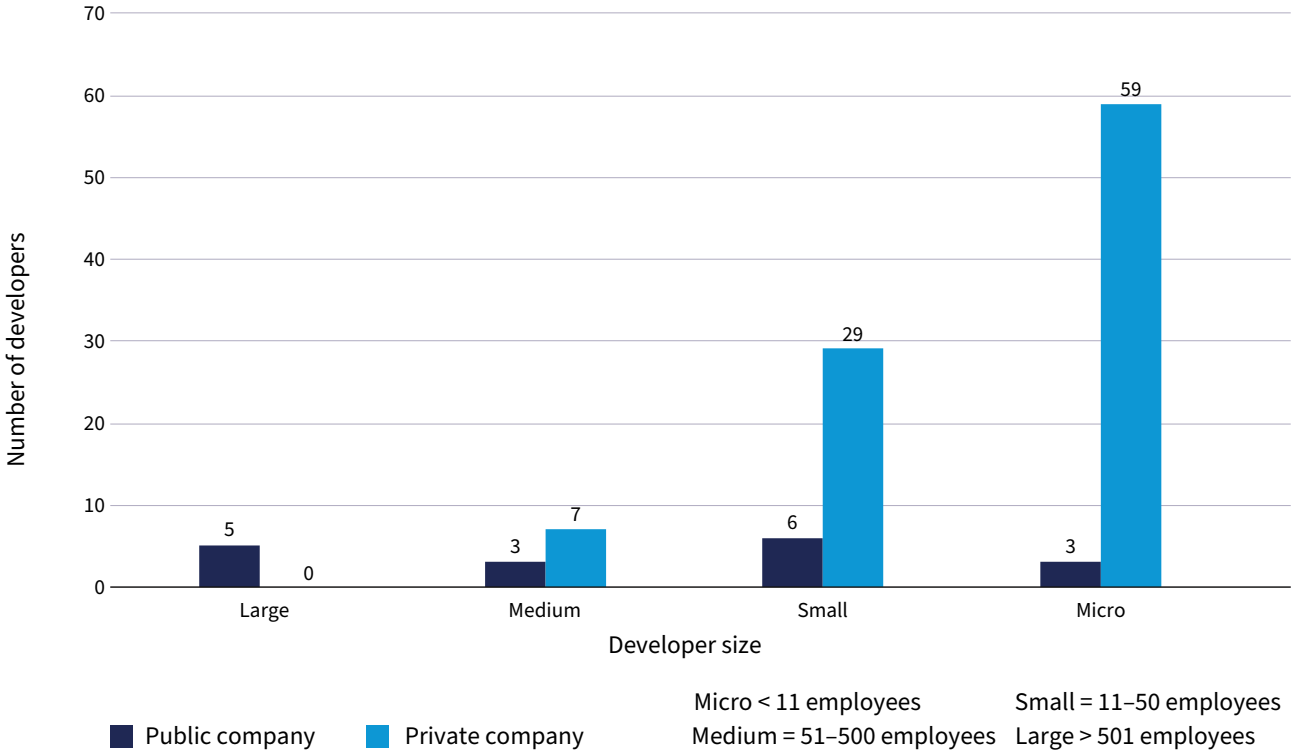


Fig. 15. Categorization of companies with preclinical pipeline projects by ownership and size



It should be noted, however, that 32 of the 121 developers (26.5%) included in the 2021 analysis were lost in the 2023 pipeline review, as the presence of the programme could not be verified. This high level of turnover in groups developing antimicrobial products continues to highlight the fragility of the overall ecosystem.

4.2 Categorization of preclinical agents

A large variety of different agents characterize preclinical development. The majority of the programmes are traditional agents, mostly represented by direct-acting small molecules) (*n* = 115, 47.1%), followed by a large number of direct-acting peptide programmes (*n* = 33, 13.5%) (Table 9).

Overall, there are 93 non-traditional products, representing 38.1% of the preclinical pipeline. The largest contributing groups are bacteriophage programmes (*n* = 29, 11.9%) and indirect-acting small molecules (*n* = 23, 9.4%) (Table 9).

Table 9. Distribution of preclinical programmes by antibacterial agent category

Product type	2023 Number	2023 %
Small molecule – direct acting	115	47.1
Small molecule – indirect acting[a]	23	9.4
Peptide – direct acting	33	13.5
Peptide – indirect acting[a]	1	0.4
Large molecule – direct acting[a]	17	7.0
Large molecule – indirect acting[a]	3	1.2
Bacteriophage / bacteriophage products[a]	29	11.9
Biologic (antibody or other biotherapeutic)[a]	7	2.9
Nucleic acid-based product[a]	1	0.4
Immunomodulators[a]	9	3.7
Microbiome-modifying agents[a]	3	1.2
Decolonization agents	3	1.2
Total	**244**	**100.0**

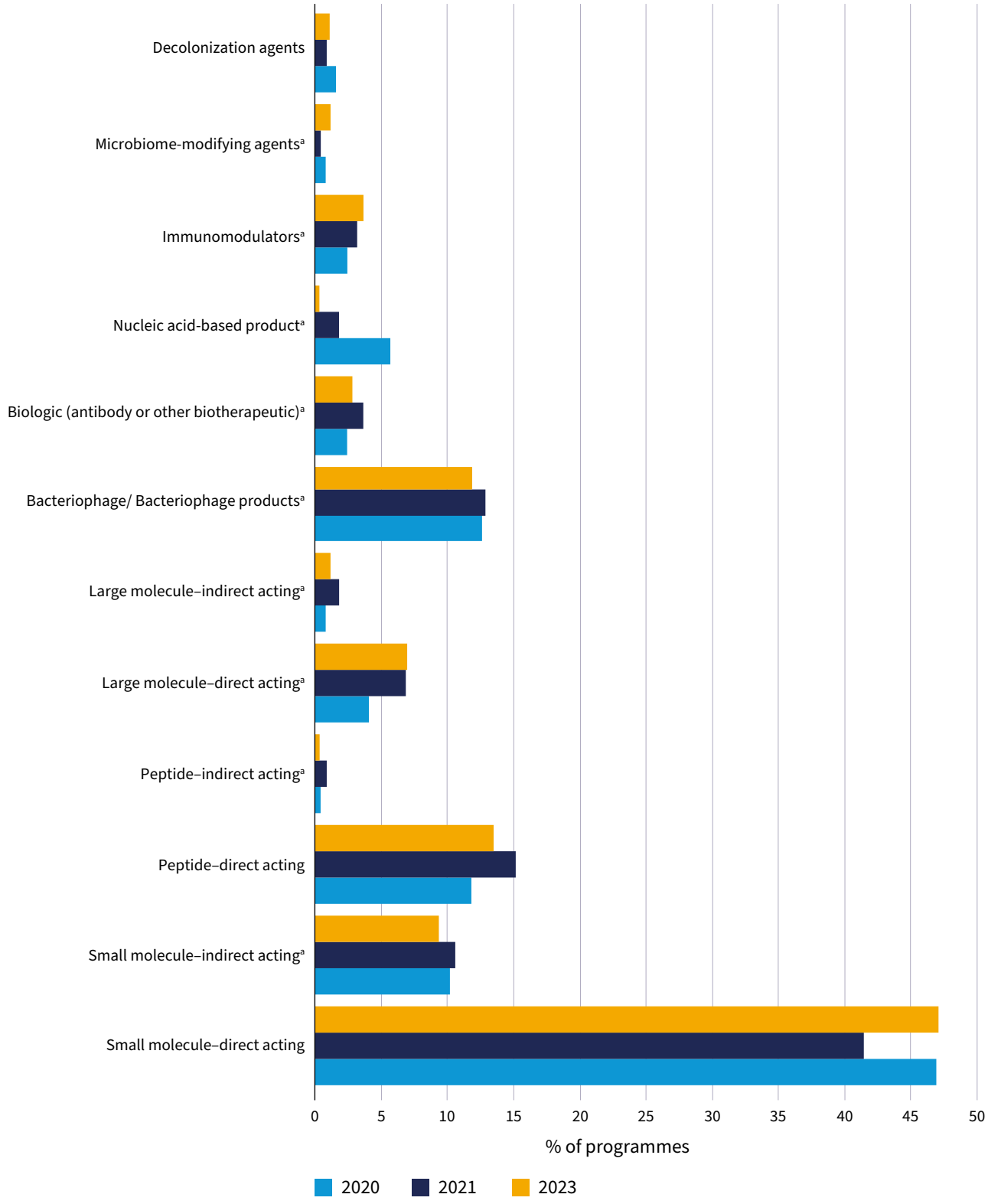
[a] Non-traditional agents.

A total of 196 (80.3%) programmes are being developed as single agents, along with 39 (16%) whose development includes a combination agent. Only nine programmes are developing a novel combination with an unapproved partner agent.

For comparison, the relative percentages of the preclinical pipeline from 2020, 2021 and 2023 that belonged to these different categories (modalities) have been assessed. However, as the programme categorization was performed differently in 2019 – i.e., it also included vaccines that now are captured by a dedicated WHO review *(100)* – those data are not included in the present review (Fig. 16). The relative stability of the pipeline composition with respect to the different modalities, despite the turnover of developers and programmes, is apparent. It does appear that the large number of non-traditional agents that were first observed using this categorization in 2020 has stabilized. Between 40% and 50% of the preclinical pipeline has remained focused on direct-acting small molecules since 2020 (Fig. 16).

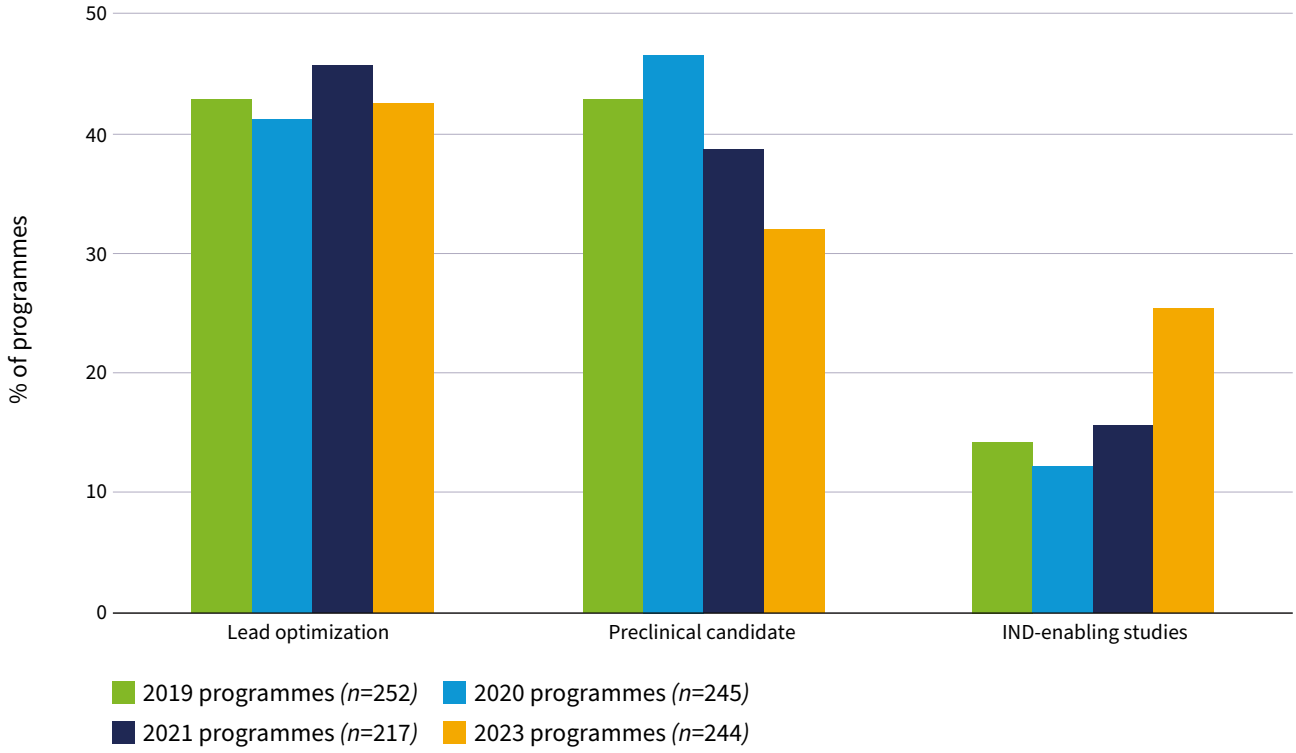
Several analyses were performed to understand the progression of the preclinical pipeline in 2023, and then compared with past analyses to understand the dynamics of the ecosystem. The programmes were grouped by their self-declared preclinical development stage and compared with data collected in previous years (Fig. 17). The relative proportion of programmes in each stage of development has remained relatively constant over the 3-year period, suggesting that as projects either fail or progress into clinical development, they are replaced by new programmes.

Fig. 16. Categorization of preclinical pipeline projects by biological modality over the last three pipeline reviews



[a]Non-traditional agents.

Fig. 17. Categorization of programmes by stage of preclinical development across four consecutive analyses



IND: Investigational New Drug.

The 2023 analysis captured 62 programmes (25.4%) that are listed as being in the Investigational New Drug (IND)-enabling phase of preclinical development, a significantly larger number than in earlier pipeline reports.

A closer inspection of these programmes revealed that 19 are listed as being at the same stage of development in 2021. However, 24 programmes progressed from earlier stages in 2021 to the IND-enabling phase. Also, 19 new programmes were not captured in the 2021 pipeline analysis, which explains the significant growth at this later stage of development. It will be important to monitor whether this growth will be maintained going forward or whether it may be due to the time passed since the last pipeline analysis.

An analysis of the 34 programmes listed in the IND-enabling stage from 2021 was also performed. In addition to the 19 programmes that were in the same phase in 2021, six have progressed into clinical studies, eight were not included in 2023 as the status of the programme could not be verified, and one programme regressed slightly.

Table 10 shows the 244 products categorized by their antibacterial MoA against their self-declared preclinical development stage. Overall, the large number of direct-acting peptide and bacteriophage programmes resulted in a significant number (n = 68, 27.9%) of products that have a direct membrane effect. For 25 (10.2%) products, no information on the MoA is available (either unknown or not disclosed) (Table 10).

Table 10. Distribution of programmes by MoA and preclinical development stage

MoA category	Total number (%)	Development stage		
		LO	PCC	IND
Anti-virulence	25 (10.2)	16	4	5
Cell wall synthesis – BL and/or BLI	7 (2.9)	1	0	6
Cell wall synthesis – other	32 (13.1)	12	10	10
Central metabolism	10 (4.1)	4	4	2
Direct membrane effect	68 (27.9)	22	30	16
DNA replication / synthesis	16 (6.6)	5	3	8
Protein synthesis	18 (7.4)	8	5	5
RNA synthesis	5 (2.0)	4	1	0
Immunomodulation	14 (5.7)	1	10	3
Other cellular function	17 (7.0)	10	4	3
Potentiator or enabling agent	6 (2.5)	5	0	1
Not disclosed	14 (5.7)	7	5	2
Unknown	11 (4.5)	9	1	1
Decolonization	1 (0.4)	0	1	0
Total	**244 (100)**	**104**	**78**	**62**

BL: β-lactam; BLI: β-lactamase inhibitor; CTA: clinical trial application; IND: Investigational New Drug; LO: lead optimization; MoA: mode of action; PCC: preclinical candidate.

4.3 Antibacterial spectrum of agents in the preclinical pipeline

Preclinical pipeline results show that a significant number of products (n = 91, 37.1%) are focused against a single pathogen, which solidifies the trend that a significant portion of the pipeline is being developed as more narrow-spectrum therapies rather than broader spectrum[10] agents. One hundred and fifty-three products are broad-spectrum agents and have claimed activity against more than one pathogen from the BPPL.

A total of 43 products target one of the WHO CPPs, of which 26 products are intended against *M. tuberculosis*. In the high priority group, a total of 20 programmes are directed against *P. aeruginosa*, along with 12 directed against *S. aureus* and eight against *N. gonorrhoeae* (Table 11).

[10] *Narrow-spectrum* refers to agents that target a single species.

Table 11. Distribution of species-specific programmes by the WHO BPPL

Organism	Total products[a]	Species-specific products	WHO PPL
A. baumannii	65	6	**Critical**
E. coli[b]	84	6	
K. pneumoniae[b]	85	5	
Enterobacter spp.[b]	65	0	
M. tuberculosis	43	26	
Salmonella spp.	29	0	**High**
Shigella spp.	22	0	
E. faecium	53	1	
P. aeruginosa	94	20	
Salmonella spp.	29	0	
S. aureus	94	12	
Group A Streptococci	3	0	**Medium**
S. pneumoniae	52	1	
H. influenzae	17	0	
Group B Streptococci	3	0	
C. difficile	24	3	
Not disclosed	4	N/A	
Broad G+/G-[c]	6	0	
Gram-negative[c]	2	0	
OMIP[d]	4	3	
Total		91	

CR: carbapenem-resistant; G+/G–: Gram-positive/Gram-negative; N/A: not applicable; OMIP: other medically important pathogens; PPL: priority pathogen list; 3GC: third-generation cephalosporin; WHO: World Health Organization.

[a] Note that products with activity against multiple species will be counted against each species.

[b] Activity against CR and 3GC isolates is not always disclosed, and so species activity is represented.

[c] Activity against individual bacterial species was not provided.

[d] Other medically important pathogens.

Examination of the 91 narrow-spectrum programmes indicated that these products against *P. aeruginosa* were distributed across most of the different product types (Table 11) as well as six different MoAs (Table 12).

Table 12. Distribution of narrow-spectrum programmes by product type and WHO BPPL

Mode-of-Action Category	Total (%)	Bacterial Pathogen																
		Critical					High						Medium				Other	
		A. baumannii	*E. coli*[b]	*K. pneumoniae*[b]	*Enterobacter* spp.[b]	*M. tuberculosis*	*Salmonella* spp.	*Shigella* spp.	*E. faecium*	*P. aeruginosa*	*N. gonorrhoeae*	*S. aureus*	Group A Streptococci	*S. pneumoniae*	*H. influenzae*	Group B Streptococci	*C. difficile*	OMIP[a]
Small molecule - direct acting	35 (38.5)	2				21				1	4	2		1			2	2
Small molecule - indirect acting	14 (15.4)					1				7	2	4						
Peptide - direct acting	4 (4.4)			1		3												
Large molecule - direct acting	6 (6.6)			1		1				2							1	1
Large molecule - indirect acting	2 (2.2)										2							
Bacteriophage/ Bacteriophage products	22 (24.2)	2	5	3					1	6		5						
Biologic (Antibody or other biotherapeutic)	5 (5.5)	1	1							2		1						
Microbiome modifying agents	1 (1.1)									1								
Immunomodulators	2 (2.2)	1								1								
Total	91 (100)	6	6	5	0	26	0	0	1	20	8	12	0	1	0	0	3	3

BPPL: bacterial priority pathogen list; CR: carbapenem-resistant; 3GCR: third-generation cephalosporin-resistant; WHO: World Health Organization.

[a] Other medically important pathogens.

[b] Activity against CR and 3GCR isolates is not always disclosed, and so species activity is represented.

Table 13. Distribution of narrow-spectrum programmes by product type and WHO BPPL

Mode-of-Action Category	Total (%)	Bacterial Pathogen																
		Critical					High						Medium				Other	
		A. baumannii	*E. coli*[b]	*K. pneumoniae*[b]	*Enterobacter* spp.[b]	*M. tuberculosis*	*Salmonella* spp.	*Shigella* spp.	*E. faecium*	*P. aeruginosa*	*N. gonorrhoeae*	*S. aureus*	Group A Streptococci	*S. pneumoniae*	*H. influenzae*	Group B Streptococci	*C. difficile*	OMIP[a]
Anti-virulence	15 (16.5)		1			1				6	1	4						2
Cell wall synthesis - BL and/or BLI	0																	
Cell wall synthesis - Other	9 (9.9)					6					2							1
Central metabolism	5 (5.5)					3				1							1	
Direct membrane effect	25 (27.5)	2	3	4					1	8		6					1	
DNA replication/ synthesis	4 (4.4)	1	1	1						1								
Protein synthesis	3 (3.3)					3												
RNA synthesis	2 (2.2)					2												
Immunomodulation	4 (4.4)	2									2							
Other cellular function	11 (12.1)		1			6				2	1						1	
Potentiator or Enabling agent	4 (4.4)									2	1	1						
Decolonization	0																	
Not disclosed	4 (4.4)	1				2					1							
Unknown	5 (5.5)					3						1		1				
Total	91 (100)	6	6	5	0	26	0	0	1	20	8	12	0	1	0	0	3	3

BL: β-lactam; BLI: β-lactamase inhibitor; BPPL: bacterial priority pathogen list; CR: carbapenem-resistant; MoA: mode of action; 3GCR: third-generation cephalosporin-resistant; WHO: World Health Organization.

[a] Other medically important pathogens.

[b] Activity against CR and 3GCR isolates is not always disclosed, and so species activity is represented.

Fig. 18 shows the results of an analysis of trends in narrow-spectrum programmes across the four preclinical pipeline reviews. The percentage of the total number of programmes has remained relatively stable since 2019, fluctuating between 37% and 45%. The two dominant pathogens against which most narrow-spectrum products are directed have remained the same over the four pipeline analyses. Products targeting *P. aeruginosa* have fluctuated between 18% and 23%, whereas for *M. tuberculosis* the range has been significantly wider, with a high of 43% in 2019 and a low of 21.1% in 2021.

Preclinical development in the context of global AMR burden

In 2022, the *Lancet* published a landmark study *(101)* (known as the GRAM study) estimating the global mortality burden either directly attributable to, or associated with, pathogens resistant to antibacterial drugs. The data gathered from this analysis of the preclinical pipeline were evaluated in relation to the global burden of disease to assess whether the antibacterial R&D ecosystem was truly addressing global needs (Fig. 19).

Limitations of this analysis include the fact that several of the pathogens included in the global burden of disease study are not listed in the WHO BPPL (Fig. 19). Consequently, programmes with activity against these species may not have been submitted by the programme sponsors to the WHO preclinical data call (see section 7.2 on the preclinical pipeline review methodology). Further, many developers may not have evaluated activity against a full panel of bacterial species and, therefore, may not have reported activity for this analysis. However, two observations of this analysis are (i) that there are fewer agents with activity against *S. pneumoniae* given the burden of mortality, although this may be impacted by the large focus on preventative immunization for this species, and (ii) that there is significant effort in the pipeline to develop agents (broad and narrow spectrum) against *P. aeruginosa* despite its ranking sixth in the burden of mortality study.

The analysis and assessment of the preclinical pipeline relies largely on data submitted by the respective developers through the open WHO data call. Data were thoroughly cleaned and, where available, other sources were used for additional information, or the developer was contacted to clarify or fill gaps in the submission. In the absence of clinical data as well as detailed data on the different molecules in development, no independent assessment was undertaken with respect to the bacterial targets or the innovativeness of individual projects. This review should be considered as a snapshot and not a complete analysis. WHO expects to hold another open WHO data call for the next preclinical pipeline review and encourages wide participation.

Fig. 18. Analysis of narrow-spectrum programmes across four consecutive preclinical pipeline reviews

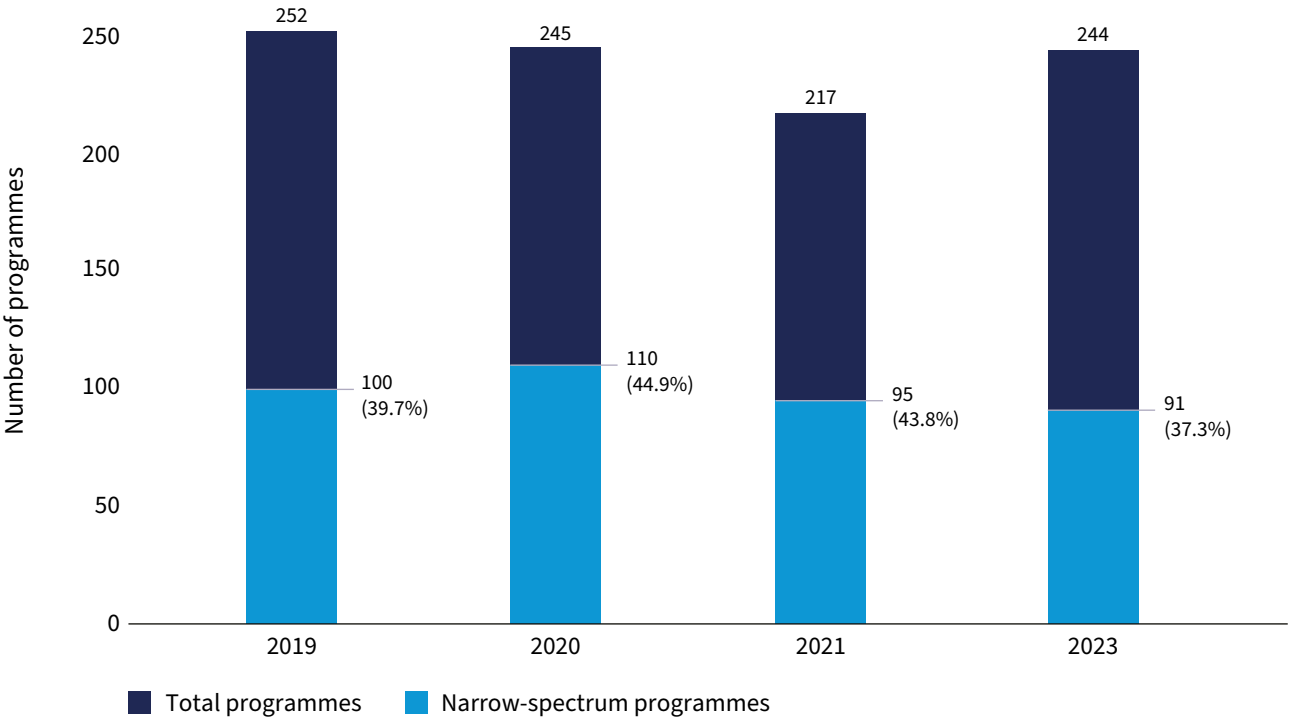
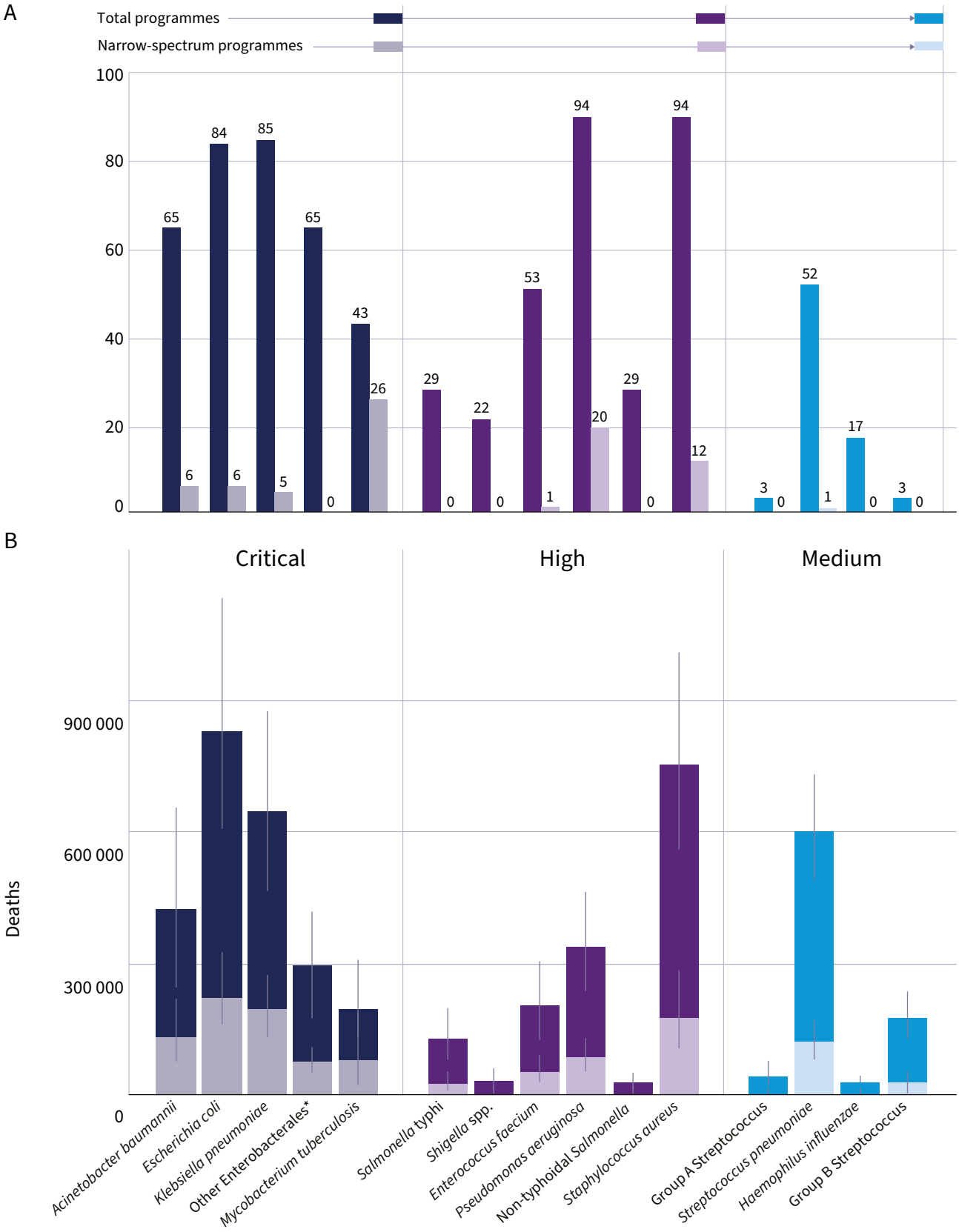


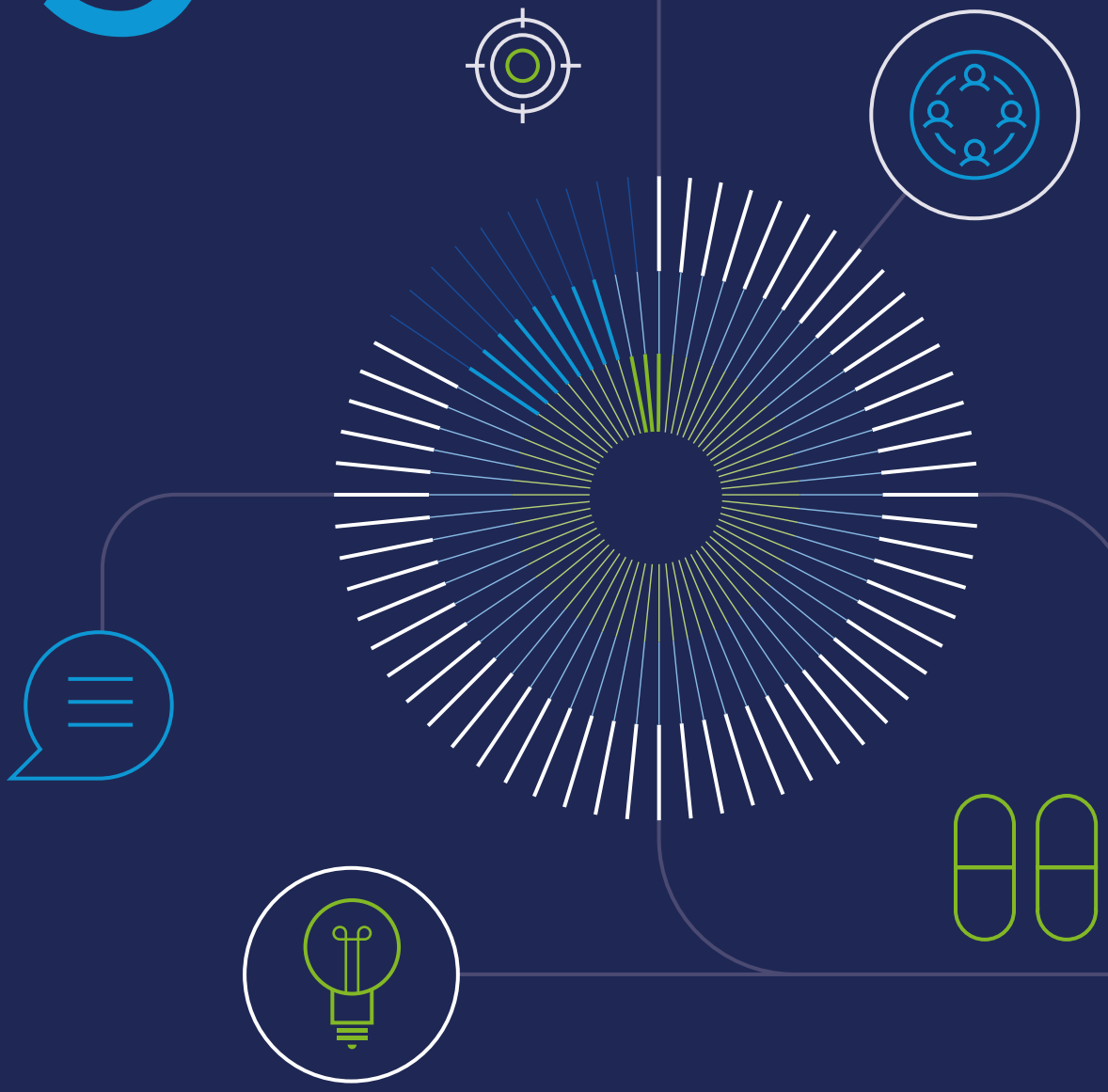
Fig. 19. Analysis of the bacterial spectrum of the total and species-specific programmes from the 2023 pipeline analysis (panel A) in the same order as the organisms associated with the largest global mortality burden (panel B)



Source: GRAM study (*Lancet*, 2022) (101).

Note: The order of the pathogens is the same in both panels and the colour-coding is based on the 2024 WHO BPPL category. In panel B: The light bars represent the number of attributable deaths to AMR, while the darker bars are the number of associated deaths to AMR. One pathogen (*N. gonorrhoeae*) ranked as "high" by WHO was not included in the GRAM study and therefore is not included in this comparison.

5



Discussion

5. Discussion

5.1 Newly approved agents against BPPs: progress made, but more is needed to address critical priority pathogens

5.1.1 Innovation

Antibiotics approved since 2017 show a limited degree of innovation. Only two of the approved agents are considered innovative, representing a new chemical class, while more than 80% of recently approved agents are derivatives of known classes to which multiple resistance mechanisms already exist. Having no newly authorized agents with a new MoA or addressing a new target underlines the scientific and technical challenge in discovering novel compounds that are both effective against bacteria and safe for humans. In the field of antibacterial R&D, effectively combatting the emergence of drug resistance stands as a primary challenge. However, this critical issue remains inadequately addressed by newly authorized agents. When assessing the absence of cross-resistance, nearly all compounds exhibit cross-resistance with other agents, while inconclusive data are associated with two compounds: vaborbactam in combination with meropenem, and lefamulin.

5.1.2 Activity assessment

In terms of indications, most authorized antibacterials are intended to treat cUTI, cIAI, CABP/HABP and/or ABSSSI. Although the 2022 GLASS analysis reported high levels of resistance in pathogens frequently causing hospital-associated BSI, few antimicrobial agents in the pipeline still include BSI as a foreseen indication. Data on bacteraemia must be provided in the context of the primary infection under investigation for a candidate antibacterial agent.

When evaluating the target of antibiotics approved since 2017, a gap is evident in products addressing Gram-negative bacteria, in particular CRAB and CRPA.

> Given that only six products have been authorized to combat critical bacterial pathogens that cause drug-resistant infections with the highest rates of mortality and morbidity, new products are urgently needed.

Most (seven out of 13) of the newly approved antibiotics are classified as Reserve according to the WHO 2023 Access, Watch Reserve (AWaRe) classification *(102)*, while three are in the Watch group. Contezolid and the combination sulbactam + durlobactam have not been evaluated yet but are likely to fall within the Reserve group, like drugs of their class. This confirms that the vast majority of newly approved antibacterials will be considered last-resort antibiotics, to be used only when previous treatment lines have failed. The tendency of Reserve antibiotics to prompt development of resistance through their use emphasizes the pressing need to establish a continuous reserve of innovative antibacterials designed to combat WHO priority pathogens. These should ideally possess the capability to overcome multiple bacterial resistance mechanisms while enabling optimal therapy.

5.1.3 The access challenge

When newly authorized products receive their first marketing authorization, say from the FDA or EMA, they still face significant access challenges even in the same geographic area where the product is authorized. From a recent analysis of a large database of hospitals (619) in the USA, researchers found that prescribers in settings with relatively high difficult-to-treat resistant Gram-negative infections are slow to adopt new therapies that are accessible to them. This is due, at least in part, to a lack of available susceptibility testing, poor evidence of efficacy generalizable to the hospitalized population with resistant Gram-negative infections, lack of hospital reimbursement and lack of perceived added benefit of new agents *(103)*.

At the same time, low- and middle-income countries face significant challenges in accessing newly registered reserve antibiotics, according to the 2023 access to medicines report *(104)*. This is mainly because new antibiotics are predominantly developed in high-income countries (section 3, Fig. 9) and are subsequently introduced into these countries with established unmet needs and antibiotic stewardship protocols *(105)*. Furthermore, LMICs often face recurring shortages of these new antibiotics once they are registered, due to high costs and fragile, fragmented antibiotic supply chains *(106)*. Satisfactory access to the full armamentarium of marketed antibiotics may also be limited in high-income countries. As pointed out by a recent publication, only three of the 14 high-income countries under study had access to the 18 new antibacterial agents identified by the authors *(107)*. In the EU, marketing authorization is not always followed by commercial availability in every state, with no significant difference in access between "innovative" and "noninnovative" antibacterials *(107)*.

A further issue limiting the clinical use of new antibiotics is that policymakers may lack sufficient data to make informed decisions about the selection of necessary antibiotics.

Post-approval usage data is needed for newly approved antibiotics to evaluate real-life pathogen-specific indications and the relevance of their use in different countries and populations.

5.2 Traditional antibacterials under development: still a long way towards an optimized armamentarium of therapeutic agents

5.2.1 Innovation

Of the 32 traditional antibiotics under development against BPPs (excluding TB drugs), 12 meet at least one of the four WHO innovation criteria; only two meet all four criteria. Of these 12, only four are active against a critical Gram-negative bacterium; none of them meet all four innovation criteria. The traditional antibacterial pipeline lacks sufficient innovation (see section 3.1).

The TB pipeline contains 19 candidates and has significantly progressed in the last decade, showing a good degree of innovation with several agents that are promising candidates for potential new treatment strategies against drug-resistant *M. tuberculosis*. Several candidates are in development with new targets and MoAs that could potentially optimize patient treatment and increase tolerability. However, there is still a high unmet medical need for efficacious treatment regimens against XDR-TB (people with MDR-TB with additional resistance to fluoroquinolones and at least one other group A drug, e.g., bedaquiline, linezolid) *(85,108)*.

Overall there are five traditional products in the pipeline for CDI, four of which are considered innovative, with two agents, ridinilazole and CRS3123, that address all four innovation criteria. All agents seem to have favourable pharmacokinetic/pharmacodynamic (PK/PD) profiles, and narrow-spectrum activity selective for *C. difficile* with no negative effect on the gut microbiota composition. Most of them inhibit *C. difficile* sporulation and toxin production, and all carry the potential for more effective and safer therapies compared to SOC.

Only one agent against *H. pylori* is currently under clinical development. Although not addressing any of the WHO innovation criteria, the drug is the first product developed specifically for *H. pylori* infection.

5.2.2 Activity assessment

The number of antibiotics with sufficient evidence of activity against WHO critical pathogens increased from 12 out of 34 agents targeting BPPs (35%) in 2017 to 18 out of 32 (56%) in 2023 (Fig. 5). This important achievement may be due, at least in part, to publication of the first WHO BPPL in 2017, which may have directed developers towards difficult-to-treat pathogens. However antibacterial agents in clinical development do not sufficiently address the problem of extensively or pan-drug-resistant Gram-negative bacteria. In particular, CRAB and CRPA continue to be insufficiently addressed. Since the last update, only two new products which have entered the clinical pipeline target CRAB (OMN6 and the combination of meropenem + ANT3310), one product selectively targets CRPA (murepavadin), and four agents target CRE. All are combinations of DBO-BLI/PBP2 binder + β-lactam. The number of traditional agents with confirmed extended-spectrum (both Gram-positive and Gram-negative) was quite small in both 2017 and 2023 (zero vs two) (Fig. 4). Three additional agents (RECCE 327, BWC0977 and OMN6) do show potential broad-spectrum activity, but at present data are insufficient for a sound conclusion.

Opinions currently differ regarding the pros and cons of extended-spectrum antibiotics. These drugs are crucial to providing timely and efficacious empiric therapy in critical situations and emergencies regardless of the bacterial phenotype; but their uncontrolled wide use also runs the risk of hampering stewardship efforts, damaging the microbiota and rapidly promoting resistance. If this trend is confirmed in the following years, regulatory agencies will probably need to set the scene for safe development of these agents together with clear indications and limitations on use.

The proportion of oral medications has decreased from 47% (*n* = 16/34) in 2017 to 37% (*n* = 12/32) (Fig. 6). In particular, the 2023 pipeline lacks oral antibiotic treatment options for ESBL-producing bacteria and CRE. Such options could enable treatment outside of a health care facility or reduce the duration of iv treatment within such a facility. No agents for oral use figure among the new entries since the last update, bringing the total number of oral traditional agents that target CRE/3GCRE to four of 15 products currently under development. A growing number of reported cases of patients with cUTI caused by ESBL bacteria has been observed, not only in patients who acquired the infection outside a hospital but also in pregnant women with bacteriuria and simple UTI. Bacteraemia caused by ESBL-producing Enterobacterales in hospital is usually resistant to current oral medicines but can be cured with iv antibacterial treatment. Having new oral and iv/oral switch options would allow patients to be discharged without the need for home iv therapy. However, only three antibacterials targeting CRE and/or 3GCRE have both iv and oral formulations – sulopenem, apramycin[11] and gepotidacin.

> Oral formulations for antimicrobials are needed that allow earlier hospital discharge and facilitate outpatient treatment.

Only one carbapenem (benapenem, Phase 2) and one penem (sulopenem, Phase 3) are currently being evaluated in late-stage clinical development against ESBL-producing infections. In addition, two β-lactam/BLI combinations (cefepime + taniborbactam and cefepime + enmetazobactam) have submitted an NDA/MAA to the FDA and to the FDA and EMA, respectively, for treatment of ESBL-producing Enterobacterales infection that could spare the use of carbapenems. Optimally, new antibacterial drugs to treat ESBL-producing Enterobacterales infection would not increase carbapenem resistance; but this is difficult to achieve, especially when new agents are so often in the same broad class as the carbapenems.

A further gap in the pipeline is the scarce number of clinical trials informing paediatric indications. PIPs/paediatric study plans are generally submitted to regulatory agencies in the late phase of development. Today, the majority of Phase 3 traditional drugs in the pipeline have no approved PIP. In addition, the few PIPs approved often grant a deferral that delays completion of the PIP and, thus, the availability of paediatric data. Based on this scenario, a considerable amount of time will be needed before extension of indication to the paediatric population will be granted for those new antibacterials that will progress to market *(109)*. This may encourage off-label use of antibiotics in children without sufficient data to correctly inform posology. Of note, suboptimal antibiotic dosing in children may result in toxicity or treatment failure and may drive AMR in both children and adults.

5.3 Non-traditional antibacterials: potential to fight AMR, but demonstration of the clinical impact of innovative approaches may be challenging

Non-traditional antibacterials could be used as an alternative to, or complementary and synergistic with, traditional antibacterial agents that are being pursued, and hold the potential to curb AMR. In the present scenario, where traditional products have a limited lifespan before resistance emerges, unconventional approaches could offer opportunities to tackle AMR from different angles.

Since the last report, three non-traditional agents have been approved, all for preventing recurrence of CDI following antibiotic treatment for recurrent CDI. The three non-traditional agents are the first microbiome-based drugs approved by regulatory authorities. The approval of these three agents represents a turning point in the authorization of non-traditional antibacterial agents.

Analysis of the clinical pipeline included 30 non-traditional antibacterials, with one agent at the NDA/MAA stage and three products at advanced clinical stages of development (Table 5). Non-traditional antibacterials encompass a variety of different approaches from phage and phage cocktails (*n* = 13) (the most represented category, which includes some clustered regularly interspersed short palindromic repeats (CRISPR)-based technology) to antibodies (*n* = 7), including some for biofilm disruption. Most common indications are prevention of CDI, pulmonary infection due to *P. aeruginosa* in patients with CF (*n* = 6) or without CF (*n* = 2), and PJI (*n* = 6). Drugs under current development are mostly narrow-spectrum agents, most of which target *S. aureus* and CDI. This selectivity confirms a trend also observed in the preclinical space. Narrow-spectrum agents require significant diagnostic availability for optimal use, which is often not available outside of specialized health care facilities and poses a

[11] PO only available in animals.

challenge in low-resource settings *(100,110)*. The 2023 pipeline also represents an increase in the number of broad-spectrum agents from zero to six, a trend similar to that observed among traditional antibacterials.

Since 2017, an encouragingly large increase has been observed in the number of non-traditional antibacterials intended for WHO CPPs (Fig. 7). However, most candidates are in early clinical stages, and it is likely that many of these will face development hurdles as/if they progress through the pipeline.

The path to conducting RCTs with non-traditional agents is still neither paved nor well worn. Regulators should engage with developers in defining how current clinical trial structures can support development of non-traditional agents. A crucial aspect to be addressed is understanding where, whether and how best to use these agents clinically.

5.4 Gaps and constraints in the current clinical R&D landscape

Traditional antibacterial agents under development still do not adequately address the enormous threat posed by AMR. Moreover, there is a major gap in developing products that address pathogens possessing a broad spectrum of resistance to current antibacterial agents.

Only two among authorized products and few among antibacterial agents under development address critical pathogens (CRAB, CRE, 3GCRE). Moreover, most of these agents belong to the same class of β-lactam/BLIs, and the added value they provide to the clinical toolbox against AMR might be partially limited by early development of cross-resistance.

Very few agents target MBLs, which continue to grow in prevalence.

Appropriate oral formulations for outpatient treatment along with optimized paediatric formulations are generally lacking across the entire clinical pipeline.

Through their diverse and novel MoAs, non-traditional antibacterials may have the potential to tackle AMR from different angles. However, it will be critical to demonstrate clinical impact for many of them. Most non-traditional agents under current clinical development are indirect-acting strategies that do not by themselves kill bacteria or affect bacterial growth. As such, these agents cannot use traditional MIC measurements as correlates of clinical outcome measures. Efforts should be devoted to identifying and validating proxies of activity on clinical outcomes.

A creative approach is needed for developing in vitro tests predictive of activity on clinical outcomes, which in most cases may require product-specific tests, further complicating the challenge. Whether current animal tests can predict the outcome of non-traditional treatments in humans remains unclear and should be further investigated.
A further challenge is posed by the development of appropriate safety testing tailored to the peculiar characteristics of non-traditional agents.

5.5 Preclinical pipeline

The preclinical pipeline is active and very dynamic, with 244 preclinical projects affiliated with 141 institutions. The number of preclinical candidates has generally remained stable over the last 4 years (Fig. 14).

The primary focus of the preclinical pipeline remains Gram-negative pathogens, although the shift towards narrow-spectrum agents targeting a single pathogen appears to have plateaued. Development of narrow-spectrum agents will also likely require increased use of rapid diagnostics both for patient stratification and enrolment during clinical trials. The use of diagnostics post-approval will also be key to ensure these narrow-spectrum products are used in the correct patients; otherwise, they may only be used as second-line therapy or in combination with other agents.

The preclinical pipeline remains innovative and includes many non-traditional approaches which may also require employment of innovative clinical trial designs. This is especially true for products that are likely to be used in combination with SOC drugs, as clear clinical benefit will need to be demonstrated.

While there is broad geographical distribution of preclinical pipeline projects as well as a large variety of product types, these are heavily focused towards Europe and the USA. With respect to the institutions and groups performing the work, the preclinical antibacterial pipeline continues to rely on micro (< 10 employees) and small (< 50 employees) entities and academic institutions to progress the science and development of innovative preventative and treatment products for drug-resistant infections. Analysis of the groups that had programmes in the preclinical antibacterial pipeline clearly indicates significant volatility in the R&D ecosystem. Over the 2019–2023 period 269 unique groups were included in the data analysis, yet only approximately 51 (19%) of these were listed in all four analyses, reflecting high turnover in this space.

Year-over-year analysis of the later stages of preclinical development indicated that while there was some progression of programmes, a significant number failed to progress meaningfully. This lack of progression may have several root causes, including scientific challenges, funding issues or even ongoing COVID-19-related impacts. Whatever the reason, the result is that despite a reasonable number of preclinical projects, the lack of significant progression in many of them since 2021 does serve to highlight the challenges that the ecosystem faces.

Greater transparency in the preclinical pipeline coupled with the clinical pipeline can lead to stronger collaboration around potentially innovative but challenging projects, support a community of scientists and drug developers and generate more interest and funding into drug development for novel antibacterial agents.

5.6 WHO 2024 BPPL changes and implications for R&D for novel antibacterial agents

The 2024 WHO BPPL represents a comprehensive assessment of the most critical bacterial species and phenotypes associated with acute antibiotic-resistant infections which are known to pose significant risks of mortality and morbidity.

Among the major changes in the 2024 BPPL, the critical group saw the separation of CRE and 3GCRE, reflecting the need for a tailored approach to address their specific challenges. Among the identified pathogens, Gram-negative bacteria continue to score highly, though there have been fluctuations in the ranking of some crucial nosocomial pathogens. *P. aeruginosa* moved from the critical to the high category; but, as noted in the BPPL report, it remains of paramount importance for R&D on new antibacterial agents.

Additionally, fluoroquinolone-resistant *Shigella* spp., responsible for community-associated infections, was moved from the medium to the high category. As noted in the BPPL report, this change indicates its growing resistance to existing treatment and its public health importance.

The 2024 BPPL report contains additions and removals as compared to the 2017 list. Group A streptococci, macrolide-resistant; group B streptococci, penicillin-resistant; and *S. pneumoniae*, macrolide-resistant were added to the prioritization framework to reflect emerging challenges in combatting resistance in these specific pathogens. At the same time, clarithromycin-resistant *H. pylori*, fluoroquinolone-resistant *Campylobacter* spp., penicillin-non-susceptible *S. pneumoniae* and vancomycin-intermediate and -resistant *S. aureus* have been removed. These updates highlight the dynamic nature of AMR.

The results of the 2023 exercise are reported in Box 1, and the major changes and implications for the R&D of new therapeutics are discussed below.

The 2024 WHO BPPL report serves as a critical tool in guiding global efforts to combat AMR. However, it is crucial to interpret these priorities while considering regional variations in pathogen prevalence and local context. With respect to R&D efforts, it is essential to consider the intended patient population for the final product and whether feasible clinical development and regulatory approval pathways exist.

The 2024 BPPL update is likely to impact future R&D strategies. Table 14 summarizes and expands on the implications of the key changes in the 2024 BPPL and their impact on for R&D, as reflected in the BPPL report.

Table 14. WHO 2024 BPPL changes and implications for R&D for novel antibacterial agents

Drug-resistant pathogen	Implications for R&D of therapeutics
CRAB is one of the top five pathogens associated with high mortality due to AMR and has been confirmed as a critical priority.	R&D efforts and investments should be concentrated on addressing the CRAB β-lactamase genotype, which predominantly contributes to its carbapenem resistance mechanisms (e.g., OXA-23, -24 and -51, -58). Carbapenem resistance is usually associated with cross-resistance with other antibiotic classes. R&D efforts and investments should explore antibiotics able to avoid this by using new MoA alternatives to β-lactamase inhibition.
CRE and 3GCRE top the BPPL ranking due to their widespread prevalence and resistance mechanisms. Infections caused by KPC-producing Enterobacterales, NDM and OXA-48 are associated with higher rates of treatment failure, increased health care costs and potentially worse clinical outcomes.	Prioritize the development of innovative and effective antibacterial agents to address CRE and 3GCRE, as they represent a significant burden among resistant Gram-negative bacteria. For an antibacterial active against CRE, activity against 3GCRE should also be tested to support the claim of activity against both. Oral options should also be prioritized for this group.
Fluoroquinolone-resistant *Shigella* spp. have become a high priority due to their significance in community infections and worrisome outbreaks among specific populations, demanding preventive strategies.	R&D efforts should target the development of broad-spectrum oral agents for symptomatic treatment of shigellosis. Additionally, preventive measures and strategies should be used and enhanced to contain the spread of this pathogen.
RR-TB. TB is a long-standing priority for WHO. RR-TB was included after an independent analysis with parallel criteria and subsequent application of an adapted MCDA matrix.	R&D should focus on the development of effective and safe treatments and regimens to address drug-resistant TB on a global scale. They should also be devoted to identifying appropriate therapeutic regimens for XDR-TB. Paediatric investigations in MDR-TB need to be accelerated.
CRPA was moved from critical to high priority status due to a global decline in resistance rates. *Pseudomonas* is significant cause of health-care-associated infection. It causes both severe acute and chronic infection, particularly in critically ill and immunocompromised patients. The biofilm formation is a key factor that increases drug resistance and escape from host defence and is responsible for colony tolerance to disinfectants on medical devices *(111)*.	Despite the decline in resistance rate, R&D should not deprioritize investment and efforts. Investment in R&D of innovative antibacterial agents against CRPA should be continued to address its fatal burden. In addition to innovative and effective antibiotics, non-traditional solutions could be explored, such as novel targets for anti-virulence strategies used as pre-emptive or adjunctive treatment in combination with traditional antibiotics *(112)*.

AMR: antimicrobial resistance; BPPL: bacterial priority pathogen list; CRAB: carbapenem-resistant *Acinetobacter baumannii*; CRE: carbapenem-resistant Enterobacterales; CRPA: carbapenem-resistant *Pseudomonas aeruginosa*; KPC: *Klebsiella pneumoniae* carbapenemase; MDR-TB: multidrug-resistant tuberculosis; MoA: mode of action; NDM: New Delhi metallo-β-lactamase; R&D: research and development; RR-TB: rifampicin-resistant tuberculosis; 3GCRE: third-generation cephalosporin-resistant Enterobacterales; WHO: World Health Organization.

6

Conclusion and policy implications to address the pipeline access crisis

6. Conclusion and policy implications to address the pipeline access crisis

Despite the critical role of antimicrobials in modern health care, the review of antibacterial agents in clinical and preclinical development reveals a glaring insufficiency in novel approaches in the R&D pipeline to effectively combat the increasing emergence and spread of AMR. The innovation, research and development of new antibacterials is led by small and medium enterprises in a system too costly and fragile to fully enable them to deliver. Furthermore, countries across all income levels struggle with availability and access to both new and authorized antibiotics, including generics. Recognizing the gravity of the situation, the Global Leaders Group on AMR, comprising world leaders, has emphasized the urgent need for both innovative financial and non-financial measures to address the serious antibiotic pipeline and access crisis *(113)*. The G7 leaders committed to enhancing G7 efforts to incentivize exploration and implementation of push and pull incentives to promote investment in R&D of antimicrobials and stimulate solutions that address the antimicrobial pipeline, and protect and work towards maximizing the effectiveness of existing antimicrobials *(114)*. In addition, the Council of the EU issued recommendations to strengthen EU action against AMR that include fostering R&D and providing incentives for innovation and access to antimicrobials *(115)*. Several countries within and outside the EU are piloting or developing different incentive models.

Antimicrobials – and antibiotics in particular – are a cornerstone of modern health care and are critical for effective health systems. As noted in this and many other reports, the R&D pipeline for new antibacterials with novel MoAs remains woefully insufficient. This gap needs to be urgently addressed by financial and non-financial incentives and efforts, which are globally aligned and coordinated.

Policy efforts on R&D and use should focus on financial and non-financial incentives and efforts to **optimize the use of authorized antibiotics, develop novel antibacterial agents and explore new fixed-dose combinations of antibiotics** for treating serious bacterial infections such as neonatal sepsis. Additionally, regulatory measures should be implemented to restrict the use of antibiotics to situations where they are strictly necessary, coupled with stewardship programmes that include avoiding over-the-counter selling and access to diagnosis at all levels including rapid, affordable diagnostic tests at point of care.

These efforts to support the R&D of pharmaceutical and non-pharmaceutical solutions to curb AMR need to be matched by equal efforts to ensure **global and equitable access, including in low- and middle-income countries**. Such access strategies should be sustainable, underpinned by stewardship programmes and strong, streamlined supply chains and strengthened regulatory systems to ensure safe use of antibiotics and maximum impact from R&D.

Efforts to regulate the availability of antibiotics in various parts of the world, including limiting their use in agriculture, hold significant potential to mitigate the AMR crisis.

As the battle against AMR intensifies, it is imperative that stakeholders collaborate and prioritize investments in research, development and implementation of comprehensive, multifaced strategies to combat AMR effectively. By doing so, the future of health care can be safeguarded and generations to come can be protected from the dire consequences of AMR.

7

Methods

7. Methods

The evaluation of antibacterial agents in clinical and preclinical development was conducted through a rigorous process led by the WHO Secretariat's pipeline team, in collaboration with the WHO advisory group on the R&D of antibacterial treatments. This advisory group consisted of highly qualified clinicians, microbiologists and experts well-versed in antibiotic R&D, PK/PD and AMR (see Acknowledgements for the complete list of members). To ensure a comprehensive and insightful evaluation, the experts were presented with pre-reading material meticulously prepared by the WHO Secretariat and soon after engaged in a pre-consultation survey encompassing both methodological and product-specific aspects. The formal consultation, held over a 2-day virtual advisory group meeting on 24–25 July 2023, provided a platform for in-depth discussions. Notably, during the consultation the advisory group reviewed and endorsed the newly developed assessment matrix, which served as a robust framework to methodically evaluate the potential activity of each agent (see section 7.1.3.1 on expected activity against BPPs).

To maintain the integrity of the process, members of the advisory group with potential conflicts of interest pertaining to specific companies or agents (as detailed in Annex 1) were excluded from relevant discussions to ensure impartiality and transparency. Prior to publication, the 2023 pipeline report was circulated among all members of the advisory group to solicit feedback, enabling refinement and improvements.

7.1 Clinical pipeline analysis

7.1.1 Scope and inclusion/exclusion criteria

This review covers new chemical entities, *traditional antibiotics* (i.e., direct-acting small molecules) and new biological entities, *non-traditional antibacterial agents* (i.e., peptides, antibodies, bacteriophages, lysins and live biotherapeutics, and oligonucleotides) in clinical (Phase 1, 2, 3 and NDA/MAA) and preclinical development worldwide that do not have marketing authorization for human use anywhere in the world as well as antibacterial agents that were approved after 1 July 2017. The review is restricted to antibacterial agents that could potentially be used to treat serious systemic bacterial infections caused by the WHO priority pathogens (Box 1), *C. difficile* and *H. pylori*.

Repurposed antibacterial agents are included in this review if the primary indication is in a therapeutic area different from infectious disease.

Fixed-dose combinations are included only if they contain a new chemical entity.

Traditional and non-traditional agents are further classified by structure and development goal (Table 15).

Table 15. Structure and development goals of traditional and non-traditional antibacterials

	Traditional	Non-traditional
Structure	Small molecule direct-acting agents.	Anything that is different from a small molecule. This includes antibodies, bacteriophages, lysins, live biotherapeutics, oligonucleotides, peptides etc. (see section 3.4 on non-traditional antibacterials)
Development goal	Treatment or prevention of bacterial infection through bacteriostatic (inhibition of growth) or bactericidal (killing) effect	Treatment or prevention of bacterial infections through other approaches that do not directly inhibit growth or kill bacteria: prevention of the development or spread of resistance, improving/restoring microbiome status and slowing the spread of resistance

Source: adapted from Rex et al. *(110)*.

The analysis does not include:

- vaccines;
- topical decolonizing agents;
- non-specific inorganic substances;
- biodefence agents;
- agents not developed for systemic use (injectable or oral formulations) or inhalation but only for topical application (e.g., creams or eye drops);
- new formulations of existing treatments; or
- extension of indication of already approved antibacterial agents.

Agents in active development or that have been approved since 1 July 2017 were included in the analysis. Agents that are not under active development and/or are no longer listed in a company's pipeline or for which there is no recent information are described in section 3.5 (Table 8).

WHO AB Pipeline analysis: exclusion criteria

The analysis does not include:


Vaccines


Topical decolonizing agent


Non-specific inorganic substances


Biodefence agents


New formulations


Extension of indication


Products not actively under development

7.1.2 Search strategy

This 2023 clinical pipeline update is based on the 2017 publication *Antibacterial agents in clinical development* and the subsequent updates in 2018, 2019, 2020 and 2021, which evolved over time (*116*,*117*,*118*,*1*). Since 2019, these publications have also included antibacterial agents in preclinical development and, from 2020, non-traditional agents in clinical and preclinical development, as well as an innovation assessment for traditional agents. In 2023 a new methodology to consistently perform the activity assessment was proposed by WHO and endorsed by the advisory group members (see section 7.1.3.1 on expected activity against BPPs).

The cut-off point was 31 December 2023, and no agents were added or removed after that date. All agents that met the inclusion criteria were included. Publications were cross-checked by compound name and synonyms (research numbers, international nonproprietary names (INNs) and brand names) to remove duplicates. Some data sources reported different phases of development in different countries or use for different indications. For these agents, the most advanced development phase was listed in this clinical pipeline update with a footnote.

Information on agents in development was sought from a variety of sources. The data for the analysis were collected from a variety of sources through desktop research as well as from relevant stakeholders, including different associations of pharmaceutical companies active in the area, global and regional public and private funders, and foundations (see Acknowledgements).

Sources were consulted as follows:

- A survey on antibacterial agents at clinical stage was proposed to drug developers through their pharmaceutical federations and associations such as the BEAM Alliance, BIO and IFPMA/AMR Industry Alliance. In addition, targeted outreach to individual companies was performed to gather additional data as needed.
- A WHO preclinical data call was launched from 6 March 2023 to 17 April 2023, inviting preclinical developers to submit their data (see section 7.2 on the preclinical pipeline review methodology).
- A literature review of peer-reviewed journal articles was performed using PubMed for traditional and non-traditional antibacterial agents (peer-reviewed articles published since 1 November 2021 through 10 October 2023, using the search terms: "antibacterial pipeline" OR "antibiotic pipeline", together with the pathogen name from the updated WHO BPPL).
- Conference abstracts and posters were collected from participation in conferences, from desktop searches or provided by developers.
- Clinical trial databases, including among others the WHO International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, EudraCT (European Union

Drug Regulating Authorities Clinical Trials Database) and ANZCTR[12] were also searched.

- A targeted desktop search of products was carried out with national experts such as developers in Japan and the Russian Federation.

In addition, a pre-survey was proposed to the advisory group and results were discussed during the consultation. For Phase 1 agents where limited data were available, information from company websites was used and evaluated by the advisory group for credibility of inclusion.

Agents developed for use against TB were first identified from published reviews, notably by the WHO TB Programme *(87)*, the Treatment Action Group *(108)* and the Stop TB Partnership, and a more comprehensive picture of TB drugs was subsequently developed with a greater degree of information reflected in the product profiles. Consultations were also performed with experts from the advisory group and the WHO TB programme.

Recommendations for developers

Register clinical trials and results

One of the main sources of data is the clinical trial registries; but not all trials are registered, and results of completed trials are not always published in a timely manner. Thus, all companies and institutions are encouraged to register clinical trials in line with the WHO *International standards for clinical trial registries*, including using a WHO primary registry or ClinicalTrials.gov and posting trial results on the registry entry no later than 12 months after study completion (https://www.who.int/news/item/09-04-2015-japan-primary-registries-network).

Ensure the company/start-up website is up to date

Maintaining a company/biotech/start-up website that is updated with references to registry entries and published peer-reviewed literature will help to more quickly identify new antibacterials.

Participate in the WHO preclinical data call and clinical survey

Providing accurate, updated and verifiable (by peer-reviewed publication) data to WHO will greatly contribute to accurate characterization of antibacterial agents under preclinical and clinical development, gain visibility and potentially attract more funds.

7.1.3 Assessment of activity against BPPs and innovation

Evidence for activity against WHO priority pathogens and innovation was retrieved from peer-reviewed publications. For agents in the early stages of development, information from presentations and posters at scientific conferences and information published by the developers was also used. Information was considered only if it was publicly available and scientifically sound, as reviewed by WHO and by the advisory group.

The evidence supporting expected activity increases with the development stage. The first level of evidence is usually gained by in vitro experiments. Subsequently, preclinical results are produced using animal disease models in the sought indication or in a broader one. Moving to the clinical phases, safety and tolerability data in healthy volunteers are usually generated followed by dose–response and efficacy data. Advanced in silico simulations are also used to support clinical and preclinical development. The WHO evaluation of antibacterial activity against priority pathogens is thus an evolving assessment that incorporates new pieces of information as they are made available during drug development.

7.1.3.1 Expected activity against BPPs

Both in vitro and in vivo data (as available) were reviewed for activity against WHO priority pathogens. The strength of evidence supporting the activity assessment is presented in Table 2, highlighting whether they are taken from peer-reviewed or not-peer-reviewed publications and whether they are based on in vivo or in vitro data (see column “Nonclinical data supporting the activity assessment”).

In the 2023 pipeline review, to standardize and define the expected products’ activity against priority pathogens, a revised matrix for assessing activity was proposed by the WHO Secretariat, then discussed and endorsed by the advisory group (Box 2).

[12] ANZCTR is an online registry of clinical trials being undertaken in Australia, New Zealand and elsewhere.

Box 2. Activity assessment matrix

Definition/symbol	Evidence required
Active •	**Peer-reviewed in vitro and in vivo data** or at least peer-reviewed in vitro data and not-peer-reviewed in vivo data or vice versa, if the MoA and/or the number of isolates tested support activity
Possibly active **?**	Not-peer-reviewed in vitro and in vivo data or company's website information; or only in vitro data without in vivo data
X **(previously "○")**	Not active
/	Activity not tested

- **For a new antibiotic belonging to an already established antibiotic class:** Activity against WHO priority pathogens was assessed by comparing the new antibiotic MIC data with susceptible MIC breakpoints for antibiotics of the same class, and taking into account in vitro susceptibility rates, PK/PD data in animals, clinical exposure levels and dose-limiting adverse effects, when available.
- To help distinguish between "active" and "possibly active", **two susceptibility thresholds** were proposed and endorsed: **> 60%** (possibly active) and **> 80%** (active). Susceptibility rates **< 60%** were assessed as inactive.
- **For first-in-class antibiotics:** Activity was assessed by comparing the new antibiotic MIC data and in vitro susceptibility rates with those of antibiotics with activity against the same pathogen and taking into account PK/PD data in animals, clinical exposure levels and dose-limiting adverse effects, when available.

7.1.3.2 Innovation

An agent was considered innovative if it had no (known) cross-resistance to existing antibiotics. In this context, cross-resistance is defined as within-class cross-resistance that can be measured by systematic susceptibility testing in vitro of a diverse panel of genetically defined pathogens, combined with genetic characterization of mutants and molecular structural analysis.

Surrogate predictors for the absence of cross-resistance which were also assessed include the following (*119*):

- new class (new scaffold);
- new target (new molecular binding site); and
- new MoA.

Each agent in clinical development or recently approved was evaluated against the four innovation criteria. If products do not meet the innovation criteria, it does not necessarily mean that they do not have clinical utility for specific patients. For example, a safety profile that improves on SOC, a less invasive route of administration (e.g., oral versus iv), better clinical outcomes or increased activity against priority pathogens could provide improvements but need to be proven in clinical trials. However, pharmaceutical optimization of existing products is not reviewed in this report.

7.2 Methodology of the preclinical pipeline review

7.2.1 Scope and inclusion criteria

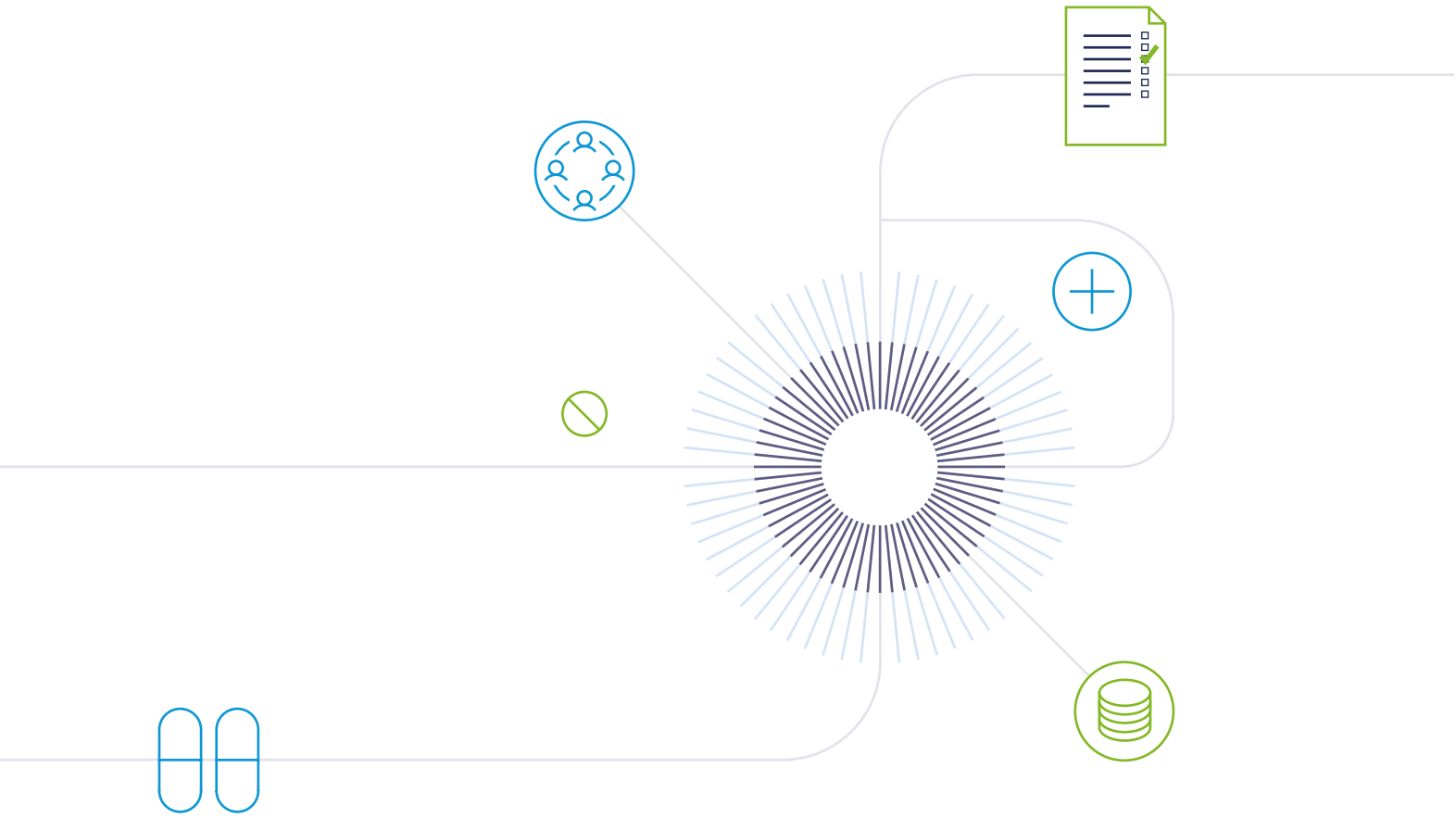
The review concentrated on antibacterial agents that target the WHO priority pathogens and *C. difficile* from lead optimization (post-hit expansion) to preclinical candidate and formal IND, also known as a Clinical Trial Application (CTA). This milestone signifies the start of human testing for regulatory bodies that do not use IND/CTA. The review covered both traditional and non-traditional approaches, including direct- and indirect-acting antibacterials, small and large molecules, anti-virulence agents and biofilm disruptors, potentiators, microbiome-modifying agents, immunomodulators, repurposed non-antibiotics and antibiotics from animal to human use, decolonization agents and combination therapies. The review did not include vaccines, diagnostics, antifungals, antivirals or anti-parasitics. Wound-care agents, unspecific supportive treatments, medical devices and industrial or animal use agents were also not included.

During this review it was noted that among the multiple groups exploring bacteriophage therapy, ongoing research reflected distinct strategies. In some cases, the goal was to develop a product that could be used to treat infections caused by a specific bacterial species across many patients. In contrast, other groups that were building a repository of well-characterized bacteriophages to be used on a patient-specific basis after susceptibility of their specific isolate had been demonstrated by screening against the repository. Where it was possible to distinguish the strategies, those programmes developing a library of bacteriophages to be stored and used to opportunistically screen isolates from individual patients for personalized treatment were omitted from the analysis.

7.2.2 Data collection

A WHO online data call was held during the first half of 2023 and generated the primary data. These data were supplemented with information from the Beam Alliance, BIO, CARB-X, Novo Repair Impact Fund and INCATE (INCubator for Antibacterial Therapies in Europe) among others. In addition, programmes from the 2021 analysis were checked through a desk review, and where required, updates were solicited by email. Data presented are self-declared from the institutions. Where possible, WHO confirmed the data through publications, conference abstracts or posters, institutional websites and other information in the public domain.

As the WHO BPPL was being updated throughout 2023, respondents were also given the opportunity to include products being developed against “other medically important bacterial pathogens” to provide additional flexibility during subsequent analyses.



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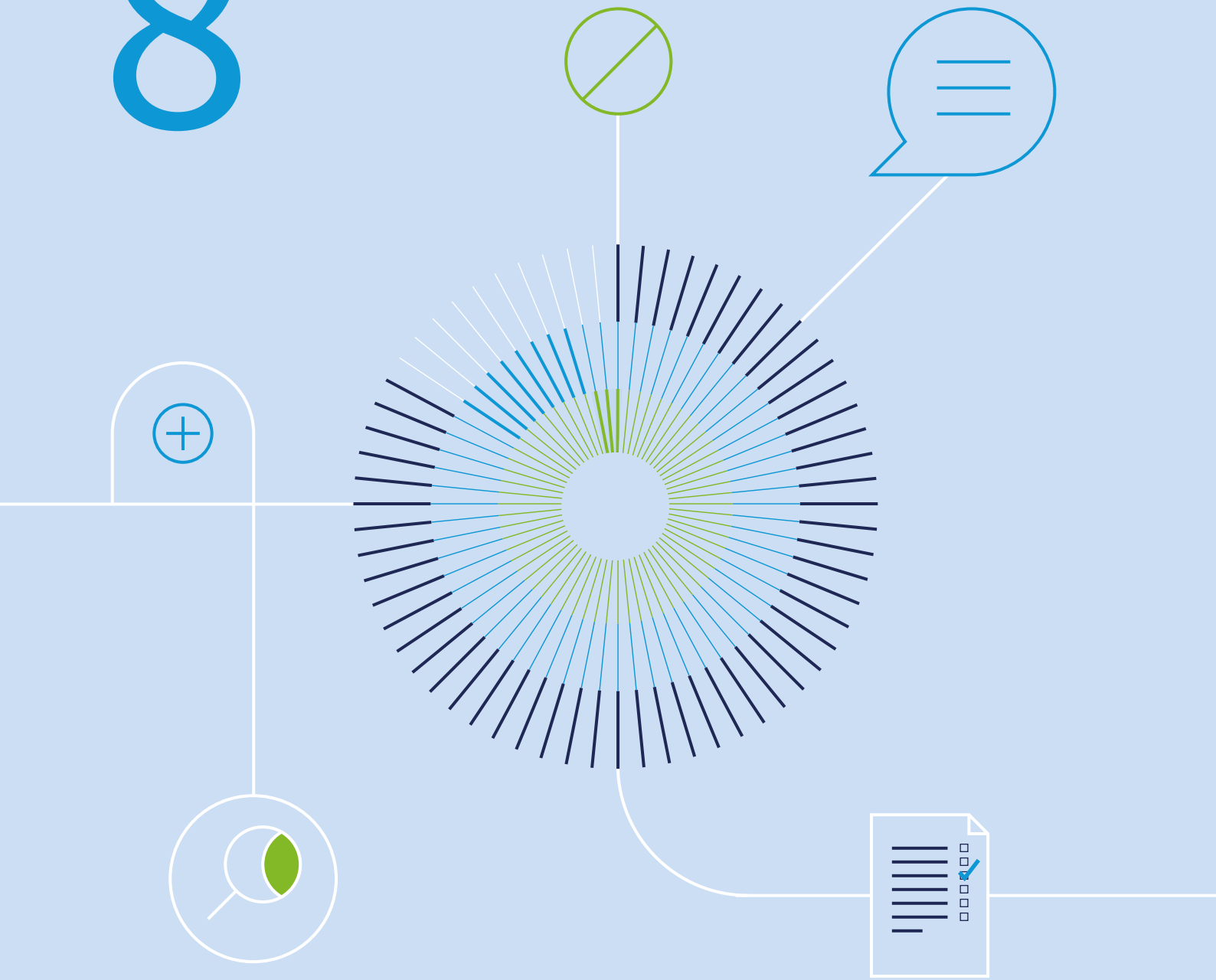


References

8. References

1. 2021 antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/354545, accessed 1 March 2024).
2. Antimicrobial resistance. In: WHO/Newsroom/Fact sheets [website]. Geneva: World Health Organization; 2023 (https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance, accessed 14 January 2024).
3. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629–55 (https://doi.org/10.1016/S0140-6736(21)02724-0, accessed 1 March 2024).
4. O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. London: Wellcome Foundation and UK Department of Health; 2014 (https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf, accessed 14 January 2024).
5. The One Health approach and key recommendations of the Quadripartite. In: WHO/Publications [website]. Geneva: World Health Organization; 2023 (chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://cdn.who.int/media/docs/default-source/universal-health-coverage/who-uhl-technical-brief-one-health.pdf?sfvrsn=353e9ad1_3&download=true, accessed 1 March 2024).
6. Global antimicrobial resistance and use surveillance system (GLASS) report 2022. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/364996, accessed 1 March 2024).
7. WHO Bacterial Priority Pathogens List, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. Geneva: World Health Organization; 2024.
8. O'Donnell JN, Lodise TP. New perspectives on antimicrobial agents: imipenem-relebactam. Antimicrob Agents Chemother. 2022;66(7):e0025622 (https://doi.org/10.1128/aac.00256-22, accessed 1 March 2024).
9. FDA approves new treatment for pneumonia caused by certain difficult-to-treat bacteria. In: FDA/press announcements [website]. Silver Spring (MD): US Food and Drug Administration; 2023 (https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-pneumonia-caused-certain-difficult-treat-bacteria, accessed 14 January 2024).
10. Shapiro AB, Moussa SH, McLeod SM, Durand-Réville T, Miller AA. Durlobactam, a new diazabicyclooctane β-lactamase inhibitor for the treatment of Acinetobacter infections in combination with sulbactam. Front Microbiol. 2021;12:709974 (https://doi.org/10.3389/fmicb.2021.709974, accessed 1 March 2024).
11. Highlights of prescribing information. XACDURO. In: FDA/Access data [website]. Silver Spring (MD); US Food and Drug Administration; 2023 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216974Orig1s000Correctedlbl.pdf, accessed 14 January 2024).
12. Alrahmany D, Omar AF, Alreesi A, Harb G, Ghazi IM. *Acinetobacter baumannii* infection-related mortality in hospitalized patients: risk factors and potential targets for clinical and antimicrobial stewardship interventions. Antibiotics (Basel). 2022;11(8):1086 (https://doi.org/10.3390/antibiotics11081086, accessed 1 March 2024).
13. Gaibani P, Bianco G, Amadesi S, Boattini M, Ambretti S, Costa C. Increased blaKPC copy number and OmpK5 and OmpK36 porins disruption mediated resistance to imipenem/relebactam and meropenem/vaborbactam in a KPC-producing *Klebsiella pneumoniae* clinical isolate. Appl Envir Microbiol. 2022 (https://journals.asm.org/doi/10.1128/aac.00191-22, accessed 18 February 2024).
14. Di Pilato V, Codda G, Niccolai C, Willison E, Wong JLC, Coppo E et al. Functional features of KPC-109, a novel 270-loop KPC-3 mutant mediating resistance to avibactam-based beta-lactamase inhibitor combinations and cefiderocol. Int J Antimicrob Agents. 2024;63(1):107030 (https://doi.org/10.1016/j.ijantimicag.2023.107030, accessed 1 March 2024).

15. VOWST Package insert. In: FDA/Media [website]. Silver Spring (MD): US Food and Drug Administration (https://www.fda.gov/media/167579/download?attachment, accessed 14 January 2024).

16. Rebyota Package insert. In: FDA/Media [website]. Silver Spring (MD): US Food and Drug Administration (https://www.fda.gov/media/163587/download, accessed 14 January 2024).

17. BiomeBank announces world first regulatory approval for donor derived microbiome drug. In: BiomeBank/News [website]. Thebarton, South Australia; 2022 (https://www.biomebank.com/news/media-release/biomebank-announces-world-first-regulatory-approval-for-donor-derived-microbiome-drug/, accessed 14 January 2024).

18. Branch S, Agranat I. "New drug" designations for new therapeutic entities: new active substance, new chemical entity, new biological entity, new molecular entity. J Med Chem. 2014;7(21):8729–65 (https://doi.org/10.1021/jm402001w, accessed 1 March 2024).

19. WHO Listed Authority (WLA). In: WHO/Initiatives [website]. Geneva: World Health Organization; 2024 (https://www.who.int/initiatives/who-listed-authority-reg-authorities, accessed 18 February 2024).

20. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017 (https://iris.who.int/handle/10665/311820, accessed 1 March 2024).

21. Antibacterial products in clinical development for propriety pathogens. In: WHO/Global Observatory on Health R&D [website]. Geneva: World Health Organization; 2017 (https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens-Sep-2017, accessed 14 January 2024).

22. Global burden of disease study 2019. Seattle: Institute for Health Metrics and Evaluation; 2019 (https://ghdx.healthdata.org/gbd-2019, accessed 30 January 2023).

23. Paediatric drug optimization for antibiotics: meeting report, 30 November, 5-7 December 2022. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/366533, accessed 1 March 2024).

24. World Bank country and lending groups. In: World Bank/Data [website]. Washington (DC): World Bank; 2024 (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups#:~:text=For%20the%20current%202024%20fiscal,those%20with%20a%20GNI%20per, accessed 14 January 2024).

25. How does the World Bank classify countries? In: World Bank/Data [website]. Washington (DC): World Bank; 2024 (https://datahelpdesk.worldbank.org/knowledgebase/articles/378834-how-does-the-world-bank-classify-countries, accessed 14 January 2024).

26. Tirlangi PK, Wanve BS, Dubbudu RR, Yadav BS, Kumar LS, Gupta A et al. Successful use of cefepime-zidebactam (WCK 5222) as a salvage therapy for the treatment of disseminated extensively drug-resistant New Delhi metallo-β-lactamase-producing *Pseudomonas aeruginosa* infection in an adult patient with acute T-cell leukemia. Antimicrob Agents Chemother. 2023;67(8):e0050023 (https://doi.org/10.1128/aac.00500-23, accessed 1 March 2024).

27. Rubin DHF, Mortimer TD, Grad YH. *Neisseria gonorrhoeae* diagnostic escape from a gyrA-based test for ciprofloxacin susceptibility and the effect on zoliflodacin resistnce: a bacterial genetics and experimental evolution study. Lancet Microb. 2023;4(4):E247–54 (https://doi.org/10.1016/S2666-5247(22)00356-1, accessed 14 February 2024).

28. Le Terrier C, Nordmann P, Sadek M, Poirel L. In vitro activity of cefepime/zidebactam and cefepime/taniborbactam against aztreonam/avibactam-resistant NDM-like-producing *Escherichia coli* clinical isolates. J Antimicrob Chemother. 2023;78(5):1191–4 (https://doi.org/10.1093/jac/dkad061, accessed 18 January 2024).

29. Li Y, Yan M, Xue F, Zhong W, Liu X, Chen X et al. In vitro and in vivo activities of novel β-lactamase inhibitor combination imipenem/XNW4107 against recent clinical Gram-negative bacilli from China. J Glob Antimicrob Resist. 2022;31:1–9 (https://doi.org/10.1016/j.jgar.2022.07.006, accessed 14 February 2024).

30. Fratoni AJ, Berry AV, Liu X, Chen X, Wu Y, Nicolau DP et al. Imipenem/funobactam (formerly XNW4107) in vivo pharmacodynamics against serine carbaprenemase-producing Gram-negative bacteria: a novel modelling approach for time-dependent killing. J Antimicrob Chemother. 2023;78(9):2343–53 (https://doi.org/10.1093/jac/dkad242, accessed 14 February 2024).

31. Zhang O, Yan W, Ahu Y, Jing N, Wang S, Yuan Y et al. Evaluation of commercial products for colistin and polymyxin B susceptibility testing for mcr-positive and negative *Escherichia coli* and *Klebsiella pneumoniae* in China. Infect Drug Resist. 2023;2023:1171–81 (https://doi.org/10.2147/IDR.S400772, accessed 14 February 2024).

32. De Bonaventura G, Lupetti V, Verginelli F, Giancristofaro S, Barbieri R, Gherardi G et al. Repurposing the veterinary antibiotic apramycin for antibacterial and antibiofilm activity against *Pseudomonas aeruginosa* from cystic fibrosis patients. Front Microbiol. 2022;12 (https://doi.org/10.3389/fmicb.2021.801152, accessed 14 February 2024).

33. Shortridge D, Rhomberg, Huband M, Castanheira M, Louvel S, Zampaloi C. In vitro activity of novel compound RG6006 against clinical isolates of *Acinetobacter baumannii*-calcoaceticus complex in the presence of 20% human serum. Presented at ECCMID, Copenhagen, Denmark, 15–18 April 2023; Poster P2173 (https://www.jmilabs.com/data/posters/ECCMID2023_RG6OO6.pdf, accessed 18 January 2024).

34. Bush K, Bradford P. β-Lactams and β-lactamase inhibitors: an overview. Cold Spring Harb Perspect Med. 2016;6(8) (https://doi.org/10.1101/cshperspect.a025247, accessed 1 March 2024).

35. Ambler R. The structure of beta-lactamases. Philos Trans R Soc L B Biol Sci. 1980;289(1036):321–31.

36. Potron A, Poirel L, Nordmann P. Emerging broad-spectrum resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: mechanisms and epidemiology. Int J Antimicrob Agents. 2015;45(6):568–85 (https://doi.org/10.1016/j.ijantimicag.2015.03.001, accessed 1 March 2024).

37. Papp-Wallace K, Bonomo R. New β-lactamase inhibitors in the clinic. Infect Dis Clin North Am. 2016;30(2):441–64 (https://doi.org/10.1016/j.idc.2016.02.007, accessed 1 March 2024).

38. Abbott C, Satola SW, Weiss DS. Heteroresistance to cefepime-taniborbactam in metallo-β-lactamase-encoding Enterobacterales. Lancet Infect Dis. 2023;23(8):E277–8 (https://doi.org/10.1016/S1473-3099(23)00426-7, accessed 14 February 2024).

39. Mushtaq S, Garello P, Vickers A, Woodford N, Livermore DM. Activity of cefepime/zidebactam (WCK 5222) against "problem" antibiotic-resistant Gram-negative bacteria sent to a national reference laboratory. J Antimicrob Chemother. 2021;76(6):1511–22 (https://doi.org/10.1093/jac/dkab067, accessed 14 February 2024).

40. Hagihara M, Kato H, Sugano T, Okade H, Sato N, Shibata Y et al. Pharmacodynamic evaluation of meropenem, cefepime, or aztreonam combined with a novel β-lactamase inhibitor, nacubactam, against carbapenem-resistant and/or carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* using a murine thigh-infection model. Int J Antimicrob Agents. 2021;57(5):106330 (https://doi.org/10.1016/j.ijantimicag.2021.106330, accessed 1 March 2024).

41. Hagihara M, Kato H, Sugano T, Okade H, Sato N, Shibata Y et al. In vivo pharmacodynamics of β-lactams/nacubactam against carbapenem-resistant and/or carbapenemase-producing Enterobacter cloacae and *Klebsiella pneumoniae* in murine pneumonia model. Antibiotics (Basel). 2021;10(10):1179 (http://doi.org/10.3390/antibiotics10101179, accessed 1 March 2024).

42. Karlowsky JA, Wisek MG, Hackel MA, Pevear DC, Moeck G, Sahm DF. Ceftibuten-ledaborbactam activity against multidrug-resistant and extended-spectrum-β-lactamase-positive clinical isolates of Enterobacterales from a 2018–2020 global surveillance collection. Antimicrob Agents Chemother. 2022;66(11):e00934-22 (https://doi.org/10.1128/aac.00934-22, accessed 18 January 2024).

43. Mushtaq S, Garello P, Vickers A, Woodford N, Livermore DM. Activity of ertapenem/zidebactam (WCK 6777) against problem Enterbacterales. J Antimicrob Chemother. 2022;77(10):2772–8 (https://doi.org/10.1093/jac/dkac280, accessed 14 February 2024).

44. Bush K. Game changers: new β-lactamase inhibitor combinations targeting antibiotic resistance in Gram-negative bacteria. ACS Infect Dis. 2018;4(2):84–7 (https://doi.org/10.1021/acsinfecdis.7b00243, accessed 1 March 2024).

45. Nowak P, Paluchowska P. *Acinetobacter baumannii*: biology and drug resistance – role of carbapenemases. Folia Histochem Cytobiol. 2016;54(2):61–74.

46. Pulzova L, Navratilova L, Comor L. Alterations in outer membrane permeability favor drug-resistant phenotype of *Klebsiella pneumoniae*. Microb Drug Resist. 2017;23(4):413–20 (https://doi.org/10.1089/mdr.2016.0017, accessed 1 March 2024).

47. Moradali M, Ghods S, Rehm B. Lifestyle: a paradigm for adaptation, survival, and persistence. Front Cell Infect Microbiol. 2017;7:39 (https://doi.org/10.3389/fcimb.2017.00039, accessed 1 March 2024).

48. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Crit Care. 2006;10(1):R27 (https://doi.org/10.1186/cc3995, accessed 1 March 2024).

49. Dawson RM, Liu CQ. Disulphide bonds of the peptide protegrin-1 are not essential for antimicrobial activity and haemolytic activity. Int J Antimicrob Agents. 2010;36(6):579–80 (https://doi.org/10.1016/j.ijantimicag.2010.08.011, accessed 1 March 2024).

50. Mishra B, Reiling S, Zarena D, Wang G. Host defense antimicrobial peptides as antibiotics: design and application strategies. Curr Opin Chem Biol. 2017;38:87–96 (https://doi.org/10.1016/j.cbpa.2017.03.014, accessed 1 March 2024).

51. Mandel S, Michaeli J, Nur N, Erbetti I, Zazoun J, Ferrari L et al. OMN6 a novel bioengineered peptide for the treatment of multidrug resistant Gram negative bacteria. Sci Rep. 2021;11(1):6603 (https://doi.org/10.1038/s41598-021-86155-9, accessed 1 March 2024).

52. Werneburg M, Zerbe K, Juhas M, Bigler L, Stalder U, Kaech A et al. Inhibition of lipopolysaccharide transport to the outer membrane in *Pseudomonas aeruginosa* by peptidomimetic antibiotics. Chembiochem. 2012;13(12):1767–75 (https://doi.org/10.1002/cbic.201200276, accessed 1 March 2024).

53. Amponnawarat A, Chompunud Na Ayudhya C, Ali H. Murepavadin, a small molecule host defense peptide mimetic, activates mast cells via MRGPRX2 and MrgprB2. Front Immunol. 2021;12:689410 (https://doi.org/10.3389/fimmu.2021.689410, accessed 1 March 2024).

54. Zampaloni C, Mattei P, Bleicher K, Winther L, Thäte C, Bucher C et al. A novel antibiotic class targeting the lipopolysaccharide transporter. Nature. 2024;625:566–71 (https://doi.org/10.1038/s41586-023-06873-0, accessed 1 March 2024).

55. Grossman T. Tetracycline antibiotics and resistance. Cold Spring Harb Perspect Med. 2016;6(4):a025387 (https://doi.org/10.1101/cshperspect.a025387, accessed 1 March 2024).

56. Lye SC. From molds to molecules: the development of tetracycline antibiotics and the transformation of the pharmaceutical industry, 1943–1963 [thesis]. Cambridge (MA): Harvard University; 1998.

57. Wangkheimayum J, Paul D, Dhar D, Nepram R, Chetri S, Bhowmik D et al. Occurrence of acquired 16S rRNA methyltransferase-mediated aminoglycoside resistance in clinical isolates of Enterobacteriaceae within a tertiary referral hospital of northeast India. Antimicrob Agents Chemother. 2017;61(6):e01037-16 (https://doi.org/10.1128/AAC.01037-16, accessed 2 March 2024).

58. Rex J, Outterson K. Plazomicin EU marketing application is withdrawn: near zero market value of newly approved antibacterials. In: AMR.Solutions/Newsletters [website]. London: Wellcome Trust; 2020 (https://amr.solutions/2020/07/11/plazomicin-eu-marketing-application-is-withdrawn-near-zero-market-value-of-newly-approved-antibacterials/, accessed 14 February 2024).

59. Withdrawal of Zemdri (Plazomicin) 500 mg/10ml injection. In: EMA/Medicines [website]. Amsterdam: European Medicines Agency; 2020 (https://www.ema.europa.eu/en/documents/withdrawal-letter/withdrawal-letter-zemdri_en.pdf, accessed 14 February 2024).

60. Svetlov MS, Koller TO, Meydan S, Shankar V, Klepacki D, Polacek N et al. Context-specific action of macrolide antibiotics on the eukaryotic ribosome. Nat Commun. 2021;12(1):2803 (https://doi.org/10.1038/s41467-021-23068-1, accessed 1 March 2024).

61. Hansen JL, Ippolito JA, Ban N, Nissen P, Moore PB, Steitz TA. The structures of four macrolide antibiotics bound to the large ribosomal subunit. Mol Cell. 2002;10(1):117–28 (https://doi.org/10.1016/s1097-2765(02)00570-1, accessed 1 March 2024).

62. Dinos G. The macrolide antibiotic renaissance. Br J Pharmacol. 2017;174(18):2967–83 (https://doi.org/10.1111/bph.13936, accessed 1 March 2024).

63. Zhanel G, Walters M, Noreddin A, Vercaigne L, Wierzbowski A, Embil J et al. The ketolides: a critical review. Drugs. 2002;62(12):1771–1804 (https://doi.org/10.2165/00003495-200262120-00006, accessed March 2024).

64. Fàbrega A, Madurga S, Giralt E, Vila J. Mechanism of action of and resistance to quinolones. Microb Biotechnol. 2009;2(1):40–61 (https://doi.org/10.1111/j.1751-7915.2008.00063.x, accessed 1 March 2024).

65. Morgan H, Lipka-Lloyd M, Warren AJ, Hughes N, Holmes J, Burton NP et al. A 2.8 Å structure of zoliflodacin in a DNA cleavage complex with *Staphylococcus aureus* DNA gyrase. Int J Mol Sci. 2023;24(2):1634 (https://doi.org/10.3390/ijms24021634, accessed 1 March 2024).

66. Payne D, Miller W, Berry V, Brosky J, Burgess W, Chen E et al. Discovery of a novel and potent class of FabI-directed antibacterial agents. Antimicrob Agents Chemother. 2002;46(10):3118–24 (https://doi.org/10.1128/AAC.46.10.3118-3124.2002, accessed 1 March 2024).

67. Yao J, Maxwell J, Rock C. Resistance to AFN-1252 arises from missense mutations in *Staphylococcus aureus* enoyl-acyl carrier protein reductase (FabI). J Biol Chem. 2013;288(51):36261–71 (https://doi.org/10.1074/jbc.M113.512905, accessed 1 March 2024).

68. Yao J, Rock C. Resistance mechanisms and the future of bacterial enoyl-acyl carrier protein reductase (FabI) antibiotics. Cold Spring Harb Perspect Med. 2016;6(3):a027045 (https://doi.org/10.1101/cshperspect.a027045, accessed 1 March 2024).

69. Araújo-Bazán L, Ruiz-Avila LB, Andreu D, Huecas S, Andreu JM. Cytological profile of antibacterial FtsZ inhibitors and synthetic peptide MciZ. Front Microbiol. 2016;7:1558 (https://doi.org/10.3389/fmicb.2016.01558, accessed 1 March 2024).

70. Kusuma KD, Payne M, Ung AT, Bottomley AL, Harry EJ. FtsZ as an antibacterial target: status and guidelines for progressing this avenue. ACS Infect Dis. 2019;5(8):1279–94 (https://doi.org/10.1021/acsinfecdis.9b00055, accessed 1 March 2024).

71. Koh AJJ, Thombare V, Hussein M, Rao GG, Li J, Velkov T. Bifunctional antibiotic hybrids: a review of clinical candidates. Front Pharmacol. 2023;14:1158152 (https://doi.org/10.3389/fphar.2023.1158152, accessed 1 March 2024).

72. Ma Z, Lynch AS. Development of a dual-acting antibacterial agent (TNP-2092) for the treatment of persistent bacterial infections. J. Med. Chem. 2016;59(14):6645–57 (https://doi.org/10.1021/acs.jmedchem.6b00485, accessed 1 March 2024).

73. Livermore DDM, Mushtaq S, Warner M, Zhang J, Maharjan S, Doumith M et al. Activities of NXL104 combinations with ceftazidime and aztreonam against carbapenemase-producing Enterobacteriaceae. Antimicrob Agents Chemother. 2011;55(1):390–94 (https://journals.asm.org/doi/10.1128/AAC.00756-10, accessed 14 February 2024).

74. Alm R, Johnstone M, Lahiri S. Characterization of *Escherichia coli* NDM isolates with decreased susceptibility to aztreonam/avibactam: role of a novel insertion in PBP3. J Antimicrob Chemother. 2018;70(5):420–28 (https://doi.org/10.1093/jac/dku568, accessed 1 March 2024).

75. Shields R, Doi Y. Aztreonam combination therapy: an answer to metallo-β-lactamase–producing Gram-negative bacteria? Clin Infect Dis. 2020;71:1099–1101 (https://doi.org/10.1093/cid/ciz1159, accessed 1 March 2024).

76. Trebosc V, Kemmer C, Lociuro S, Gitzinger M, Dale G. Rifabutin for infusion (BV100) for the treatment of severe carbapenem-resistant *Acinetobacter baumannii* infections. Drug Discov Today. 2021;26(9):2099–2104 (https://doi.org/10.1016/j.drudis.2021.07.001, accessed 1 March 2024).

77. Phillips M, Wald-Dickler N, Loomis K, Luna B, Spellberg B. Pharmacology, dosing, and side effects of rifabutin as a possible therapy for antibiotic-resistant Acinetobacter infections. Open Forum Infect Dis. 2020;7(11):ofaa460 (https://doi.org/10.1093/ofid/ofaa460, accessed 1 March 2024).

78. Luna B, Trebosc V, Lee B, Bakowski M, Ulhaq A, Yan J et al. A nutrient-limited screen unmasks rifabutin hyperactivity for extensively drug-resistant *Acinetobacter baumannii*. Nat Microbiol. 2020;5(9):1134–43 (https://doi.org/10.1038/s41564-020-0737-6, accessed 1 March 2024).

79. Trebosc V, Schellhorn B, Schill J, Lucchini V, Bühler J, Bourotte M et al. In vitro activity of rifabutin against 293 contemporary carbapenem-resistant *Acinetobacter baumannii* clinical isolates and characterization of rifabutin mode of action and resistance mechanisms. J Antimicrob Chemother. 2020;75(12):3552–62 (https://doi.org/10.1093/jac/dkaa370, accessed 1 March 2024).

80. Eckburg PB, Muir L, Critchley IA, Walpole S, Kwak H, Phelan AM et al. Oral tebipenem pivoxil hydrobromide in complicated urinary tract infection. N Engl J Med. 2022;386(14):1327-1338 (https://doi.org/10.1056/NEJMoa2105462, accessed 1 March 2024).

81. Gordon EM, Duncton MAJ, Gallop MA. Orally absorbed derivatives of the β-lactamase inhibitor avibactam. Design of novel prodrugs of sulfate containing drugs. J Med Chem. 2018;61(22):10340–4 (https://doi.org/10.1021/acs.jmedchem.8b01389, accessed 1 March 2024).

82. Karlowsky JA, Hackel MA, Stone GG, Sahm DF. In vitro activity of ceftibuten-avibactam against β-lactamase-positive Enterobacterales from the ATLAS global surveillance program. Antimicrob Agents Chemother. 2023;67(1):e0134622 (https://doi.org/10.1128/aac.01346-22).

83. Sader HS, Carvalhaes CG, Huband MD, Mendes RE, Castanheira M. 1687. Antimicrobial activity of ceftibuten-avibactam against a global collection of Enterobacterales from patients with complicated urinary tract infections (2021). Open Forum Infect Dis. 2022;9(Suppl 2):9 (https://doi.org/10.1093/ofid/ofac492.1317, accessed 1 March 2024).

84. Pfizer product pipeline. In: Pfizer/Pipeline [website]. New York: Pfizer; 2024 (https://www.pfizer.com/science/drug-product-pipeline, accessed 14 January 2024).

85. Global tuberculosis report 2022. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/363752, accessed 1 March 2024).

86. Political declaration of the high-level meeting on the fight against tuberculosis: draft resolution / submitted by the president of the general assembly. In: United Nations/Digital library [website]. New York: United Nations; 2023 (https://digitallibrary.un.org/record/4022582?ln=en, accessed 14 January 2024).

87. TB research and innovation. In: Global tuberculosis report 2022 [website]. Geneva: World Health Organization; 2022 (https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-research-and-innovation, accessed 14 January 2024).

88. TBD09 (MK7762). In: Working Group on New TB Drugs/Pipeline. New York: Working Group on* New TB Drugs; 2024 (https://www.newtbdrugs.org/pipeline/compound/tbd09-mk7762, accessed 14 January 2024).

89. Czaplewski L, Bax R, Clokie M, Dawson M, Fairhead H, Fischetti V et al. Alternatives to antibiotics – a pipeline portfolio review. Lancet Infect Dis. 2016;16(2):239–51 (https://doi.org/10.1016/S1473-3099(15)00466-1, accessed 1 March 2024).

90. Theuretzbacher U, Piddock L. Non-traditional antibacterial therapeutic options and challenges. Cell Host Microbe. 2019;26(1):61–72 (https://doi.org/10.1016/j.chom.2019.06.004, accessed 1 March 2024).

91. Troisi M, Marini E, Abbiento V, Stazzoni S, Andreano E, Rappuoli R. A new dawn for monoclonal antibodies against antimicrobial resistant bacteria. Front Microbiol. 2022;13:1080059 (https://doi.org/10.3389/fmicb.2022.1080059, accessed 1 March 2024).

92. Motley M, Banerjee K, Fries B. Monoclonal antibody-based therapies for bacterial infections. Curr Opin Infect Dis. 2019;32(3):210–16 (https://doi.org/10.1097/QCO.0000000000000539, accessed 1 March 2024).

93. Dehbanipour R, Ghalavand Z. Anti-virulence therapeutic strategies against bacterial infections: recent advances. Germs. 2022;12(2):262–75 (https://doi.org/10.18683/germs.2022.1328, accessed 1 March 2024).

94. Summers W. The strange history of phage therapy. Bacteriophage. 2012;2(2):130–33 (https://doi.org/10.4161/bact.20757, accessed 1 March 2024).

95. Pirnay JP, Verbeken G. Magistral phage preparations: is this the model for everyone? Clin Infect Dis. 2023;77(Suppl 5):S360–9 (https://doi.org/10.1093/cid/ciad481, accessed 14 February 2024).

96. Cryan J, Dinan T. Talking about a microbiome revolution. Nat Microbiol. 2019;4(4):552–3 (https://doi.org/10.1038/s41564-019-0422-9, accessed 1 March 2024).

97. Smith L, Wissel E. Microbes and the mind: how bacteria shape affect, neurological processes, cognition, social relationships, development, and pathology. Perspect Psychol Sci. 2019;14(3):397–418 (https://doi.org/10.1177/1745691618809379, accessed 1 March 2024).

98. Viprey VF, Davis GL, Benson AD, Ewin D, Spittal W, Vernon JJ. A point-prevalence study on community and inpatient *Clostridioides difficile* infections (CDI): results from Combatting Bacterial Resistance in Europe CDI (COMBACTE-CDI), July to November 2018. Euro Surveill. 2022;27(26):2100704 (https://doi.org/10.2807/1560-7917.ES.2022.27.26.2100704, accessed 1 March 2024).

99. Sholeh M, Krutova M, Forouzesh M, Mironov S, Sadeghifard N, Molaeipour L et al. Antimicrobial resistance in Clostridioides (Clostridium) difficile derived from humans: a systematic review and meta-analysis. Antimicrob Resist Infect Control. 2020;9(1):158 (https://aricjournal.biomedcentral.com/articles/10.1186/s13756-020-00815-5, accessed 14 January 2024).

100. Bacterial vaccines in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/359172, accessed 1 March 2024).

101. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629-655 (https://doi.org/10.1016/S0140-6736(21)02724-0, accessed 1 March 2024).

102. AWaRe classification of antibiotics for evaluation and monitoring of use, 2023. In: WHO/Publications [website]. Geneva: World Health Organization; 2023 (https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04, accessed 14 January 2024).

103. Strich JR, Warner S, Lai YL, Demirkale CY, Powers JH 3rd, Danner RL et al. Needs assessment for novel Gram-negative antibiotics in US hospitals: a retrospective cohort study. Lancet Infect Dis. 2020 Oct;20(10):1172–81 (https://doi.org/10.1016/S1473-3099(20)30153-5, accessed 1 March 2024).

104. Martínez C. Companies have a collectively broad regulatory reach in LMICs, yet many essential products are not widely registered. In: Access to Medicine Foundation/Resource centre [website]. Amsterdam: Access to Medicine Foundation; 2023 (https://accesstomedicinefoundation.org/resource/companies-have-a-collectively-broad-regulatory-reach-in-lmics-yet-many-essential-products-are-not-widely-registered, accessed 14 February 2024).

105. 2021 update: antibiotic use in the United States: progress and opportunities. Atlanta (GA): Centers for Disease Control and Prevention; 2021 (https://www.cdc.gov/antibiotic-use/stewardship-report/2021.html, accessed 14 February 2024).

106. Kamere N, Rutter V, Munkombwe D, Aywak DA, Muro EP, Kaminyoghe F et al. Supply chain factors and antimicrobial stewardship. Bull World Health Organ. 2023;101(6):403–11 (https://dx.doi.org/10.2471/BLT.22.288650, accessed 14 February 2024).

107. Outterson K, Orubu ESF, Rex J, Årdal C, Zaman MH. Patient access in 14 high-income countries to new antibacterials approved by the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010–2020. Clin Infect Dis. 2022;74(7):1183–90 (https://doi.org/10.1093/cid/ciab612, accessed 1 March 2024).

108. McKenna L. Tuberculosis treatment pipeline report. New York: Treatment Action Group; 2022 (https://www.treatmentactiongroup.org/wp-content/uploads/2023/01/pipeline_TB_Treatment_2022_final.pdf, accessed 14 February 2024).

109. Paediatric drug optimization for antibiotics: meeting report, 30 November, 5–7 December 2022. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/366533, accessed 2 March 2024).

110. Rex J, Fernandez Lynch H, Cohen I, Darrow J, Outterson K. Designing development programs for non-traditional antibacterial agents. Nat Commun. 2019;10(1):3416 (https://doi.org/10.1038/s41467-019-11303-9, accessed 1 March 2024).

111. Reig S, Le Gouellec A, Bleves S. What is new in the anti-*pseudomonas aeruginosa* clinical development pipeline since the 2017 WHO alert? Front Cell Infect Microbiol. 2022;12:909731 (https://doi.org/10.3389/fcimb.2022.909731, accessed 1 March 2024).

112. Dickey SW, Cheung GYC , Otto M. Different drugs for bad bugs: antivirulence strategies in the age of antibiotic resistance. Nat Rev Drug Discov. 2017;16(7):457–71 (https://doi.org/10.1038/nrd.2017.23, 1 March 2024).

113. Global Leaders Group on Antimicrobial Resistance. Recommendations to address the antibiotic pipeline and access crisis in human health. In: AMR Leaders/ Resources [website]; 2024 (https://www.amrleaders.org/resources/m/item/glg-recommendations-to-address-the-antibiotic-pipeline-and-access-crisis-in-human-health, accessed 5 March 2024).

114. G7 Nagasaki Health Ministers' Communiqué. In: G7 2023 Hiroshima Summit [website]. Tokyo: Ministry of Health, Labour and Welfare; 2023 (https://www.mhlw.go.jp/content/10500000/001096403.pdf, accessed 14 January 2024).

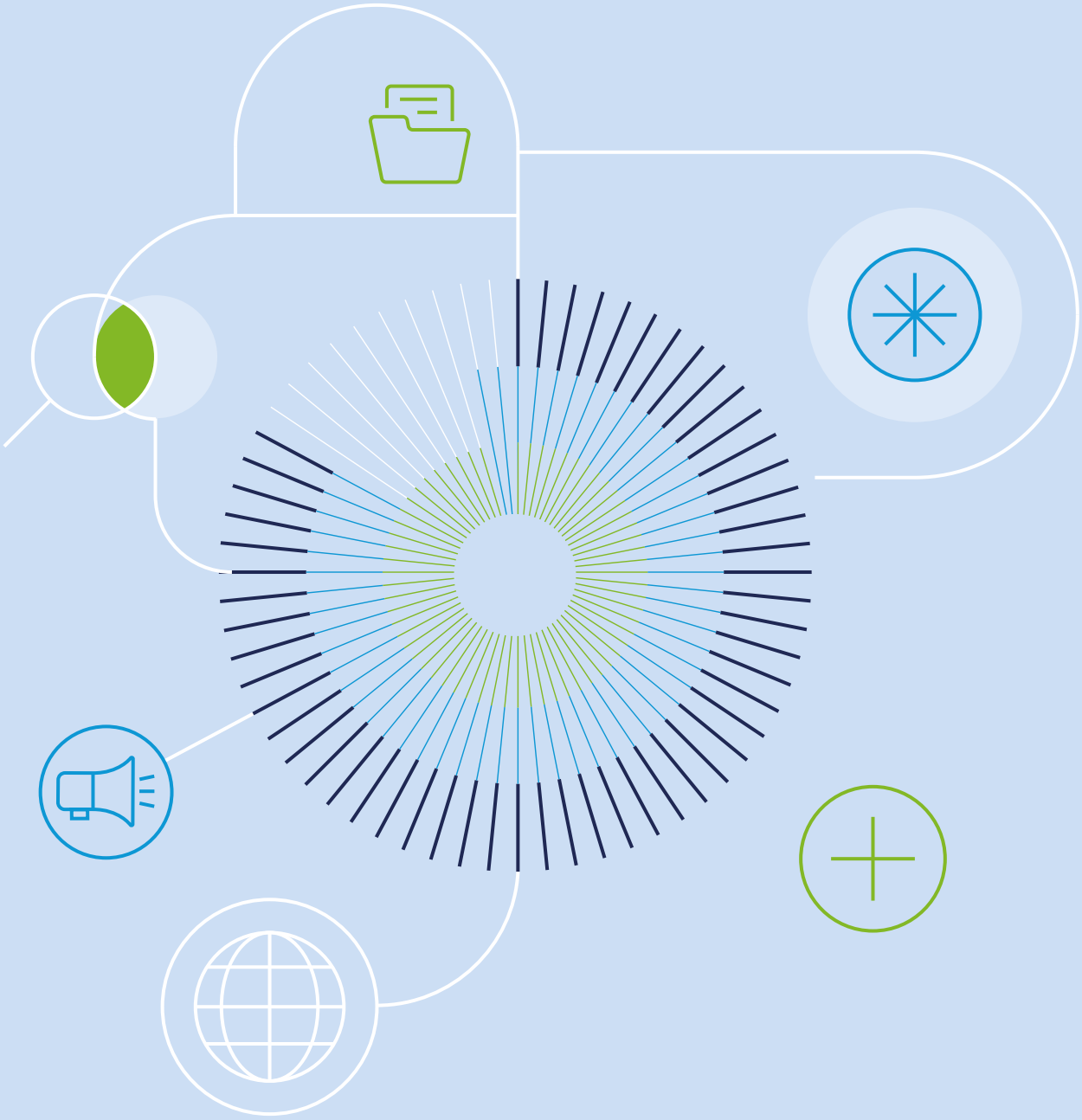
115. Council recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach. In: Council of the European Union [website]. Brussels: Council of the European Union; 2023 (https://data.consilium.europa.eu/doc/document/ST-9581-2023-INIT/en/pdf, accessed 14 January 2024).

116. Update on antibacterial agents in clinical development. Geneva: World Health Organization; 2018 (https://iris.who.int/handle/10665/275487, accessed 1 March 2024).

117. 2019 antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. Geneva: World Health Organization; 2019 (https://iris.who.int/handle/10665/330420, accessed 1 March 2024).

118. 2020 antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/340694, accessed 1 March 2024).

119. Theuretzbacher U, Gottwalt S, Beyer P, Butler M, Czaplewski L, Lienhardt C et al. Analysis of the clinical antibacterial and antituberculosis pipeline. Lancet Infect Dis. 2019;19(2):e40–50 (https://doi.org/10.1016/S1473-3099(18)30513-9, accessed 1 March 2024).



Annexes

Annex 1. Declaration of interests of advisory group members

Management of conflicts of interest was a priority throughout the analysis and decision-making for the antibacterial clinical and preclinical pipeline. The declarations of interest (DOIs) were collected and thoroughly reviewed by the WHO AMR Division following WHO standard operating procedures.

Prior to the advisory group meeting, all the experts submitted written disclosures of competing interests that had arisen during a period of 4 years preceding the WHO advisory work and that were relevant for consideration before their confirmation as participants in the meeting, including employment by a commercial entity, consultancy, board or advisory board membership, lecture fees, expert witness income, industry-sponsored grants (including contracted research, patents received or pending, royalties, stock ownership or options), other personal financial interests, as well as whether the institution or employer had a financial relationship with a commercial entity that had an interest in antibacterial products evaluated by the advisory group.

Experts were also asked to disclose academic or scientific activities that included leadership of research or grant applications, in either primary clinical studies or reviews, directly bearing on a decision about an antibacterial product. In addition, at the start of the meeting, all members were asked to provide updates about their declaration if any new conflicts had arisen in the meantime.

The experts who declared no potential conflicts of interest were Prabha Fernandes, Stephan Harbarth, Christian Lienhardt, Mical Paul and Norio Ohmagari. These experts were allowed full participation in the meeting.

The experts who disclosed potentially significant conflicts of interest were Cesar Arias, Lloyd Czaplewski, Roman Kozlov, John Rex and Lynn Silver.

Cesar Arias disclosed in his DOI that his former institution was awarded financial support more than 3 years previously from Merck Sharp and Dohme and Entasis Therapeutics.

Lloyd Czaplewski disclosed in his DOI that he provided consultancies and had been awarded financial support in the previous 4 years from Clarametyx, Novo Repair Impact Fund, Novo Holdings, Chemical Biology Ventures Ltd and Curza.

Roman Kozlov disclosed in his DOI that his research unit had been awarded financial support in the previous 4 years from Merck Sharp and Dohme, Pfizer and Astellas Pharma.

John H. Rex disclosed in his DOI having provided consulting services, received research grants/support, held shares or commercial interest in the previous 4 years from Basilea Pharmaceutica (SAB), Novo Holdings, Bugworks Research, Forge Therapeutics, Sumitovant, GlaxoSmithKline, AstraZeneca Pharmaceuticals, F2G, Advent Life Sciences, Iterum Therapeutics and Pfizer.

Lynn Silver reported in her DOI having provided consultancy, reviewed programmes or grants in the previous 4 years for Appili, Curza, Debiopharm, Forge, CDD-SPARK, Novo-Repair Fund and Dartmouth.

Following assessment of the DOIs, Cesar Arias, Lloyd Czaplewski, Roman Kozlov, John Rex and Lynn Silver were excluded from discussions involving products from commercial entities or other organizations listed above.

All reported interests were disclosed to the meeting participants by the technical unit in a slide show presentation; the interests are also disclosed in this report and in relevant publications.

Annex 2. Results from antibiotic paediatric development (PIPs)

To assess the potential of traditional late-stage clinical candidates to address severe drug-resistant infections in children and neonates, a survey and a search in the EMA PIP repository were conducted.

Results are summarized in Table A2.1.

Table A2.1. Paediatric development resulting from search of registries search and survey

INN (company code)	Phase	PIP	Registration Code	Date of completion of the PIP	CTs information retrieved from registries
Afabicin (Debio-1450)	2	Not found	no		
Aztreonam-Nacubactam (OP0595)	3	Not found	no		
Benapenem	2	Not found	no		
Cefepime (EXBLIFEP)+ Enmetazobactam (AAI-101)	NDA and MAA	Date of PIP Adoption 10 August 2022	NCT05826990	By September 2025	Single Group Phase 2 Study to Investigate Pharmacokinetics, Safety and Tolerability of Cefepime-Enmetazobactam Administered by IV Over 2 Hr in Male or Female Participants From Birth to Less Than 18 Years of Age Hospitalised With cUTI
Cefepime+ Nacubactam (OP0595)	3	Not found	no		
Cefepime + Taniborbactam (VNRX-5133)	MAA and NDA (EMA 1/23; FDA 8/2023)	Date of PIP Adoption 04/12/2020	no	By June 2027	No
Cefepime+Zidebactam (WCK 5222)	3	Date of PIP adoption 11 August 2021	no	Date of completion of the paediatric investigation plan: By July 2029	
Funobactam (XNW4107) + Imipenem + Cilastatin	3	Not found	no		
Gepotidacin	3	Date of PIP modification 28/10/2022	NCT04079790	By March 2028	A Phase 1, Double-Blind, Two-Part, Sequential Study to Evaluate the Pharmacokinetics of Gepotidacin Tablets in Healthy Adult and Adolescent (12 to <18) Participants. Completed 2019-11-25

Table A2.1 (continued). Paediatric development resulting from search of registries search and survey

INN (company code)	Phase	PIP	Registration Code	Date of completion of the PIP	CTs information retrieved from registries
Nafithromycin (WCK-4873)	3	Not found	no		
Solithromycin (T-4288)	NDA	Date of PIP adoption 15/07/2016	NCT02268279	By August 2016	A Phase 1, Open-label, Multi-center Pediatric study to Determine the Pharmacokinetics and Safety of Solithromycin (oral and intravenous) as Add-on Therapy in Adolescents and Children, ages 0 to 17, with Suspected or Confirmed Bacterial Infection. Completed 2016.
			NCT01966055		A Phase 1, Open-label, Multi-center Study to Determine the PK and Safety of Solithromycin as Add-on Therapy in Adolescents With Suspected or Confirmed Bacterial Infection. A study of the safety and PK of solithromycin capsules in adolescents from 12 to 17 years old. Completed September 2014
			NCT02605122		A Phase 2/3, Randomized, Open-Label, Multi-center Study to Determine the Safety and Efficacy of Solithromycin in Adolescents and Children With Suspected or Confirmed Community-Acquired Bacterial Pneumonia. Completed March 21, 2018
Sulopenem; Sulopenem Etzadroxil/Probenecid	3	Not found	NCT04700787		A Phase 1, Multi-Center, Open-Label Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Sulopenem and Sulopenem Etzadroxil + Probenecid in Adolescent Patients (12-18 years) With Bacterial Infection
TNP-2092	2	Not found	no		
Zoliflodacin	3	Date of PIP modification 9 September 2022	no	By June 2024	No

CT: clinical trial; cUTI: complicated urinary tract infection; INN: international nonproprietary name; MAA: Marketing Authorization Application; NDA: New Drug Application; PIP: paediatric investigational plan; PK: pharmacokinetics.

Annex 3. Cell wall inhibitors – β-lactams and BLIs

Product name (INN or company code): cefepime + enmetazobactam (AAI-101) (EXBLIFEP)

Pharmacology: chemical class and MoA: Enmetazobactam is a serine BLI derivative of tazobactam with enhanced bacterial cell penetration, being studied in combination with the fourth-generation cephalosporin, cefepime.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: Activity against ESBL-producing cephalosporin-resistant Enterobacterales and some CRE (Class A). In vitro data *(1,2,3)*; in vivo data: neutropenic murine thigh infection models *(4,5)*. No reported cross-resistance.

Sought therapeutic indication: Cefepime + enmetazobactam is being studied as an empiric carbapenem-sparing treatment for cUTI. Potential to be an empiric option for treating Gram-negative pathogens in endemic settings with a high incidence of ESBL-producing Enterobacterales.

Pharmaceutical form, route of the administration and proposed posology: Intravenous, as a q8h 2 h infusion of enmetazobactam 500 mg and cefepime 2 g, for 7–14 days

Phase of clinical development: 3

Clinical trial(s):

- **Phase 3:** Randomized, double-blind, non-inferiority clinical trial comparing the efficacy and safety of enmetazobactam (0.5 g) + cefepime (2 g) with tazobactam (0.5 g) + piperacillin (4 g) in the treatment of cUTI, including AP (NCT03687255) *(6)*.
  - **Study population:** 1041 adult patients with clinical signs and/or symptoms of cUTI or AP due to a Gram-negative pathogen determined to be non-resistant to intervention drugs were randomized 1:1 to either treatment.
  - **Time period:** 24 September 2018 to 15 February 2020.
  - **Sites:** 115 sites in 19 countries (located in Central and South America, EU, South Africa, USA).
  - **Primary end-point:** The composite successful outcome of clinical cure (symptom resolution) and microbiological eradication (< 103 CFU/mL in urine culture) at TOC: 7 days after end of treatment (EOT) (± 2 days).
  - **Primary efficacy evaluation** was performed in the microbiologic-modified intent-to-treat (micro-MITT) population for patients infected with a Gram-negative pathogen determined to be non-resistant to enmetazobactam + cefepime (MIC ≤ 8 mg/L) and piperacillin + tazobactam (MIC ≤ 64 mg/L). Of note, the study was completed prior to the change in the Clinical and Laboratory Standards Institute (CLSI) piperacillin + tazobactam breakpoints in 2022 and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints in 2021 *(7,8)*, both of which established lower breakpoints for piperacillin + tazobactam. Therefore, the primary analysis included a certain number of patients in the control arm who were resistant to the study comparator. A 10% non-inferiority margin was prespecified with superiority to be tested in the event of confirmed non-inferiority.

Product name (INN or company code) cefepime + enmetazobactam (AAI-101) (EXBLIFEP) (continued)

- **Study results** *(6,9)*: Among the primary analysis set, 79.1% (*n* = 273/345) of patients receiving cefepime + enmetazobactam met the primary outcome compared with 58.9% (196/333) of patients receiving piperacillin + tazobactam (between-group difference, 21.2% (95% CI: 14.3–27.9), indicating that cefepime + enmetazobactam was non-inferior to piperacillin + tazobactam.

  A post hoc analysis was performed that excluded patients with a baseline pathogen piperacillin + tazobactam MIC of greater than 8 µg/mL, accounting for the new piperacillin + tazobactam breakpoints (susceptible, ≤ 8 µg/mL). In this analysis, the primary outcome occurred in 79.1% (*n* = 250/316) of patients treated with cefepime + enmetazobactam compared with 60.3% (*n* = 182/302) in the piperacillin + tazobactam group (treatment difference, 18.8% (95% CI: 11.6–25.7); P < .001) *(6,9)*.

  Cefepime + enmetazobactam also met the criterion for superiority compared with piperacillin + tazobactam; however, results on superiority were driven by a significantly higher rate of microbiological eradication compared with piperacillin + tazobactam (82.9% (*n* = 286/345) vs 64.9% (*n* = 216/333); treatment difference, 19.0% (95% CI: 12.3–25.4)) at day 14. There was no significant difference in the clinical cure rate between the two groups (n = 319/345 (92.5%) for the cefepime + enmetazobactam group and *n* = 296/333 (88.9%) for the piperacillin + tazobactam group at day 14; treatment difference, 3.5% (95% CI: –1.0 to 8.0)).

  Additionally, among 142 patients (20.9%) with ESBL-producing pathogens at baseline, cefepime + enmetazobactam was more effective than piperacillin + tazobactam for the primary end-point (difference, 30.2% (95% CI: 13.4–45.1)).

Adverse events: TEAEs occurred in 50.0% (*n* = 258/516) of patients treated with cefepime + enmetazobactam and 44.0% (*n* = 228/518) with piperacillin + tazobactam; most were mild to moderate in severity (89.9% vs 88.6%, respectively). The most common TEAE was elevation of liver function parameters: alanine aminotransferase (11.4% vs 11.6%), aspartate aminotransferase (9.1% vs 8.9%) and blood bilirubin (5.8% vs 3.9%). A total of 1.7% (*n* = 9/516) of participants who received cefepime + enmetazobactam and 0.8% (*n* = 4/518) of those who received piperacillin + tazobactam did not complete the assigned therapy due to adverse events.

Product name (INN or company code): sulopenem

Pharmacology: chemical class and MoA: β-Lactam, synthetic penem (cell wall synthesis inhibition).

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: Activity against Class A ESBL-producing cephalosporin-resistant Enterobacterales (but not CRE); also active against Class C cephalosporinases from a variety of strains. However, sulopenem was not stable against most Class D oxacillinases (in vitro data *(10,11,12)*; in vivo poster data in neutropenic mouse thigh infections against clinical strains of *S. pneumoniae* and *K. pneumoniae* *(10,13)*. Cross-resistance with existing carbapenems has been reported *(10,11,13,14)*; in vivo poster data in neutropenic mouse thigh infections show activity against clinical strains of *S. pneumoniae* and *K. pneumoniae* *(13)*. Cross-resistance with existing carbapenems has been reported *(14)*.

Sought therapeutic indication: Sulopenem is being evaluated for treatment of uUTI (oral), cUTI and cIAI (iv/oral prodrug) due to Enterobacterales, including ESBL producers. The drug is intended to reduce or shorten hospitalization of patients treated for some MDR Gram-negative bacteria by providing a step-down oral therapy option *(14)*.

Pharmaceutical form, route of administration and proposed posology in Phase 3 trials: Intravenous/oral prodrug. The oral formulation is an ester prodrug; when administered with probenecid, absorption of sulopenem increases by 62%.

Proposed posology in uUTI: 500 mg PO bid for 5 days.

Proposed posology in cUTI and cIAI: 1000 mg iv once daily for at least 5 days, followed by sulopenem-etzadroxil/probenecid 500 mg PO bid for 7–10 days.

Product name (INN or company code): sulopenem (continued)

Phase of clinical development: 3

Clinical trial(s): Sulopenem has been evaluated as a treatment for uUTI, cUTI and cIAI, in a series of Phase 3 RCTs that labelled sulopenem for resistant Enterobacterales (SURE 1 through 3) (NCT03354598, NCT03357614, NCT03358576).

- **Sulopenem SURE 1 Phase 3 study** (NCT03354598): A prospective, multicentre, double-blind, randomized study that compared the efficacy and safety of oral sulopenem-etzadroxil 500 mg/probenecid 500 mg bid for 5 days with oral ciprofloxacin 250 mg bid for 3 days for the treatment of uUTI in adult females.
  - **Study population:** 1671 adult female patients were randomized and parallelly assigned to receive either treatment. Patients had to present within 24 h to ≤ 96 h of at least two uUTI symptoms/signs, plus a midstream urine specimen positive for nitrite and/or evidence of pyuria, and no signs or symptoms suggestive of AP.
  - **Time period:** 1 August 2018 to 20 January 2020.
  - **Sites:** 60 sites located in 14 states of the USA.
  - **Primary efficacy end-point** was the composite successful outcome of clinical success (symptom resolution and no new symptoms) and microbiological success (defined as eradication of the baseline pathogen) at the TOC visit on day 12.
  - **Primary efficacy evaluation:** Superiority was tested in the quinolone-non-susceptible micro-MITT population. Non-inferiority was tested in the quinolone-susceptible micro-MITT population.
  - **SURE 1 trial results** (*15*): Sulopenem demonstrated superiority to ciprofloxacin in female patients with quinolone-resistant pathogens at baseline with an overall response rate at TOC visit of 62.6% (*n* = 92/147 patients) in the sulopenem arm compared with 36% (*n* = 50/139 patients) in the ciprofloxacin arm, for a percentage difference of 26.6% (95% CI: 15.1–37.4; P < 0.001).
  - However, sulopenem was found not to be non-inferior to ciprofloxacin in patients with organisms susceptible to quinolones, with an overall response rate at TOC visit of 66.8% (*n* = 247/370 patients) in the sulopenem arm compared with 78.6% (*n* = 326/415 patients) in the ciprofloxacin arm, for a percentage difference of 11.8% (95% CI: –18.0 to –5.6; P < 0.001). The developer attributed this difference in outcome to the lower rates of asymptomatic bacteriuria in patients receiving ciprofloxacin (3.9%) compared with those receiving sulopenem (12.7%) and called for further research on the influence of asymptomatic bacteriuria on the assessment of outcome of treatment of uUTI.
  - **Adverse events** (sulopenem-etzadroxil/probenecid 500 mg PO bid for 5 days): Diarrhoea was the most reported adverse event, affecting almost 12% of patients (*n* = 103/883 in the sulopenem arm) receiving the drug, of whom 6.8% (*n* = 60/883) had clinically significant diarrhoea. The overall number of diarrhoeal episodes reported was 781, with a median duration of 3 days. Other side effects reported included nausea, headache, vomiting and dizziness.
- **Sulopenem SURE 2 Phase 3 study** (NCT03357614): A prospective, multicentre, double-blind, double-dummy, randomized, non-inferiority study that compared the efficacy and safety of sulopenem iv once daily for 5 days followed by sulopenem-etzadroxil/probenecid bid vs ertapenem iv 1000 mg once daily followed by oral ciprofloxacin 500 mg or amoxicillin-clavulanate 875 mg bid, for the treatment of cUTI in adults.
  - **Study population:** 1395 adults hospitalized cUTI patients, presenting with pyuria, bacteriuria and over 24 h of clinical signs and symptoms of cUTI during the previous 72 h, were randomized and parallelly assigned to either treatment. The main exclusion criterion was the record of an ertapenem-resistant organism isolated from patient's urine within the last year. Duration of treatment was to be 7–10 days. Treatment could be extended to 14 days for patients with bacteraemia at baseline.
  - **Time period:** 18 September 2018 to 14 December 2019.
  - **Sites:** The study took place in 32 sites located in Estonia, Georgia, Hungary, Latvia, USA.
  - **Primary efficacy end-point** used was the composite successful outcome of clinical success, and microbiological success at the TOC visit on day 21.
  - **Primary efficacy evaluation:** Non-inferiority was tested in the quinolone-susceptible micro-MITT population.

Product name (INN or company code): sulopenem (continued)

- **SURE 2 trial results** *(16)*: Sulopenem followed by oral sulopenem-etzadroxil/probenecid was not non-inferior to ertapenem followed by oral step-down therapy for treatment of cUTI, with a difference in outcome of –6.1% (95% CI: –12.0 to –0.1) using a non-inferiority margin of 10%. The developer showed that the difference was driven by a lower rate of asymptomatic bacteriuria among patients who received ciprofloxacin as oral step-down therapy.
- **Among** the approximately 40% of patients who had fluoroquinolone-resistant organisms, outcomes were numerically similar in the two treatment arms, independent of ESBL positivity.
- **Regulatory agency input:** The FDA required additional clinical studies to demonstrate further activity in the quinolone-resistant patient population in cUTI trials, and with additional agents for uUTI trials.
- **Adverse events in adults** (sulopenem 1000 mg iv once daily for at least 5 days, followed by sulopenem-etzadroxil/probenecid 500 mg PO bid for 7–10 days): Headache was the most reported adverse event, affecting 3% of patients (*n* = 21/695) receiving the drug, followed by diarrhoea (2.7%, *n* = 19/695) and nausea (1.3%, *n* = 9/695).

- **Sulopenem SURE 3 Phase 3 study** (NCT03358576): A prospective, multicentre, double-blind, randomized, non-inferiority study that compared the efficacy and safety of sulopenem 1000 mg iv once daily for 5 days, followed by a 500 mg tablet of sulopenem-etzadroxil/probenecid bid to complete 7–10 days of treatment, vs ertapenem 1000 mg iv once daily for 5 days, followed by oral ciprofloxacin 500 mg bid (or amoxicillin-clavulanate 875 mg bid, depending on the susceptibility of the baseline uro-pathogen), along with metronidazole 500 mg four times a day, in the treatment of cIAI in adults.
  - **Study population:** 674 cIAI adult patients were randomized and parallelly assigned to either treatment. Patients known to have a cIAI caused by pathogens resistant to the study's antimicrobial agents were excluded. Also excluded were patients diagnosed with intra-abdominal gastrointestinal organ perforation undergoing surgery within 12–24 h, patients with biliary infection without rupture, or simple appendicitis, or infected necrotizing pancreatitis or pancreatic abscess.
  - **Time period:** 18 September 2018 to 2 October 2019.
  - **Sites:** The study took place at 42 sites located in Bulgaria, Estonia, Georgia, Hungary, Latvia, Poland, USA.
  - **Primary efficacy end-point** was overall success (combined clinical and microbiological success) at TOC visit on day 28 in patients with positive intra-abdominal culture at baseline. Clinical outcome on day 28 was defined as cure for patients who were alive and showed resolution of signs and symptoms of the index infection, and for whom no new antibiotics or interventions for treatment failure were required.
  - **Primary efficacy evaluation:** Non-inferiority was tested in the micro-MITT population.
  - **SURE 3 trial results** *(17)*: Sulopenem was not non-inferior to the comparator (ertapenem), with a difference in outcome of 4.7% (95% CI: –10.3 to 1.0) using a non-inferiority margin of 10%.
  - **Adverse events** (sulopenem 1000 mg iv once daily for at least 5 days, followed by sulopenem-etzadroxil/probenecid 500 mg PO bid for 7–10 days): Treatment-related adverse events were reported in 6.0% and 5.1% of the 668 patients on sulopenem and ertapenem, respectively. Diarrhoea was the most reported adverse event, affecting 2.4% of patients receiving the drug. Serious adverse events unrelated to study treatment were seen in 7.5% of patients on sulopenem and 3.6% of patients on ertapenem.
- **Sulopenem REASSURE Phase 3 study** (NCT05584657, active): A Phase 3, randomized, multicentre, double-blind, double-dummy, controlled study to compare oral sulopenem etzadroxil/probenecid, 500 mg/500 mg PO bid for 5 days, to oral amoxicillin/clavulanate for 5 days, for the treatment of adult female patients with uUTI.
  - **Study population:** Approximately 1966 adult women with ≥ 24 h and ≤ 96 h of urinary symptoms attributable to a UTI, with pyuria, and without AP, will be randomized in a 1:1 fashion to either treatment.
  - **Time period:** 18 October 2022 to 31 March 2024.
  - **Sites:** 157 sites located in the USA.
  - **Primary efficacy end-point** will be the overall success (combined clinical and microbiologic success) on day 12 (± 1 day/TOC. Clinical success is defined as resolution of uUTI symptoms present at study entry and no new symptoms. Microbiologic success is defined as eradication of the baseline pathogen.
  - **Primary efficacy evaluation** will be conducted in three populations: micro-MITT participants, microbiologic-modified intent-to-treat susceptible (micro-MITTS) participants and microbiologic-modified intent-to-treat resistant (micro-MITTR) participants.

Product name (INN or company code): cefepime + taniborbactam (VNRX-5133)

Pharmacology: chemical class and MoA: β-Lactam/BLI combination. Taniborbactam (VNRX-5133) is a boronate-based BLI with activity against Class A, C and D β-lactamases, through reversible covalent inhibition (and slow dissociation). It also exerts action on MBL through competitive inhibition. Cefepime is a fourth-generation cephalosporin.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: Inhibitory activity against some CREs: Class A (ESBL CTX-M, KPC-2,-3 *(18,19)*; Class B (MBLs, especially NDM, not universal *(20,21)*; and VIM, not IMP *(22)*; heteroresistance described by Abbott et al. (2023) *(23)*; and Class D (OXA-48 *(18)*). Activity against CRPA *(24,25)*. In vivo data is described in a neutropenic murine thigh infection model, murine cUTI model and neutropenic murine pneumonia model *(26,27,28)*. Cross-resistance with aztreonam-avibactam has been shown *(29)*.

Sought therapeutic indication: Serious Gram-negative infections, including cUTI and HABP/VABP (both supported by BARDA (Biomedical Advanced Research and Development Authority) in the USA).

Pharmaceutical form, route of the administration and proposed posology: 2/0.5 g q8h iv (2 h infusion) for cUTI; a 4 h infusion is proposed for the HABP/VABP indication; however only data from a Phase 1 trial investigating the bronchopulmonary disposition of iv cefepime/taniborbactam are currently available *(30)* (NCT03870490).

Phase of clinical development: 3

Clinical trial(s):

- **Phase 3:** A double-blind, randomized, active-controlled, non-inferiority study evaluating the efficacy, safety and tolerability of cefepime-taniborbactam, administered q8h iv over a 2 h period, compared with that of meropenem, administered q8h iv over 30 min, in adults with cUTI, including AP (NCT03840148).
  - **Study population:** 661 adult patients diagnosed with cUTI or AP were randomized, of whom 436 patients (66.0%) infected with a Gram-negative pathogen determined to be non-resistant to study drugs were included in the microbiologic intent-to-treat (micro-ITT) population, including 42.2% with AP and 57.8% with cUTI. Patients were randomized 2:1 to cefepime-taniborbactam 2.5 g iv q8h or MEM 1 g iv q8h for 7 days or up to 14 days in patients with bacteraemia.
  - **Time period:** 7 August 2019 to 14 December 2021.
  - **Sites:** The study was conducted at 78 sites in 14 countries (Argentina, Brazil, Bulgaria, China, Croatia, Latvia, Mexico, Peru, Romania, Russian Federation, Serbia, Türkiye, Ukraine, USA).
  - **Primary end-point:** The composite successful outcome of clinical cure (symptom resolution or return to premorbid baseline of all UTI core symptoms and patient is alive, and patient has not received additional antibacterial therapy for cUTI) and microbiological eradication (defined as any Gram-negative target pathogens found at study entry ≥ 105 CFU/mL eradicated to < 103 CFU/mL) at TOC visit (after receiving three rounds of iv therapy, days 19–23). The non-inferiority margin was –15.0%, and a pre-specified test for superiority for the primary end-point was performed following confirmation of non-inferiority.
  - **Primary efficacy evaluation** was performed in the micro-MITT population, for patients infected with a Gram-negative pathogen determined to be non-resistant to study drugs.
  - **Trial results:** Cefepime-taniborbactam met the primary efficacy end-point of statistical non-inferiority to meropenem in the micro-ITT population at TOC with composite microbiologic and clinical success occurring in 70.6% of cefepime-taniborbactam-treated patients and 58.0% of meropenem-treated patients. Cefepime-taniborbactam was statistically superior to meropenem for the primary end-point at TOC (treatment difference (cefepime-taniborbactam – meropenem), 12.6 percentage points (95% CI: 3.1–22.2; $P = 0.009$)). Differences in treatment response were sustained at late follow-up (trial days 28–35), when cefepime-taniborbactam had higher composite success and clinical success *(31)*.
  - **Adverse events:** TEAEs were observed in 35.5% of cefepime-taniborbactam patients and 29.0% of meropenem patients. Serious adverse events occurred in 2.0% and 1.8% of cefepime-taniborbactam and meropenem patients, respectively. The most common TEAEs were headache (cefepime-taniborbactam 6.1%, meropenem 3.7%) and diarrhoea (cefepime-taniborbactam 4.1%, meropenem 2.3%). The frequency of serious adverse events was similar in the two groups.

Product name (INN or company code): benapenem

Pharmacology: Chemical class and pharmacology: chemical class and MoA: Benapenem is a broad-spectrum β-lactam (carbapenem) that inhibits bacterial cell wall synthesis. It is structurally related to ertapenem *(32)*.

Spectrum of activity and potential resistance: Unpublished in vitro preclinical data showed that benapenem was a time-dependent bactericidal drug and had an antibacterial spectrum similar to that of other carbapenems, with an MIC50 less than 1 mg/L to most bacteria *(33,34)*. In vivo research has shown potential for treating complicated ascending UTIs, such as AP caused by *E. coli (35)*.

Sought therapeutic indication: Treatment of cUTI or AP.

Route of administration: Intravenous injection administered as a 1 g iv infusion over 30 min once daily for 7–14 days.

Phase of clinical development: 2

- Completed two Phase 1 trials and one Phase 2/3 trial *(32)*:
  - a study to assess efficacy and safety intravenous benapenem in patients with cUTI or AP (NCT04505683);
  - a PK study of benapenem in subjects with renal impairment (NCT04476407); and
  - a single-dose PK study of benapenem in healthy subjects (NCT03588156).

Clinical trial(s):

- **Phase 2/3 (**NCT04505683**):** Randomized, double-blind, positive-control, multicentre, prospective study to assess efficacy and safety of iv benapenem injection administered as a 1 g iv infusion vs ertapenem for iv injection administered as a 1 g iv infusion, in 112 participants with cUTI or AP.
  - **Patient population:** 18–75-year-olds with a diagnosis of cUTI or AP with no recent antibiotic therapy more than 24 h within 72 h prior to randomization or other exclusionary diagnosis.
  - **Time period:** 13 December 2018 to 8 May 2020.
  - **Sites:** Peking University First Hospital, Beijing, China.
  - **Primary end-point:** Percentage of patients with clinical cure at test-of-cure (TOC) visit (time frame: day 7 +/– 1 day after end of treatment (EOT)). Clinical cure is defined as complete resolution of signs, symptoms and related laboratory tests of cUTI or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted.

Preclinical PK and safety / adverse events: The clearance and elimination half-life (t1/2) of benapenem in rats is 0.18 L/h/kg of body weight and 2.3 h, respectively *(35)*. From published results of the first-in-human safety, tolerability and pharmacokinetics study of benapenem in humans, there were no serious adverse events. Minor events included: white blood cell (WBC) count decreasing (two cases), alanine aminotransferase (ALT; two cases) or aspartate transaminase (AST; one case) increasing, and erythema (one case) *(34)*.

Product name (INN or company code): cefepime + zidebactam (WCK 5222)

Pharmacology: chemical class and MoA: Zidebactam is a DBO-type BLI with activity against *P. aeruginosa* (36), *A. baumannii* (37) and some Enterobacterales (38), due to PBP2 inhibition and inhibition of Class A, C and some D β-lactamases. Cefepime is a fourth-generation cephalosporin, and an inhibitor of bacterial cell wall synthesis.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs): Synergistic activity of this combination against Enterobacterales (including ESBL and KPC producers), but elevated MICs in MBL producers from in vitro data (39,40,41,42). In vivo humanized exposure of the combination showed synergistic activity against CRAB and CRPA in a neutropenic murine lung infection model and neutropenic thigh infection model, despite elevated MICs (42,43,44,45). Two recent case reports described activity in XDR NDM-expressing *P. aeruginosa* infection both in an intra-abdominal infection-induced sepsis patient and an acute T-cell leukaemia patient (46).

Note: The enhanced in vivo bactericidal action of the combination, despite elevated MICs, is thought to be due to zidebactam-induced reduction of the percentage of time that the cefepime free drug concentration remains above the MIC (% fT > MIC) required for in vivo killing of A. baumannii and P. aeruginosa. Human simulated regimens achieved eradication of CRAB and CRPA up to a MIC of 64 mg/L (2–3 log10 kill) in translational animal models (42,44,45).

Resistance: Cefepime-zidebactam showed activity against aztreonam-avibactam-resistant NDM-like producing E. coli (29).

Sought therapeutic indication: cUTI and AP (currently in Phase 3 clinical development), and HABP/VABP (not yet in clinical development. A Phase 1 study (NCT03630094), to determine plasma and intrapulmonary concentrations in healthy individuals, was completed in 2017 (47).

Pharmaceutical form, route of administration and proposed posology: 3 g (2 g cefepime + 1 g zidebactam) iv q8h.

Phase of clinical development: 3

Clinical trial(s):

- **Phase 3:** A randomized, double-blind, multicentre, non-inferiority study to evaluate the efficacy, safety and tolerability of cefepime-zidebactam (3 g (2 g cefepime + 1 g zidebactam) iv q8h) vs meropenem (1 g iv q8h) for treatment of hospitalized adults with cUTI or AP (NCT04979806).
  - **Study population:** Approximately 528 hospitalized adult subjects (≥ 18 years of age) diagnosed with cUTI or AP, based on a combination of clinical symptoms and signs plus the presence of pyuria, will be randomized to receive either treatment for 7–10 days.
  - **Time period:** August 2022 to May 2024.
  - **Sites:** 46 sites located in nine countries (Bulgaria, China, Estonia, India, Lithuania, Mexico, Peru, Poland, USA).
  - **Primary end-point:** Percentage of subjects with overall success at TOC (day 17 ± 2 days). Overall success is defined as complete resolution of cUTI or AP symptoms present at study entry (or return to premorbid state) and no new cUTI or AP symptoms, together with microbiologic eradication of the bacterial pathogen found at study entry (reduced to < 1000 CFU/mL).

Product name (INN or company code): cefpodoxime proxetil + ETX0282

Pharmacology: chemical class and MoA: cefpodoxime proxetil + ETX0282 is a combination DBO-BLI/PBP2 binder + β-lactam (third-generation cephalosporin); ETX0282 is an orally bioavailable prodrug of the BLI ETX1317. It is an "unsaturated DBO" and can be considered a DBO sub-series with PBP2 inhibition, similar to durlobactam *(48)*. Cefpodoxime proxetil inhibits synthesis of peptidoglycan in bacterial cell walls by binding preferentially to PBP3.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: In vitro cefpodoxime proxetil + ETX0282 has displayed broad-spectrum activity against Ambler Class A, C and D serine β-lactamases *(49)*. It is active against ESBL, OXA-48 and KPC, but not MBL-producing Enterobacterales. In vivo: In a neutropenic mouse thigh infection model it was effective against *E. coli* strains expressing ESBL and a carbapenem-resistant strain of *K. pneumoniae (50)*. In the murine UTI model, it inhibited ESBL-producing organisms *(51)*, and ETX0282 restored cefpodoxime antimicrobial activity in a UTI model against uropathogenic strains of *E. coli* expressing CTX-M-14 and *K. pneumoniae* expressing KPC-2 (li). Ceftazidime-avibactam (CAZ-AVI) resistance mutations in KPC-3 did not confer resistance in in vitro data *(52)*.

Sought therapeutic indication: cefpodoxime proxetil + ETX0282 is under investigation as an oral treatment option against MDR Gram-negative Enterobacterales infections.

Route of administration and proposed posology: Oral gelatin capsules.

Phase of clinical development: 1

Clinical trial(s): Phase 1 trial (NCT03491748) was a double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability and PK of oral ETX0282 administered in 99 healthy adults 18–55 years old, between March 2018 and September 2019. There are no published results as yet.

Preclinical PK and safety: In vitro and in vivo studies by O'Donnell et al. (2020) *(53)*:

PK/PD evaluation in both in vitro dynamic model systems and in vivo models of infection suggest the combination would be expected to demonstrate cidal activity when unbound exposures of CPD exceed 50%Time > MIC and ETX1317 exceeds a concentration 2× the MIC for 60% of the dosing interval. Bioavailability and conversion of ETX0282 to ETX1317 systemically have been demonstrated across multiple preclinical species. Allometric scaling of animal PK suggests clinical kinetics of ETX1317 would behave similarly to cefpodoxime.

Product name (INN or company code): meropenem + nacubactam (OP0595)

Pharmacology: chemical class and MoA: Meropenem + nacubactam (OP0595) is a β-lactam (carbapenem) and DBO-BLI/PBP2 binder combination. The DBO-BLI/PBP2 binder acts as a BLI and antibacterial agent by means of PBP2 inactivation, and the β-lactam (carbapenem) inhibits cell wall synthesis by binding to PBPs.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: In vitro, nacubactam has been shown to restore and extend the activity of β-lactam antibiotics, such as meropenem, when used in combination against a variety of CREs *(54,55)*. It shows inhibition of Class A and C β-lactamases *(56,57)* and some Class D (OXA) enzymes *(56)*. BLI activity in vitro was shown in early studies only in *P. aeruginosa* and not in CRPA *(58)*; however, activity was observed in a neutropenic murine lung infection model against meropenem-resistant KPC-producing strains of *P. aeruginosa*, despite the use of subtherapeutic meropenem exposure *(54)*. Meropenem + nacubactam has shown no added benefit in treating CRAB *(57)*.

In vivo, the combination has shown activity against Class A serine carbapenemase-producing Enterobacteriaceae (CPE) isolates in the neutropenic murine lung infection model *(59)*. Lack of antimicrobial activity towards carbapenem-resistant *K. pneumoniae* (CRKP) (strain 594, IMP6) in murine thigh infection and pulmonary infection models *(53,58)* is probably due to competition with meropenem for PBP2 binding. Nacubactam combinations, including those using MBL-labile β-lactams, e.g., meropenem and cefepime, have been shown to overcome most MBL-mediated resistance *(60)*.

Sought therapeutic indication: Being evaluated in the treatment of bacterial CRE and CPE pneumonia.

Route of administration and proposed posology: Intravenous.

Phase of clinical development: 1

Clinical trial(s): Five completed Phase 1 trials, investigating:

- PK of RO7079901 and meropenem in 20 participants with cUTI (NCT03174795), ended December 2017);
- effect of renal function and haemodialysis on the PK of RO7079901 in 29 participants (NCT02975388), ended July 2017);
- intrapulmonary lung penetration of nacubactam in 21 healthy participants (NCT03182504), ended August 2017);
- safety, tolerability and PK of RO7079901 and the combination of RO7079901 with meropenem in 46 adult healthy volunteers (NCT02972255), ended in March 2017; and
- safety, tolerability and PK of OP0595 administered intravenously in healthy male subjects (NCT02134834, ended November 2014).

Preclinical PK and safety: Results available only in healthy adults (NCT02972255). Following iv single doses of nacubactam up to 8000 mg and multiple doses up to 4000 mg q8h in combination with meropenem for up to 7 days, nacubactam was generally well tolerated, with the most frequently reported adverse events associated with iv access and headache. There was no apparent relationship between drug dose and the pattern, incidence or severity of adverse events. No serious adverse events, dose-limiting adverse events or deaths were reported. Nacubactam was excreted largely unchanged into urine *(61)*.

Product name (INN or company code): xeruborbactam (QPX7728) + β-lactam (S-649228) (OMNIvance)

Pharmacology: chemical class and MoA: Xeruborbactam (QPX7728) + β-lactam (S-649228) is a bicyclic boronate BLI (new class) + β-lactam (undisclosed). QPX7831 is the oral prodrug of xeruborbactam (QPX7728) *(62,63)*, similarly co-administered with an undisclosed β-lactam.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: In vitro, QPX7728 displays broad-spectrum β-lactamase inhibition, showing activity against numerous serine and MBLs, including carbapenemases such as Class A KPC, Class B NDM and VIM, and Class D OXA-48 in CREs and OXA-23 in *A. baumannii*, respectively *(64,65,66)*. It was tested in vitro in combination with meropenem; compared with other BLI combinations (meropenem-vaborbactam, ceftazidime-avibactam and imipenem-relebactam), QPX7728 + meropenem showed activity against CREs with multiple resistance mechanisms *(67)*. Limited data show in vitro activity against *P. aeruginosa (68,69)*.

In vivo activity of QPX7728 at 12.5, 25 or 50 mg/kg of body weight in combination with multiple β-lactams (including cephalosporins, carbapenems and monobactams) against carbapenem-resistant *K. pneumoniae* isolates in a neutropenic mouse thigh infection model showed bacterial killing utility at all doses *(70)*. This inhibitory activity of QPX7728 was also seen in mouse thigh and lung infection models of infections, where meropenem showed efficacy against KPC-producing strains of Enterobacteriaceae (*K. pneumoniae, Enterobacter cloacae*), OXA-23-producing strains of *A. baumannii* and MDR strains of *P. aeruginosa* that did not respond to meropenem alone *(63)*.

Sought therapeutic indication: Xeruborbactam (QPX7728) + β-lactam (S-649228) is being studied as treatment in carbapenem-resistant *Acinetobacter*, *Pseudomonas* and Enterobacterales infections.

Route of administration and proposed posology: Oral and iv administration.

Phase of clinical development: Two Phase 1 trials are complete for iv administration (NCT04380207 and NCT05072444), and one Phase 1 trial is complete for oral administration (NCT03939429).

Clinical trial(s):

- **Phase 1** complete (NCT04380207): Randomized, double-blind, placebo-controlled, ascending single and multiple-dose study of the safety, tolerability and PK of iv QPX7728 alone and in combination with QPX2014 in 82 healthy adults 18–55 years old.
- **Phase 1** complete (NCT05072444): Randomized, double-blind, single-dose, drug–drug interaction study to determine the impact of co-administration of QPX7728 on the PK of QPX2014 in 12 healthy adult subjects 18–55 years old.
- **Phase 1** complete (NCT03939429): Randomized, double-blind, placebo-controlled, ascending single and multiple-dose study of the safety, tolerability, PK of oral QPX2015 in 40 healthy adult subjects 18–55 years old.

There are no results as yet.

Preclinical PK and safety: Plasma protein binding in the rat is 85% and it displays oral bioavailability in fasted rats, with values ranging between 43% and 53% at doses of 30–100 mg/kg, whereas it declined to 24–28% at higher doses *(63)*. QPX7728 was studied in a 7-day pilot toxicology study at daily doses of 30, 100 and 300 mg/kg in rats (five males, five females per dose level) administered by iv infusion. No changes were observed (tissue histology and clinical chemistry) *(63)*.

Product Name (INN or company code: funobactam (XNW4107) + imipenem + cilastatin

Pharmacology: chemical class and MoA: Funobactam (XNW4107) is a DBO-type BLI that confers protection against hydrolysis by Ambler Class A, C and D β-lactamases, including OXA-23 and -24 being developed in combination with imipenem and cilastatin. Imipenem is a carbapenem; inhibitor of bacterial wall synthesis. Cilastatin is a renal dehydropeptidase inhibitor that is used to prevent degradation of imipenem. The XNW4107 combination is under developement against both cUTI and HABP/VABP *(71)*.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs : In vitro and in vivo studies showed activity towards OXA-23, -27 and -51-producing CRAB, but susceptibility rate of 57.5% *(72)*. No activity vs MLB *(71)*. Activity was also shown against KPC-producing CRKP, but not against carbapenem-resistant *E. coli* (CR-EC). Active against 3GCR *K. pneumoniae*, but insufficient data against 3GCR *E. coli*. Activity against CRPA appears poor; the susceptibility rate was 35.6% *(71,73)*.

Sought therapeutic indication: cUTI and HABP/VABP.

Pharmaceutical form, route of the administration and proposed posology: Imipemen/cilastatin/funobactam 500/500/250 mg q6h, 0.5 h infusion.

Phase of clinical development: 3

Clinical trial(s): Two Phase 3 clinical trials in cUTI (NCT05204368) and HABP/VABP (NCT05204563) are listed.

- **Phase 3 trial** in cUTI (NCT05204368): A multicentre, randomized, double-blind, double-dummy, comparative, Phase 3 study to evaluate the efficacy and safety of iv imipenem/cilastatin/XNW4107 (500/500/250 mg q6h) in comparison with meropenem (1 g, q8h) in hospitalized adults with cUTI infection, including AP.
  - **Study population:** Adult male or female patients (roughly 780), hospitalized or requiring hospitalization for cUTI or AP, showing least one of the following: nausea or vomiting, chills or rigours or warmth associated with fever (temperature > 38°C), peripheral WBC count > 10 000/mm^3 or bandaemia , regardless of WBC count, with at least one complicating factor for cUTI (not required for AP).
  - **Time period:** March 2023 and December 2025.
  - **Sites:** Only one location listed at present: Baltimore (MD), USA.
  - **Primary end-point:** The proportion of patients who achieve overall success at the TOC day 21 (± 2 days) visit. Overall success requires symptomatic clinical success and microbiologic success at the TOC visit.
  - **Primary efficacy evaluation** will be performed in the micro-MITT population.
- **Phase 3 trial in HABP/VABP** (NCT05204563): A multicentre, randomized, double-blind, comparative, Phase 3 study to evaluate the efficacy and safety of iv imipenem/cilastatin/XNW4107 (500/500/250 mg q6h) in comparison with imipenem/cilastatin/relebactam (1.25 g for injection) in adults with HABP or VABP (REITAB-2).
  - **Study population:** Adult patients (roughly 450) with HABP or VABP from a suspected Gram-negative infection with fever or hypothermia or leukocytosis/leukopenia or > 15% immature neutrophils on peripheral blood smear, fulfilling at least one of the following clinical criteria: new onset or worsening of pulmonary symptoms or signs, or requirement for mechanical ventilation; hypoxaemia; need for acute changes in the ventilator support system to enhance oxygenation; new onset of or increase in suctioned respiratory secretions, demonstrating evidence of inflammation and absence of contamination. All patients must have a chest radiograph showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia.
  - **Time period:** July 2022 to December 2025.
  - **Sites:** 35 sites in France, Israel, Spain and USA.
  - **Primary end-point:** Day 14 all-cause mortality rate.
  - **Primary efficacy evaluation** will be performed in the micro-MITT population.

Product name (INN or company code): ceftibuten + ledaborbactam (VNRX-7145)

Pharmacology: chemical class and MoA: Ceftibuten + ledaborbactam (VNRX-7145) is a boronate-BLI + β-lactam (third-generation cephalosporin). Ledaborbactam (VNRX-7145) is an esterase-cleavable prodrug of the bicyclic boronate-type BLI (new class) of ledaborbactam etzadroxil (VNRX-5236) *(74)*, while ceftibuten is a third-generation cephalosporin that inhibits cell wall synthesis. It was first approved by the FDA for paediatric use in 1995.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: Active against clinically derived Enterobacterales that express ESBLs and serine carbapenemases. In vitro, the combination has shown potent inhibitory activity against MDR Enterobacterales expressing Ambler Class A, C and D β-lactamases, including those that hydrolyse carbapenems, such as KPCs and OXA-48 *(75,76)*, but not in MBL-producing isolates *(75)*. VNRX-5236 alone does not demonstrate antibacterial activity. In vivo, ledaborbactam (VNRX-7145) restored ceftibuten activity in a mouse model of UTI due to ESBL- and KPC-carbapenemase-producing strains of *E. coli* and *K. pneumoniae (77)*.

Sought therapeutic indication: Under development as a carbapenem-sparing oral treatment in cUTI caused by Enterobacterales (ESBL, KPC and OXA-48 groups) *(75)*.

Route of administration and proposed posology: Oral.

Phase of clinical development: Currently being evaluated in a Phase 1 trial and previously completed three other Phase 1 trials.

Clinical trial(s):

- **Current Phase 1 trial:**
  - An open-label study to evaluate the PK, safety and tolerability of ceftibuten/VNRX-7145 in 32 participants with varying degrees of renal function (NCT05488678).
- **Completed Phase 1 trials:**
  - A randomized, double blind, placebo-controlled, sequential group, dose-escalation study to evaluate the safety and PK of single and repeat doses of VNRX-7145 in 83 healthy adult volunteers (January 2020 to April 2021); no published results (NCT04243863).
  - A randomized, drug–drug interaction study to assess the safety and PK of VNRX-7145 and VNRX-5024 (ceftibuten) in 53 healthy adult volunteers (June 2021 to November 2021); no published results (NCT04877379).
  - An open-label, crossover study to evaluate the effect of food on the PK, safety and tolerability of ceftibuten/VNRX-7145 in 36 healthy participants (September 2022 to January 2023) (NCT05527834).

Preclinical PK and safety: In vivo, VNRX-5236 showed oral bioavailability in rats, dogs and monkeys *(76)*. It has been studied in patients with mild, moderate, or severe renal impairment or end-stage renal disease undergoing standard intermittent dialysis, pending results.

Product Name (INN or company code): ertapenem + zidebactam (WCK 5107) (combination WCK 6777)

Pharmacology: chemical class and MoA: Ertapenem + zidebactam (WCK 5107) is a DBO-BLI/PBP2 binder and β-lactam (carbapenem) combination. The DBO-BLI/PBP2 binder acts as a β-lactamase inhibitor and antibacterial agent by means of PBP2 inactivation, and the β-lactam (carbapenem) inhibits cell wall synthesis by binding to PBPs.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: In vitro, WCK 6777 is active against *E. coli* with AmpC, ESBLs, KPC, metallo- or OXA-48 carbapenemases *(78)*. Zidebactam inhibits PBPs and several β-lactamases, while enhancing β-lactam *A. baumannii*, *P. aeruginosa* and CREs *(37,79)*. In vivo, human-simulated exposures of WCK 6777 demonstrated activity against carbapenemase-producing *K. pneumoniae* in a neutropenic murine pneumonia model, including those with WCK 6777 MICs up to 8 mg/L *(80)*.

Sought therapeutic indication: Ertapenem + zidebactam is being developed as a potential once-daily outpatient therapeutic option to manage infections caused by carbapenem Gram-negative pathogens *(81)*.

Route of administration and proposed posology: Intravenous.

Phase of clinical development: 1

Clinical trial(s):

- A Phase 1 (NCT05645757, currently recruiting) randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety, tolerability and PK of iv ertapenem in combination with zidebactam (WCK 6777) in 52 healthy adult subjects (18–45 years old). Beginning 19 April 2023, and completed in November 2023, the crucial primary end-points are the incidence of TEAEs and treatment-emergent serious adverse events.

Preclinical PK and safety: Not yet publicly available.

Product name (INN or company code): cefepime + nacubactam (OP0595); aztreonam + nacubactam (OP0595)

Pharmacology: chemical class and MoA: Nacubactam is a DBO-type BLI with inhibiting activity against Class A and C β-lactamases and some class D (OXA) enzymes, and some intrinsic activity against serine β-lactamase-producing Enterobacterales due to PBP2 inhibition *(82)*. Cefepime is a fourth-generation cephalosporin that inhibits cell wall synthesis.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: Nacubactam has synergistic activity with various partners in serine β-lactamase-producing Enterobacterales. The combination with cefepime is active against Class A β-lactamase-producing CREs and 3GCREs (murine thigh infection model *(53)*, and murine pneumonia model *(58)*), including some MBL producers (elevated MICs; *(59)*). Limited data suggest activity against AmpC-derepressed *P. aeruginosa* *(6)*, and a murine pneumonia model *(58)*, including some MBL producers (elevated MICs *(59)*.

In in intro data, the combination with aztreonam is active against Class A, B and D β-lactamase-producing CRE and 3GCRE *(83,84)*; murine thigh infection and pneumonia models by *(58)*. Among MBL-producing *P. aeruginosa* isolates, the susceptibility rates to aztreonam/nacubactam were 66.7% (in vitro data) *(83)*.

Sought therapeutic indications: cUTI/AP; HABP/VABP and cIAI.

Pharmaceutical form, route of the administration and proposed posology: 2 g cefepime or 2 g aztreonam combined with 1 g nacubactam q8h (60 min iv infusion).

Phase of clinical development: 3

Clinical trial(s): Two Phase 3 studies are currently ongoing in cUTI/AP (NCT05887908), and in cUTI/AP, HABP/VABP and cIAI (NCT05905055).

- **Phase 3** (NCT05887908): Multicentre, randomized, double-blind study to assess the efficacy and safety of cefepime/nacubactam or aztreonam/nacubactam compared to imipenem/cilastatin in the treatment of cUTI or AP.
  - **Study population:** Male or female adult patients (roughly 600) expected to require treatment with at least 5 days of iv antibiotics for cUTI or AP, not due to a known imipenem- and/or meropenem-resistant Gram-negative uropathogen. Patients will be randomized to receive: 2 g cefepime and 1 g nacubactam q8h (60 min infusion), 2 g aztreonam and 1 g nacubactam q8h (60 min infusion) or combination of 1 g imipenem/1 g cilastatin q8h (60 min infusion).
  - **Time period:** May 2023 to August 2024.
  - **Sites:** Estonia; listed Bulgaria, Czechia, Latvia and Lithuania.
  - **Primary end-point:** The proportion of patients who achieve composite clinical and microbiological success at TOC (time frame: 7 (± 2) days after EOT (days 10–23)). Composite clinical and microbiological success is defined as the composite clinical outcome of cure and the microbiological outcome of eradication.
  - **Primary efficacy evaluation** will be performed in the micro-MITT population.
- **Phase 3** (NCT05905055): A multicentre, randomized, single-blind, parallel-group study to assess efficacy and safety when 1 g nacubactam is co-administered with 2 g cefepime or 2 g aztreonam (both q8h for 5–14 days, 60 min infusion), compared with best available therapy (dosage based per site's SOC), in the treatment of patients with cUTI, AP, HABP, VABP and cIAI, due to CRE.
  - **Study population:** Male or female adult patients (roughly 150) with known (evidence of positivity within 72 h or 96 h for cIAI, prior to the first dose of study drug) or suspected CRE infection. In case of known CRE infection, patients have either (i) received no more than 24 h of an antimicrobial agent to which the known CRE is known to be susceptible or (ii) documented clinical evidence of failure (i.e., clinical deterioration or failure to improve) after at least 48 h of treatment, within 72 h (or 96 h for cIAI) prior to the first dose of the study drug. In the case of suspected CRE infection, evidence may be determined within 90 days prior to the first dose of the study drug together with documented clinical evidence of failure after at least 48 h of treatment with empiric antimicrobial therapy for Gram-negative organisms within 72 h (or 96 h for cIAI) prior to the first dose of the study drug. Patients with known or suspected single or concurrent infection with *Acinetobacter* species or MBL-producing *P. aeruginosa* will be excluded
    Note: CRE is defined as Enterobacterales by susceptibility data of MIC at least 2 mg/mL to imipenem or meropenem OR imipenem or meropenem disk diffusion (zone diameter < 22 mm).

Product name (INN or company code): cefepime + nacubactam (OP0595); aztreonam + nacubactam (OP0595) (continued)

- **Time period:** June 2023 to February 2025.
- **Sites:** Greece, Japan, Spain.
- **Primary end-point:** The proportion of patients with overall treatment success at TOC across all infection types (i.e., cUTI, AP, HABP, VABP cIAI), which is a composite end-point derived from the efficacy outcomes of each infection type (time frame: 7 (± 2) days after EOT (days 10–23)). For cUTI and AP, the composite clinical outcome of cure and the microbiological outcome of eradication are defined as the outcome of cure. For HABP and VABP, the clinical success is defined as the outcome of cure. For cIAI, the clinical success is defined as the outcome of cure.

Product name (INN or company code): meropenem + ANT3310

Pharmacology: chemical class and MoA: Meropenem + ANT3310 is a DBO-BLI + β-lactam (carbapenem). ANT3310 has a fluorine atom replacing the carboxamide, distinguishing it from other DBOs in restoring carbapenem activity against OXA-CRAB as well as SBL-carrying CRE pathogens *(85)*.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: Reports of unpublished in vitro data show that meropenem + ANT3310 β-lactamases, including KPCs and OXA-type enzymes found in CRE and CRAB, and that it restores meropenem activity against these pathogens *(86)*.

Sought therapeutic indication: FDA qualified infectious disease product status was granted to Meropenem + ANT3310 for treatment of cUTI, HABP, VABP and cIAI in 2019 *(85)*.

Route of administration and proposed posology: Intravenous.

Phase of clinical development: 1

Clinical trial(s): A **Phase 1** (NCT05905913) randomized, double-blind, placebo-controlled study to assess the safety, tolerability and pharmacokinetics of single- and multiple-ascending doses of iv ANT3310 alone (parts A and B) and in combination with meropenem (part C) in 72 healthy subjects, 18–55 years old. The predicted period is between April 2023 and January 2024, with a primary end-point of number and severity of TEAEs.

Preclinical PK and safety: Not yet publicly available.

Product name (INN or company code): meropenem + KSP-1007 (MEROPEN)

Pharmacology: chemical class and MoA: Meropenem + KSP-1007 is a novel BLI and β-lactam (carbapenem) combination.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: KSP-1007 exhibits broad-spectrum inhibition of serine- and metallo-β-lactamases in combination with meropenem *(87,88)*.

Sought therapeutic indication: Carbapenem-resistant bacterial infections – cUTI, cIAI, HABP and VABP *(86)*.

Route of administration: Intravenous.

Phase of clinical development: 1

Clinical trial(s):

- **Phase 1:** A randomized, double-blind, placebo-controlled, dose-escalation study to assess the safety, tolerability and PK of single and repeat Doses of KSP-1007 alone and co-administered with meropenem in approximately 123 healthy subjects (NCT05226923, completed October 2022).

Preclinical PK and safety: Dansky et al. (2023) *(87)*: After single and multiple doses, a dose-proportional increase in mean maximum concentration (Cmax) and area under the concentration–time curve (AUC) was observed, and KSP-1007 was predominately excreted in urine (> 90%) with T1/2 of 2–4 h. No serious adverse events were observed in the study. The most common adverse events at the highest dose (KSP-1007 1500 mg + 2 g merepenum) were nausea, vomiting and transient increases of serum creatinine (peak changes ranged from 0.31–0.74 mg/dl).

References

1. Crandon JL, Nicolau DP. In vitro activity of cefepime/AAI101 and comparators against cefepime non-susceptible Enterobacteriaceae. Pathogens. 2015;4(3):620–5 (https://doi.org/10.3390/pathogens4030620, accessed 2 March 2024).
2. Belley A, Huband MD, Fedler KA, Watters AA, Flamm RK, Shapiro S et al. Development of broth microdilution MIC and disk diffusion antimicrobial susceptibility test quality control ranges for the combination of cefepime and the novel β-lactamase inhibitor enmetazobactam. J Clin Microbiol. 2019;57(8) (https://doi.org/10.1128/jcm.00607-19, accessed 2 March 2024).
3. Morrissey I, Magnet S, Hawser S, Shapiro S, Knechtle P. In vitro activity of cefepime-enmetazobactam against Gram-negative isolates collected from U.S. and European hospitals during 2014–2015. Antimicrob Agents Chemother. 2019;63(7) (https://doi.org/10.1128/aac.00514-19, accessed 2 March 2024).
4. Crandon JL, Nicolau DP. In vivo activities of simulated human doses of cefepime and cefepime-AAI101 against multidrug-resistant gram-negative Enterobacteriaceae. Antimicrob Agents Chemother. 2015;59(5):2688-94 (https://doi.org/10.1128/aac.00033-15, accessed 2 March 2024).
5. Bernhard F, Odedra R, Sordello S, Cardin R, Franzoni S, Charrier C et al. Pharmacokinetics-pharmacodynamics of enmetazobactam combined with cefepime in a neutropenic murine thigh infection model. Antimicrob Agents Chemother. 2020;64(6) (https://doi.org/10.1128/aac.00078-20, accessed 3 March 2024).
6. Advani SD, Claeys K. Cefepime/enmetazobactam for complicated urinary tract infections. JAMA. 2022;328(13):1299–301 (https://doi.org/10.1001/jama.2022.15228, accessed 3 March 2024).
7. Tamma PD, Harris PNA, Mathers AJ, Wenzler E, Humphries RM. Breaking down the breakpoints: rationale for the 2022 Clinical and Laboratory Standards Institute revised piperacillin-tazobactam breakpoints against Enterobacterales. Clin Infect Dis. 2023;77(11):1585–90 (https://doi.org/10.1093/cid/ciac688, accessed 3 March 2024).
8. EUCAST [website]. Värjö: European Committee on Antimicrobial Susceptibility Testing; 2024 (https://www.eucast.org, accessed 4 March 2024).
9. Kaye KS, Belley A, Barth P, Lahlou O, Knechtle P, Motta P et al. Effect of cefepime/enmetazobactam vs piperacillin/tazobactam on clinical cure and microbiological eradication in patients with complicated urinary tract infection or acute pyelonephritis: a randomized clinical trial. JAMA. 2022;328(13):1304–14 (https://doi.org/10.1001/jama.2022.17034, accessed 3 March 2024).
10. Maher JM, Huband MD, Blankers CG, Puttagunta S, Aronin SI, Castanheira M. In vitro activity of sulopenem and comparator agents against Enterobacterales and anaerobic clinical isolates collected during the SENTRY Antimicrobial Surveillance Program. J Antimicrob Chemother. 2023;78(6):1406–14 (https://doi.org/10.1093/jac/dkad099, accessed 3 March 2024).
11. Hamilton-Miller JMT. Chemical and microbiologic aspects of penems, a distinct class of β-lactams: focus on faropenem. Pharmacotherapy. 2003;23(11):1497–507 (https://doi.org/10.1592/phco.23.14.1497.31937, accessed 3 March 2024).
12. Karlowsky JA, Adam HJ, Baxter MR, Denisuik AJ, Lagacé-Wiens PRS, Walkty AJ et al. In vitro activity of sulopenem, an oral penem, against urinary isolates of *Escherichia coli*. Antimicrob Agents Chemother. 2019;63(1) (https://doi.org/10.1128/AAC.01832-18, accessed 3 March 2024).
13. O'Donnell J, Finegan S, Girard D. Pharmacokinetics and pharmacodynamics of sulopenem in preclinical species. Presented at the Infectious Diseases Society of America Annual Meeting, Washington, DC, USA, 25–28 October 2008 (https://www.researchgate.net/publication/267530393_Pharmacokinetics_and_Pharmacodynamics_of_Sulopenem_in_Preclinical_Species, accessed 4 March 2024).
14. Zhanel GG, Pozdirca M, Golden AR, Lawrence CK, Zelenitsky S, Berry L et al. Sulopenem: an intravenous and oral penem for the treatment of urinary tract infections due to multidrug-resistant bacteria. Drugs. 2022;82(5):533–57 (https://doi.org/10.1007/s40265-022-01688-1, accessed 3 March 2024).

15. Dunne MW, Das AF, Zelasky M, Akinapelli K, Boucher H, Aronin SI. LB-1. Efficacy and safety of oral sulopenem Etzadroxil/Probenecid versus oral ciprofloxacin in the treatment of uncomplicated urinary tract infections (uUTI) in adult women: results from the SURE-1 trial. Open Forum Infect Dis. 2020;7(Suppl 1):S844 (https://doi.org/10.1093/ofid/ofaa515.1898, accessed 3 March 2024).

16. Dunne MW, Aronin SI, Das AF, Akinapelli K, Breen J, Zelasky MT et al. Sulopenem or ciprofloxacin for the treatment of complicated urinary tract infections including pyelonephritis: a Phase 3, randomized trial. Clin Infect Dis. 2023;76(1):66–77 (https://doi.org/10.1093/cid/ciac738, accessed 12 January 2024).

17. Iterum therapeutics announces topline results from Phase 3 clinical trial of oral and iv sulopenem for the treatment of complicated intra-abdominal infections. Iterum Therapeutics plc (ITRM) [Internet]. In: Iterum Therapeutics/News [website]. Chicago (IL): Iterum Therapeutics; 2019 (https://www.iterumtx.com/news/press-releases/detail/29/iterum-therapeutics-announces-topline-results-from-phase-3, accessed 27 February 2024).

18. Hamrick JC, Docquier JD, Uehara T, Myers CL, Six DA, Chatwin CL et al. VNRX-5133 (taniborbactam), a broad-spectrum inhibitor of serine- and metallo-lactamases, restores activity of cefepime in Enterobacterales and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. 2020;64(3):e01963-19. (https://journals.asm.org/doi/10.1128/aac.01963-19, accessed 3 March 2024).

19. Liu B, Trout RE, Chu GH, McGarry D, Jackson RW, Hamrick JC et al. Discovery of taniborbactam (VNRX-5133): a broad-spectrum serine-and metallo-β-lactamase inhibitor for carbapenem-resistant bacterial infections. J Med Chem. 2020;63(6):2789–801 (https://pubs.acs.org/doi/10.1021/acs.jmedchem.9b01518, accessed 3 March 2024).

20. Wang X, Zhao C, Wang Q, Wang Z, Liang X, Zhang F et al. In vitro activity of the novel β-lactamase inhibitor taniborbactam (VNRX-5133), in combination with cefepime or meropenem, against MDR Gram-negative bacterial isolates from China. J Antimicrob Chemother. 2020;75(7):1850–8 (https://doi.org/10.1093/jac/dkaa053, accessed 3 March 2024).

21. Le Terrier C, Gruenig V, Fournier C, Nordmann P, Poirel L. NDM-9 resistance to taniborbactam. *Lancet* Infect Dis. 2023;23(4):401–2 (https://doi.org/10.1016/S1473-3099(23)00069-5, accessed 3 March 2024).

22. Piccirilli A, Segatore B, Brisdelli F, Amicosante G, Perilli M. Potent inhibitory activity of taniborbactam towards NDM-1 and NDM-1Q119X mutants, and in vitro activity of cefepime/taniborbactam against MBLs producing Enterobacterales. Int J Antimicrob Agents. 2021;57(1):106228 (https://doi.org/10.1016/j.ijantimicag.2020.106228, accessed 3 March 2024).

23. Abbott C, Satola SW, Weiss DS. Heteroresistance to cefepime-taniborbactam in metallo-β-lactamase-encoding Enterobacterales. *Lancet* Infect Dis. 2023;23(8):e277–8 (https://doi.org/10.1016/s1473-3099(23)00426-7).

24. Meletiadis J, Paranos P, Georgiou PC, Vourli S, Antonopoulou S, Michelaki A et al. In vitro comparative activity of the new beta-lactamase inhibitor taniborbactam with cefepime or meropenem against *Klebsiella pneumoniae* and cefepime against *Pseudomonas aeruginosa* metallo-beta-lactamase-producing clinical isolates. Int J Antimicrob Agents. 2021;58(5):106440 (https://doi.org/10.1016/j.ijantimicag.2021.106440, accessed 3 March 2024).

25. Hernández-García M, García-Castillo M, Ruiz-Garbajosa P, Bou G, Siller-Ruiz M, Pitart C et al. In vitro activity of cefepime-taniborbactam against carbapenemase-producing Enterobacterales and *Pseudomonas aeruginosa* isolates recovered in Spain. Antimicrob Agents Chemother. 2022;66(3):e0216121 (https://doi.org/10.1128/aac.02161-21, accessed 3 March 2024).

26. Abdelraouf K, Nicolau DP. In vivo pharmacokinetic/pharmacodynamic evaluation of cefepime/taniborbactam combination against cefepime-non-susceptible Enterobacterales and *Pseudomonas aeruginosa* in a murine pneumonia model. J Antimicrob Chemother. 2023;78(3):692–702 (https://doi.org/10.1093/jac/dkac446, accessed 3 March 2024).

27. Lasko MJ, Nicolau DP, Asempa TE. Clinical exposure-response relationship of cefepime/taniborbactam against Gram-negative organisms in the murine complicated urinary tract infection model. J Antimicrob Chemother. 2022;77(2):443–7 (https://doi.org/10.1093/jac/dkab405, accessed 3 March 2024).

28. Abdelraouf K, Abuhussain SA, Nicolau DP. In vivo pharmacodynamics of new-generation β-lactamase inhibitor taniborbactam (formerly VNRX-5133) in combination with cefepime against serine-β-lactamase-producing Gram-negative bacteria. J Antimicrob Chemother. 2020;75(12):3601–10 (https://academic.oup.com/jac/article/75/12/3601/5899249, accessed 4 March 2024).

29. Le Terrier C, Nordmann P, Sadek M, Poirel L. In vitro activity of cefepime/zidebactam and cefepime/taniborbactam against aztreonam/avibactam-resistant NDM-like-producing *Escherichia coli* clinical isolates. J Antimicrob Chemother. 2023;78(5):1191–4 (https://doi.org/10.1093/jac/dkad061, accessed 4 March 2024).

30. Asempa TE, Kuti JL, Nascimento JC, Pope SJ, Salerno EL, Troy PJ et al. Bronchopulmonary disposition of IV cefepime/taniborbactam (2-0.5 g) administered over 2 h in healthy adult subjects. J Antimicrob Chemother. 2023;78(3):703–9 (https://doi.org/10.1093/jac/dkac447, accessed 4 March 2024).

31. McGovern PC, Wagenlehner F, Gasink L, Moeck G, McLeroth PL, Beth M et al. 731. CERTAIN-1: a Phase 3 study of cefepime-taniborbactam efficacy and safety in the treatment of complicated urinary tract infections (cUTI), including acute pyelonephritis (AP). Open Forum Infect Dis. 2022;9(Suppl 2):731 (https://doi.org/10.1093/ofid/ofac492.022, accessed 4 March 2024).

32. Benepem. PubChem CID 58326208. In: PubChem/ Compound summary [website]. Bethesda (MD): PubChem, National Center for Biotechnology Information; 2023 (https://pubchem.ncbi.nlm.nih.gov/compound/Benapenem, accessed 19 January 2024).

33. Ji XW, Xue F, Kang ZS, Zhong W. Kuan IHS, Yang XP et al. Model-informed drug development, pharmacokinetic/pharmacodynamic cutoff value determination, and antibacterial efficacy of benapenem against Enterobacteriaceae. Antimicrob Agents Chemother. 2020;64(3) (https://journals.asm.org/doi/10.1128/aac.01751-19, accessed 4 March 2024).

34. Zhao CY, Lv Y, Zhu Y, Wei MJ, Liu MY, Ji XW et al. A first-in-human safety, tolerability, and pharmacokinetics study of benapenem in healthy Chinese volunteers. Antimicrob Agents Chemother. 2019;63(3):e02188-18 (https://doi.org/10.1128/AAC.02188-18, accessed 4 March 2024).

35. Lu X. Pharmacodynamic evaluation of benapenem,a new carbapenem antibiotic, in mouse urinary tract infection model. Chin Med Biotechnol. 2015 (https://api.semanticscholar.org/CorpusID:87690082, accessed 19 January 2024).

36. Moya B, Barcelo IM, Bhagwat S, Patel M, Bou G, Papp-Wallace KM et al. WCK 5107 (zidebactam) and WCK 5153 are novel inhibitors of PBP2 showing potent "β-lactam enhancer" activity against *Pseudomonas aeruginosa*, including multidrug-resistant metallo-β-lactamase-producing high-risk clones. Antimicrob Agents Chemother. 2017;61(6):e02529-16 (https://doi.org/10.1128/AAC.02529-16, accessed 4 March 2024).

37. Moya B, Barcelo IM, Bhagwat S, Patel M, Bou G, Papp-Wallace KM et al. Potent β-lactam enhancer activity of zidebactam and WCK 5153 against *Acinetobacter baumannii*, including carbapenemase-producing clinical isolates. Antimicrob Agents Chemother. 2017;61(11):e01238-17 (https://doi.org/10.1128/AAC.01238-17, accessed 4 March 2024).

38. Mushtaq S, Garello P, Vickers A, Woodford N, Livermore DM. Activity of cefepime/zidebactam (WCK 5222) against "problem" antibiotic-resistant Gram-negative bacteria sent to a national reference laboratory. J Antimicrob Chemother. 2021;76(6):1511–22 (https://doi.org/10.1093/jac/dkab067, accessed 4 March 2024).

39. Livermore DM, Mushtaq S, Warner M, Vickers A, Woodford N. In vitro activity of cefepime/zidebactam (WCK 5222) against Gram-negative bacteria. J Antimicrob Chemother. 2017;72(5):1373–85 (https://doi.org/10.1093/jac/dkw593, accessed 4 March 2024).

40. Sader HS, Mendes RE, Duncan LR, Carvalhaes CG, Castanheria M. Antimicrobial activity of cefepime/zidebactam (WCK 5222), a β-lactam/β-lactam enhancer combination, against clinical isolates of Gram-negative bacteria collected worldwide (2018-19). J Antimicrob Chemother. 2022;77(10):2642–9 (https://doi.org/10.1093/jac/dkac233, accessed 4 March 2024).

41. Karlowsky JA, Hackel MA, Bouchillon SK, Sahm DF. In vitro activity of WCK 5222 (cefepime-zidebactam) against worldwide collected Gram-negative bacilli not susceptible to carbapenems. Antimicrob Agents Chemother. 2020;64(12):e01432-20 (https://doi.org/10.1128/AAC.01432-20, accessed 4 March 2024).

42. Bhagwat SS, Periasamy H, Takalkar SS, Palwe SR, Khande HN, Patel MV. The novel β-lactam enhancer zidebactam augments the in vivo pharmacodynamic activity of cefepime in a neutropenic mouse lung *Acinetobacter baumannii* infection model. Antimicrob Agents Chemother. 2019;63(4):e02146-18 (https://doi.org/10.1128/aac.02146-18, accessed 4 March 2024).

43. Avery LM, Abdelraouf K, Nicolau DP. Assessment of the in vivo efficacy of WCK 5222 (cefepime-zidebactam) against carbapenem-resistant *Acinetobacter baumannii* in the neutropenic murine lung infection model. Antimicrob Agents Chemother. 2018;62(11):e00948-18 (https://doi.org/10.1128/AAC.00948-18, accessed 4 March 2024).

44. Almarzoky Abuhussain SS, Avery LM, Abdelraouf K, Nicolau DP. In vivo efficacy of humanized WCK 5222 (cefepime-zidebactam) exposures against carbapenem-resistant *Acinetobacter baumannii* in the neutropenic thigh model. Antimicrob Agents Chemother. 2019;63(1):e01931-18 (https://doi.org/10.1128/AAC.01931-18, accessed 4 March 2024).

45. Kidd JM, Abdelraouf K, Nicolau DP. Efficacy of human-simulated bronchopulmonary exposures of cefepime, zidebactam and the combination (WCK 5222) against MDR *Pseudomonas aeruginosa* in a neutropenic murine pneumonia model. J Antimicrob Chemother. 2020;75(1):149–55 (https://doi.org/10.1093/jac/dkz414, accessed 4 March 2024).

46. Egge SL, Lewis JS, Hakki M. Case commentary: successful use of cefepime/zidebactam (WCK 5222) as a salvage therapy for the treatment of disseminated extensively drug-resistant New Delhi metallo-β-Lactamase-Producing *Pseudomonas aeruginosa* infection in an adult patient with acute T-cell leukemia. Antimicrob Agents Chemother. 2023;67(8) (https://journals.asm.org/doi/10.1128/aac.00663-23, accessed 12 January 2024).

47. Rodvold KA, Gotfried MH, Chugh R, Gupta M, Patel A, Chavan R et al. Plasma and intrapulmonary concentrations of cefepime and zidebactam following intravenous administration of WCK 5222 to healthy adult subjects. Antimicrob Agents Chemother. 2018;62(8):e00682-18 (https://doi.org/10.1128/AAC.00682-18, accessed 4 March 2024).

48. Durand-Réville TF, Comita-Prevoir J, Zhang J, Wu X, May-Dracka TL, Romero JAC et al. Discovery of an orally available diazabicyclooctane inhibitor (ETX0282) of class A, C, and D serine β-lactamases. J Med Chem. 2020;63(21):12511–25 (https://doi.org/10.1021/acs.jmedchem.0c00579, accessed 4 March 2024).

49. Miller AA, Shapiro AB, McLeod SM, Carter NM, Moussa SH, Tommasi R et al. In vitro characterization of ETX1317, a broad-spectrum β-lactamase inhibitor that restores and enhances β-lactam activity against multi-drug-resistant Enterobacteriales, including carbapenem-resistant strains. ACS Infect Dis. 2020;6(6):1389–97 (https://doi.org/10.1021/acsinfecdis.0c00020, accessed 4 March 2024).

50. O'Donnell J, Tanudra A, Chen A, Hines D, Tommasi R, Mueller J. Pharmacokinetic/pharmacodynamic determination and preclinical pharmacokinetics of the β-lactamase inhibitor ETX1317 and its orally available prodrug ETX0282. ACS Infect Dis. 2020;6(6):1378–88 (https://doi.org/10.1021/acsinfecdis.0c00019, accessed 4 March 2024).

51. Weiss, W., K. Carter, M. Pulse, P. Nguyen, D. Valtierra, K. Peterson, R. Tommasi, J. Mueller, J. O'Donnell. 2019. Efficacy of cefpodoxime proxetil and ETX0282 in a murine UTI model with *Escherichia coli* and *Klebsiella pneumoniae*. 29th ECCMID, Amsterdam, NE.

52. Shapiro AB, Moussa SH, Carter NM, Gao N, Miller AA. Ceftazidime-avibactam resistance mutations V240G, D179Y, and D179Y/T243M in KPC-3 β-lactamase do not alter cefpodoxime-ETX1317 susceptibility. ACS Infect Dis. 2021;7(1):79–87 (https://doi.org/10.1021/acsinfecdis.0c00575, accessed 4 March 2024).

53. O'Donnell J, Tanudra A, Chen A, Hines D, Tommasi R, Mueller J. Pharmacokinetic/Pharmacodynamic Determination and Preclinical Pharmacokinetics of the β-Lactamase Inhibitor ETX1317 and Its Orally Available Prodrug ETX0282. ACS Infect Dis. 2020;6(6):1378-1388. (https://doi.org/10.1021/acsinfecdis.0c00019, accessed 4 March 2024).

54. Hagihara M, Kato H, Sugano T, Okade H, Sato N, Sakanashi D et al. Pharmacodynamic evaluation of meropenem, cefepime, and aztreonam combined 2 with a novel β-lactamase inhibitor, nacubactam, against carbapenem-resistant 3 and/or carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* using a murine thigh infection model. 2021;57(5)5:106330 (https://doi.org/10.1016/j.ijantimicag.2021.106330, accessed 4 March 2024).

55. Asempa TE, Motos A, Abdelraouf K, Bissantz C, Zampaloni C, Nicolau DP. Efficacy of human-simulated epithelial lining fluid exposure of meropenem-nacubactam combination against Class A serine β-lactamase-producing Enterobacteriaceae in the neutropenic murine lung infection model. Antimicrob Agents Chemother. 2019;63(4):e02382-18 (https://doi.org/10.1128/aac.02382-18, accessed 4 March 2024).

56. Morinaka A, Tsutsumi Y, Yamada M, Suzuki K, Watanabe T, Abe T et al. OP0595, a new diazabicyclooctane: mode of action as a serine β-lactamase inhibitor, antibiotic and β-lactam "enhancer". J Antimicrob Chemother. 2015;70(10):2779–86 (https://academic.oup.com/jac/article/70/10/2779/829602, accessed 28 February 2024).

57. Doumith M, Mushtaq S, Livermore DM, Woodford N. New insights into the regulatory pathways associated with the activation of the stringent response in bacterial resistance to the PBP2-targeted antibiotics, mecillinam and OP0595/RG6080. J Antimicrob Chemother. 2016;71(10):2810-4 (https://doi.org/10.1093/jac/dkw230, accessed 4 March 2024).

58. Okujava R, Garcia-Alcalde F, Haldimann A, Zampaloni C, Morrissey I, Magnet S et al. 1359. Activity of meropenem/nacubactam combination against Gram-negative clinical isolates: ROSCO global surveillance 2017. Open Forum Infect Dis. 2018;5(Suppl 1):S416 (https://doi.org/10.1093/ofid/ofy210.1190, accessed 4 March 2024).

59. Hagihara M, Kato H, Sugano T, Okade H, Sato N, Shibata Y et al. In vivo pharmacodynamics of β-lactams/nacubactam against carbapenem-resistant and/or carbapenemase-producing *Enterobacter* cloacae and *Klebsiella pneumoniae* in murine pneumonia model. Antibiotics (Basel). 2021;10(10):1179 (https://doi.org/10.3390/antibiotics10101179, accessed 4 March 2024).

60. Mushtaq S, Vickers A, Woodford N, Haldimann A, Livermore DM. Activity of nacubactam (RG6080/OP0595) combinations against MBL-producing Enterobacteriaceae. J Antimicrob Chemother. 2019;74(4):953-60 (https://doi.org/10.1093/jac/dky522, accessed 4 March 2024).

61. Mallalieu NL, Winter E, Fettner S, Patel K, Zwanziger E, Attley G et al. Safety and pharmacokinetic characterization of nacubactam, a novel β-lactamase inhibitor, alone and in combination with meropenem, in healthy volunteers. Antimicrob Agents Chemother. 2020;64(5):e02229-19 (https://doi.org/10.1128/AAC.02229-19, accessed 4 March 2024).

62. Lomovskaya O, Tsivkovski R, Sun D, Reddy R, Totrov M, Hecker S et al. QPX7728, an ultra-broad-spectrum β-lactamase inhibitor for intravenous and oral therapy: overview of biochemical and microbiological characteristics. Front Microbiol. 2021;12:697180 (https://doi.org/10.3389/fmicb.2021.697180, accessed 4 March 2024).

63. Reddy KR, Parkinson J, Sabet M, Tarazi Z, Boyer SH, Lomovskaya O et al. Selection of QPX7831, an orally bioavailable prodrug of boronic acid β-lactamase inhibitor QPX7728. J Med Chem. 2021;64(23):17523–9 (https://doi.org/10.1021/acs.jmedchem.1c01722, accessed 4 March 2024).

64. Hecker S, Reddy K, Lomovskaya O, Griffith D, Rubio-Aparicio D, Nelson K et al. Discovery of cyclic boronic acid QPX7728, an ultrabroad-spectrum inhibitor of serine and metallo-β-lactamases. J Med Chem. 2020;63(14):7491–507 (https://doi.org/10.1021/acs.jmedchem.9b01976, accessed 4 March 2024).

65. Tsivkovski R, Totrov M, Lomovskaya O. Biochemical characterization of QPX7728, a new ultrabroad-spectrum beta-lactamase inhibitor of serine and metallo-beta-lactamases. Antimicrob Agents Chemother. 2020;64(6):e00130-20 (https://journals.asm.org/doi/10.1128/aac.00130-20, accessed 4 March 2024).

66. Sun D, Tsivkovski R, Pogliano J, Tsunemoto H, Nelson K, Rubio-Aparicio D et al. Intrinsic antibacterial activity of xeruborbactam in vitro: assessing spectrum and mode of action. Antimicrob Agents Chemother. 2022;66(10):e0087922 (https://doi.org/10.1128/aac.00879-22, accessed 4 March 2024).

67. Nelson K, Rubio-Aparicio D, Sun D, Dudley M, Lomovskaya O. In vitro activity of the ultrabroad-spectrum-beta-lactamase inhibitor QPX7728 against carbapenem-resistant Enterobacterales with varying intrinsic and acquired resistance mechanisms. Antimicrob Agents Chemother. 2020;64(8) (https://doi.org/10.1128/AAC.00757-20, accessed 4 March 2024).

68. Lomovskaya O, Rubio-Aparicio D, Tsivkovski R, Loutit J, Dudley M. The ultrabroad-spectrum beta-lactamase inhibitor QPX7728 restores the potency of multiple oral beta-lactam antibiotics against beta-lactamase-producing strains of resistant Enterobacterales. Antimicrob Agents Chemother. 2022;66(2):e02168-21 (https://doi.org/10.1128/AAC.02168-21, accessed 4 March 2024).

69. Lomovskaya O, Nelson K, Rubio-Aparicio D, Tsivkovski R, Sun D, Dudley MN. Impact of intrinsic resistance mechanisms on potency of QPX7728, a new ultrabroad-spectrum beta-lactamase inhibitor of serine and metallo-beta-lactamases in Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Antimicrob Agents Chemother. 2020;64(6):e00552-20 (https://doi.org/10.1128/AAC.00552-20, accessed 4 March 2024).

70. Sabet M, Tarazi Z, Griffith DC. In vivo activity of QPX7728, an ultrabroad-spectrum beta-lactamase inhibitor, in combination with beta-lactams against carbapenem-resistant *Klebsiella pneumoniae*. Antimicrob Agents Chemother. 2020;64(11):e01267-20 (https://doi.org/10.1128/AAC.01267-20, accessed 4 March 2024).

71. Butler MS, Gigante V, Sati H, Paulin S, Al-Sulaiman L, Rex JH et al. Analysis of the clinical pipeline of treatments for drug-resistant bacterial infections: despite progress, more action is needed. Antimicrob Agents Chemother. 2022;66(3):e0199121 (https://doi.org/10.1128/AAC.01991-21, accessed 4 March 2024).

72. Li Y, Yan M, Xue F, Zhong W, Liu X, Chen X et al. In vitro and in vivo activities of a novel β-lactamase inhibitor combination imipenem/XNW4107 against recent clinical Gram-negative bacilli from China. J Glob Antimicrob Resist. 2022;31:1-9 (https://doi.org/10.1016/j.jgar.2022.07.006, accessed 4 March 2024).

73. Fratoni AJ, Berry AV, Liu X, Chen X, Wu Y, Nicolau DP et al. Imipenem/funobactam (formerly XNW4107) in vivo pharmacodynamics against serine carbapenemase-producing Gram-negative bacteria: a novel modelling approach for time-dependent killing. J Antimicrob Chemother. 2023;78(9):2343–53 (https://doi.org/10.1093/jac/dkad242, accessed 4 March 2024).

74. Lence E, González-Bello C. Bicyclic boronate β-lactamase inhibitors: the present hope against deadly bacterial pathogens. Adv Ther. 2021 Feb 15;4(5):2000246 (https://doi.org/10.1002/adtp.202000246, accessed 18 January 2024).

75. Mendes RE, Rhomberg PR, Watters AA, Castanheira M. In vitro activity of the orally bioavailable ceftibuten/VNRX-7145 (VNRX-5236 etzadroxil) combination against a challenge set of Enterobacterales pathogens carrying molecularly characterized β-lactamase genes. J Antimicrob Chemother. 2022;77(3):689–94 (https://doi.org/10.1093/jac/dkab425, accessed 4 March 2024).

76. Karlowsky JA, Wise MG, Hackel MA, Pevear DC, Moeck G, Sahm DF. Ceftibuten-ledaborbactam activity against multidrug-resistant and extended-spectrum-β-lactamase-positive clinical isolates of Enterobacterales from a 2018–2020 global surveillance collection. Antimicrob Agents Chemother. 2022;66(11):e00934-22 (https://doi.org/10.1128/aac.00934-22, accessed 4 March 2024).

77. Trout RE, Zulli A, Mesaros E, Jackson RW, Boyd S, Liu B et al. Discovery of VNRX-7145 (VNRX-5236 etzadroxil): an orally bioavailable β-lactamase inhibitor for Enterobacterales expressing ambler class A, C, and D enzymes. J Med Chem. 2021;64(14):10155–66 (https://doi.org/10.1021/acs.jmedchem.1c00437, accessed 4 March 2024).

78. Mushtaq S, Garello P, Vickers A, Woodford N, Livermore DM. Activity of ertapenem/zidebactam (WCK 6777) against problem Enterobacterales. J Antimicrob Chemother. 2022;77(10):2772–8 (https://doi.org/10.1093/jac/dkac280, accessed 4 March 2024).

79. Mushtaq S, Vickers A, Chaudhry A, Woodford N, Livermore DM. Inoculum effects of cefepime/zidebactam (WCK 5222) and ertapenem/zidebactam (WCK 6777) for Enterobacterales in relation to β-lactamase type and enhancer effect, as tested by BSAC agar dilution. J Antimicrob Chemother. 2022;77(7):1916–22 (https://doi.org/10.1093/jac/dkac108, accessed 4 March 2024).

80. Gethers M, Chen I, Abdelraouf K, Nicolau DP. In vivo efficacy of WCK 6777 (ertapenem/zidebactam) against carbapenemase-producing *Klebsiella pneumoniae* in the neutropenic murine pneumonia model. J Antimicrob Chemother. 2022;77(7):1931–7 (https://doi.org/10.1093/jac/dkac110, accessed 4 March 2024).

81. Wockhardt [website]. Aurangabad: Wockhardt; 2024 (https://www.wockhardt.com/, accessed 19 January 2024).

82. Morinaka A, Tsutsumi Y, Yamada K, Takayama Y, Sakakibara S, Takata T et al. In vitro and in vivo activities of OP0595, a new diazabicyclooctane, against CTX-M-15-Positive *Escherichia coli* and KPC-positive *Klebsiella pneumoniae*. Antimicrob Agents Chemother. 2016;60(5):3001–6 (https://doi.org/10.1128/AAC.02704-15, accessed 4 March 2024).

83. Igarashi Y, Takemura W, Liu X, Kojima N, Morita T, Chuang VTG et al. Development of an optimized and practical pharmacokinetics/pharmacodynamics analysis method for aztreonam/nacubactam against carbapenemase-producing *K. pneumoniae*. J Antimicrob Chemother. 2023;78(4):991–9 (https://doi.org/10.1093/jac/dkad033, accessed 4 March 2024).

84. Le Terrier C, Nordmann P, Poirel L. In vitro activity of aztreonam in combination with newly developed β-lactamase inhibitors against MDR Enterobacterales and *Pseudomonas aeruginosa* producing metallo-β-lactamases. J Antimicrob Chemother. 2022;78(1):101–7 (https://doi.org/10.1093/jac/dkac360, accessed 4 March 2024).

85. Davies DT, Leiris S, Zalacain M, Sprynski N, Castandet J, Bousquet J et al. Discovery of ANT3310, a novel broad-spectrum serine β-lactamase inhibitor of the diazabicyclooctane class, which strongly potentiates meropenem activity against carbapenem-resistant Enterobacterales and *Acinetobacter baumannii*. J Med Chem. 2020;63(24):15802–20 (https://doi.org/10.1021/acs.jmedchem.0c01535, accessed 4 March 2024).

86. Antabio receives FDA qualified infectious disease product (QIDP) designation for MEM-ANT3310, a novel broad-spectrum combination therapy targeting WHO's priority pathogens. In: Antabio/News [website]. Labège: Antabio; 2020 (https://antabio.com/2020/05/06/antabio-receives-fda-qualified-infectious-disease-product-qidp-designation-for-mem-ant3310-a-novel-broad-spectrum-combination-therapy-targeting-whos-priority-pathogens/, accessed 12 January 2024).

87. Kitasato Institute and Sumitomo Dainippon Pharma start Phase 1 study on new drug candidate compound discovered in joint research as treatment for carbapenem-resistant bacterial infections. In: Sumitomo Pharma/News room [website]. Osaka: Sumitomo Pharma; 2022 (https://www.sumitomo-pharma.com/news/20220113.html, accessed 19 January 2024).

88. Dansky H, Naik H, Shen S, Bordelon N, Meyer J, Tomita Y et al. Safety, tolerability, and pharmacokinetics of KSP-1007 after single and multiple ascending doses alone or in combination with meropenem in healthy subjects. Presented at ASM Microbe, Houston, TX, USA, 15–19 June 2023; Poster AAR-FRIDAY-519 (https://www.abstractsonline.com/pp8/#!/10789/presentation/6827, accessed 15 January 2024).

Annex 4. Cell membrane disruptors – polymyxins

Product name (INN or company code): MRX-8

Pharmacology: chemical class and MoA: MRX-8 is a polymyxin analogue of an undisclosed structure.

Spectrum of activity and potential resistance: In an in vitro study *(1)* MRX-8, colistin and PMB exhibited nearly identical antimicrobial activities against Enterobacterales, *P. aeruginosa* and *A. baumannii* isolate sets. MRX-8 is not active against PMB / colistin-resistant *E. coli* and *K. pneumoniae* isolates; MIC90 was > 32 mg/L *(1,2)*, and in *Shigella* spp. ranged from 0.06 to 0.25 mg/L *(2)*. In vivo, activity has been observed against clinically relevant Gram-negative species, including *P. aeruginosa*, *K. pneumoniae* and *A. baumannii* in neutropenic mouse thigh and lung infection models *(3)*.

Sought therapeutic indication: In development for the treatment of infections caused by MDR Gram-negative pathogens, including *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii (4)*.

Route of administration: Intravenous.

Phase of clinical development: Completed a Phase 1 trial in 2021 (NCT04649541); another Phase 1 trial is ongoing in China.

Clinical trial(s): Phase 1 trial (NCT04649541) was an adaptive, randomized, double-blind, placebo-controlled three-part study of the safety, tolerability and PK of MRX-8 administered iv to healthy volunteers in single and multiple ascending dose cohorts between November 2020 and 30 August 2021. The primary end-point was adverse events and other key laboratory and vitals parameters. No published results are available.

Preclinical PK and safety: In vivo using PMB as a comparator, both MRX-8 and PMB exhibited increased effects with increasing doses *(3)*.

Product name (INN or company code): QPX9003 (F365, BRII-693)

Pharmacology: chemical class and MoA: QPX9003 (previously F365) is a synthetic lipopolypeptide PMB derivative of an undisclosed structure *(5)*.

Spectrum of activity and potential resistance: QPX9003 has been reported to confer slightly better in vitro activity against *P. aeruginosa*, *A. baumannii* and *K. pneumoniae* isolates compared to PMB *(5,6)*. QPX9003 is shown to be less prone to developing resistance than PMB in serial passaging experiments *(5)*. QPX9003 was also tested in vivo in a neutropenic mouse lung infection model against polymyxin-susceptible MDR clinical isolates of *K. pneumoniae*, CRPA and CRAB *(5)*. In a neutropenic mouse thigh infection model, QPX9003 exhibited a reduction in CFU/thigh as compared to PMB against polymyxin-susceptible CRAB clinical isolates *(5)*.

Sought therapeutic indication: The drug is being studied as treatment for MDR *Pseudomonas* or *Acinetobacter* infections.

Route of administration and proposed posology: Intravenous.

Phase of clinical development: 1

Clinical trial(s): Phase 1 (NCT04808414) to assess the safety, tolerability and PK of single and multiple iv-administered single and multiple ascending doses of iv QPX9003 in 104 healthy adult subjects between 3 June 2021 and 14 July 2022.

Product name (INN or company code): QPX9003 (F365, BRII-693) (continued)

Primary end-points were emergent adverse events and relevant lab parameters.

Preclinical PK and safety: In vivo, QPX9003 has not been associated with nephrotoxicity, even at a dose of up to 72 mg/kg/day in a mouse model *(5,6)*. In PK analyses of mouse pulmonary epithelial lining fluid, QPX9003 attained a threefold higher Cmax than PMB after a single subcutaneous dose of 40 mg/kg *(5,6)*. It was safe and well tolerated at all doses tested based on preliminary data from the Phase 1 trial *(6,7)*.

Product name (INN or company code): upleganan (SPR-206)

Pharmacology: chemical class and MoA: SPR-206 is a novel semi-synthetic PMB analogue.

Spectrum of activity and potential resistance: SPR-206 has shown in vitro activity against MDR Gram-negative drug-resistant bacteria, Ambler Class A, B, C, and D β-lactamase-producing Enterobacterales strains *(8,9)*, and activity against OXA-23-expressing *A. baumannii*, *Klebsiella pneumoniae* carbapenemase (KPC) and NDM-expressing Enterobacterales *(9,10)*. In vivo studies (poster data) in thigh, lung and UTI models in mice suggest that SPR206 achieves efficacy end-points at similar or lower required doses than PMB *(10,11)*.

Sought therapeutic indication: Drug-resistant Gram-negative bacterial infection caused by CRAB, CRPA, CRE and ESBL-producing Enterobacterales, e.g., in cUTI, HABP, VABP and BSI.

Route of administration: Intravenous.

Phase of clinical development: 1

Clinical trial(s): SPR206 has completed three Phase 1 trials (NCT03792308, NCT04868292 and NCT04865393). Spero Therapeutics announced that it has received US FDA clearance for a Phase 2, cross-indication resistant pathogen clinical trial designed to enrol patients. The most recently completed study (NCT04865393) was an open-label study to assess the safety and PK of SPR206 following a single iv dose of SPR206 in 38 adult participants with varying degrees of renal function. It occurred between June 2021 to December 2021, in New Zealand with primary end-points of time to the maximum plasma concentration (Tmax) and Cmax.

Preclinical PK and safety: In vivo toxicology studies in mice, rats and primates show reduced nephrotoxicity compared to polymyxin *(12)*. It remains unclear whether lower MIC values in vitro will translate into useful activity in colistin-resistant strains and what role nephrotoxicity will play in the clinical management of patients *(12)*. SPR206 was generally safe and generally well tolerated in Phase 1 trials *(13)* While the incidence of adverse events increased with dose, most were of mild severity *(13)*. Urinary excretion of unchanged SPR206 was dose-dependent across single and multiple ascending dose cohorts, and approximately 50% of the dose was excreted as SPR206 *(13)*.

References

1. Duncan LR, Wang W, Sader HS. In vitro potency and spectrum of the novel polymyxin MRX-8 tested against clinical isolates of Gram-negative bacteria. Antimicrob Agents Chemother. 2022;66(5):e00139-22 (https://doi.org/10.1128/aac.00139-22, accessed 12 January 2024).
2. Wu S, Yin D, Zhi P, Guo Y, Yang Y, Zhu D et al. In vitro activity of MRX-8 and comparators against clinical isolated Gram-negative bacilli in China. Front Cell Infect Microbiol. 2022;12:829592 (https://doi.org/10.3389/fcimb.2022.829592, accessed 19 January 2024.
3. Lepak AJ, Wang W, Andes DR. Pharmacodynamic evaluation of MRX-8, a novel polymyxin, in the neutropenic mouse thigh and lung infection models against Gram-negative pathogens. Antimicrob Agents Chemother. 2020 Oct 1;64(11) (https://doi.org/10.1128/AAC.01517-20, accessed 18 January 2024).
4. Gordeev MF, Liu J, Wang X, Yuan Z. Antimicrobial polymyxins for treatment of bacterial infections. US Patent 9,771,394; 2017 (https://patents.justia.com/assignee/micurx-pharmaceuticals-inc, accessed 12 January 2024).
5. Roberts KD, Zhu Y, Azad MAK, Han ML, Wang J, Wang L et al. A synthetic lipopeptide targeting top-priority multidrug-resistant Gram-negative pathogens. Nat Commun. 2022;13(1):1625 (https://doi.org/10.1038/s41467-022-29234-3, accessed 19 January 2024).
6. Aslan AT, Akova M, Paterson DL. Next-generation polymyxin class of antibiotics: a ray of hope illuminating a dark road. Antibiotics. 2022;11(12):1711 (https://doi.org/10.3390/antibiotics11121711, accessed 12 January 2024).
7. Griffith DC, Carmeli Y, Gehrke S, Morgan EE, Dudley MN, Loutit JS. 217. A Phase 1 study of the safety, tolerability and pharmacokinetics of multiple doses of the lipopeptide QPX9003 in healthy adult subjects. Open Forum Infect Dis. 2022;9(Suppl 2):ofac492.295 (https://doi.org/10.1093/ofid/ofac492.295, accessed 15 January 2024).
8. Zhang Y, Zhao C, Wang Q, Wang X, Chen H, Li H et al. Evaluation of the in vitro activity of new polymyxin B analogue SPR206 against clinical MDR, colistin-resistant and tigecycline-resistant Gram-negative bacilli. J Antimicrob Chemother. 2020;75(9):2609–15 (https://doi.org/10.1093/jac/dkaa217, accessed 28 February 2024).
9. Mendes RE, Sader HS, Arends SJR, Cotroneo N, Critchley IA, Castanheira M. 1676. Activity of SPR206 and comparator agents against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* causing infections in United States hospitals. Open Forum Infect Dis. 1676;2022:9(Supplement_2):S645 (https://doi.org/10.1093/ofid/ofac492.1306, accessed 28 February 2024).
10. Grosser L, Heang K, Teague J, Warn P, Corbett D, Dawson MJ et al. In vivo efficacy of SPR206 in murine lung and thigh infection models caused by multidrug resistant pathogens *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Abstr ESCMID-ASM. In: Spero Therapeutics/Posters and publications [website]. Cambridge (MA): Spero Therapeutics; 2018 (https://assets-global.website-files.com/62e0c10f4b3bff39a9369757/6303a8e9ff8604254315aa3d_620183ef69941702d465f719_ASM%20Microbe%202019%20-%20Poster%20799%20-%20In%20vivo%20efficacy%20of%20SPR206%20in%20murine.png, accessed 15 January 2024).
11. Grosser L, Lister T, Heang K, Brown P, Dawson M, Rubio A. In vivo efficacy of next-generation polymyxin SPR206 in an immunocompetent murine ascending UTI infection model caused by *Escherichia coli*. Presented at ASM Microbe 2019, San Francisco, CA, USA, 20–24 June 2019; Poster AAR-798.
12. Brown P, Abbott E, Abdulle O, Boakes S, Coleman S, Divall N et al. Design of next generation polymyxins with lower toxicity: the discovery of spr206. ACS Infect Dis:. 2019;5(10):1645–56 (https://doi.org/10.1021/acsinfecdis.9b00217, accessed 28 February 2024).
13. Bruss J, Lister T, Gupta VK, Stone E, Morelli L, Lei Y et al. Single- and multiple-ascending-dose study of the safety, tolerability, and pharmacokinetics of the polymyxin derivative SPR206. Antimicrob Agents Chemother. 2021 Oct 1;65(10):e0073921 (https://doi.org/10.1128/aac.00739-21, accessed 12 January 2024).

Annex 5. Cell membrane disruptors – host defence peptides

Product name (INN or company code):
OMN6

Pharmacology: chemical class and MoA: OMN6 is a synthetic cyclic peptide composed of 40 amino acids that exerts a bactericidal effect by causing selective disruption of bacterial membrane integrity *(1)*.

Spectrum of activity and potential resistance: OMN6 showed in vitro activity against laboratory strains and clinical isolates of drug-resistant Gram-negative *A. baumannii* and other Gram-negative pathogens (colistin-resistant *E. coli* and MDR *K. pneumoniae* at higher MICs) *(1,2)*. It was efficacious in two murine models of lethal bacteraemia and lung infection caused by CRAB *(1,2)*. Due to its MoA, OMN6 is expected to be efficacious against *A. baumanni* regardless of the bacteria genotype; the resistance phenotype exhibited a low propensity for resistance development in vitro as well as enhanced activity in the presence of lung surfactant *(2)*.

Sought therapeutic indication: OMN6 is being developed as a novel therapy to treat life-threatening *A. baumannii* infections such as bacteraemia and severe pulmonary infections *(2)*.

Route of administration and proposed posology: Intravenous.

Phase of clinical development: 1

Clinical trial(s): Phase 1 was a randomized, double-blind, placebo-controlled, single ascending dose study of 80 healthy volunteers, including a cohort of elderly patients in Gröningen, Netherlands (Kingdom of the). The primary end-point was the safety and tolerability of single ascending iv doses of OMN6. There are no published results as yet. In a company topline data press release, the study met all end-points, and no severe or serious adverse events were observed at any dose level in the study. Clinically meaningful levels of OMN6 were reached in the blood, and the drug cleared completely, allowing multiple daily infusions *(3)*.

Preclinical PK and safety: OMN6 has shown enhanced resistance to proteolysis, and no toxicity towards eukaryotic or mammalian cells in vivo *(2)*.

Product name (INN or company code): murepavadin (POL7080, iMPV (inhaled))

Pharmacology: chemical class and MoA: Murepavadin (POL7080; iMPV) is a novel peptidomimetic antibiotic from the outer membrane protein targeting antibiotics class that inhibits LptD, an outer membrane protein involved in lipopolysaccharide biogenesis in Gram-negative bacteria *(4)*. By binding to LptD, murepavadin inhibits the lipopolysaccharide transport function of LptD and causes lipopolysaccharide alterations in the outer membrane of the bacterium and, ultimately, cell death *(5)*.

Spectrum of activity and potential resistance: iMPV activity is restricted towards *P. aeruginosa*, including carbapenemase-producing and colistin-resistant *P. aeruginosa*. In vitro studies have demonstrated activity of murepavadin against a large collection of XDR *P. aeruginosa* from Europe and North America (MIC90 = 0.12 mg/L) and *P. aeruginosa* isolates recovered from people with CF (MIC90=2 mg/L) (6,7,8). Intratracheal administration of murepavadin in a murine *P. aeruginosa* lung infection model resulted in > 2 log10 reduction in CFUs against *P. aeruginosa* strains at doses below 1 mg/kg with a > 1 log10 CFU reduction of *P. aeruginosa* at 1.25 mg/kg (9). Aguilar et al. reported that murepavadin's affinity for the cell surface may be reduced by mutations in genes related to lipopolysaccharide biosynthesis and transport, and that its resistance may also be caused by genes coding for multidrug efflux pumps (acrB) or genes that regulate colistin resistance (7). Evidence of potential cross-resistance with colistin, involving lipopolysaccharide modifications that mitigate antibiotic cell membrane binding, has been shown by Romano et al. (2019) *(10)*.

Sought therapeutic indication: inhaled murepavadin (iMPV) is being investigated in *P. aeruginosa* infection; CF and non-CF bronchiectasis (NCFB).

Route of administration: Orally inhaled. *Note: Two previous Phase 3 trials evaluating the efficacy and safety of the iv formulation of murapavadin in patients with HABP or VABP due to P. aeruginosa were terminated due to safety concerns. The new formulation for inhalation (iMPV), characterized by low systemic bioavailability, is currently under clinical development.*

Phase of clinical development: 1b/2a

Clinical trial (s): The Phase 1 trial was a single-centre, double-blind, randomized, placebo-controlled trial to investigate the safety, tolerability and PK of single ascending doses of iMPV in 39 healthy volunteers.

Results: From a Spexis press release *(11)*: "In Part A of the trial, three single-dose levels, 12.5mg, 25mg, and 50mg of the macrocycle compound were evaluated in four subjects per cohort. In Part B, single doses of 75mg, 150mg, and 300mg were evaluated in nine subjects per cohort. The PK of iMPV were assessed in blood samples and in epithelial lining fluid (ELF) obtained by bronchoalveolar lavage. At the highest single dose tested:

- Systemic bioavailability of MPV was lower than 5 percent
- Peak plasma concentrations were observed at 1–2 hours post start of inhalation
- In the ELF, the concentration of MPV at the 24-hour timepoint was still above the concentration that would inhibit the growth of 90% of *P. aeruginosa* isolates (MIC90) obtained from people with CF."

References

1. Mandel S, Michaeli J, Nur N, Erbetti I, Zazoun J, Ferrari L et al. OMN6 a novel bioengineered peptide for the treatment of multidrug resistant Gram negative bacteria. Sci Rep. 2021;11(1):6603 (https://doi.org/10.1038/s41598-021-86155-9, accessed 28 February 2024).
2. Michaeli J, Mandel S, Maximov S, Zazoun J, Savoia P, Kothari N et al. In vitro and in vivo antimicrobial activity of the novel peptide OMN6 against multidrug-resistant *Acinetobacter baumannii*. Antibiotics. 2022;11(9):1201 (https://doi.org/10.3390/antibiotics11091201, accessed 19 January 2024).
3. Omnix Medical announces excellent topline data from the Phase 1 clinical trial of its novel anti-infective OMN6. In: Omnix Medical/Omnix news [website]. Jerusalem: Omnix Medical; 2023 (https://omnixmedical.com/2023/05/10/omnix-medical-announces-excellent-topline-data-from-the-phase-i-clinical-trial-of-its-novel-anti-infective-omn6/, accessed 15 January 2024).
4. Srinivas N, Jetter P, Ueberbacher BJ, Werneburg M, Zerbe K, Steinmann J et al. Peptidomimetic antibiotics target outer-membrane biogenesis in *Pseudomonas aeruginosa*. Science. 2010;327(5968):1010–3 (https://www.science.org/doi/10.1126/science.1182749, accessed 28 February 2024).
5. Werneburg M, Zerbe K, Juhas M, Bigler L, Stalder U, Kaech A et al. Inhibition of lipopolysaccharide transport to the outer membrane in *Pseudomonas aeruginosa* by peptidomimetic antibiotics. ChemBioChem. 2012;13(12):1767–75 (https://doi.org/10.1002/cbic.201200276, accessed 28 February 2024).
6. Ekkelenkamp MB, Cantón R, Díez-Aguilar M, Tunney MM, Gilpin DF, Bernardini F et al. Susceptibility of *Pseudomonas aeruginosa* recovered from cystic fibrosis patients to Murepavadin and 13 comparator antibiotics. Antimicrob Agents Chemother. 2020;64(2) (https://doi.org/10.1128/aac.01541-19, accessed 28 February 2024).
7. Díez-Aguilar M, Hernández-García M, Morosini MI, Fluit A, Tunney MM, Huertas N et al. Murepavadin antimicrobial activity against and resistance development in cystic fibrosis *Pseudomonas aeruginosa* isolates. J Antimicrob Chemother. 2021;76(4):984-92 (https://doi.org/10.1093/jac/dkaa529, accessed 16 January 2024).
8. Sader HS, Flamm RK, Dale GE, Rhomberg PR, Castanheira M. Murepavadin activity tested against contemporary (2016-17) clinical isolates of XDR *Pseudomonas aeruginosa*. J Antimicrob Chemother. 2018;73(9):2400–4 (https://doi.org/10.1093/jac/dky227, accessed 28 February 2024).
9. Wang Y, Chang RYK, Britton WJ, Chan HK. Advances in the development of antimicrobial peptides and proteins for inhaled therapy. Adv Drug Deliv Rev. 2022;180:114066 (https://doi.org/10.1016/j.addr.2021.114066, accessed 28 February 2024).
10. Romano KP, Warrier T, Poulsen BE, Nguyen PH, Loftis AR, Saebi A et al. Mutations in pmrB confer cross-resistance between the LptD inhibitor POL7080 and colistin in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. 2019;63(9) (https://doi.org/10.1128/aac.00511-19, accessed 28 February 2024).
11. Eckford C. Promising first-in-human study results for orally inhaled antibiotic. In: EPR/News [website]. Kent: European Pharmaceutical Review; 2023 (https://www.europeanpharmaceuticalreview.com/news/178380/promising-first-in-human-study-results-for-orally-inhaled-antibiotic-macrocycle-compound/, accessed 19 January 2024).

Annex 6. Cell membrane disruptors – tethered macrocyclic peptides

Product name (INN or company code): zosurabalpin/RG6006 (also RO7223280, Abx MCP)

Pharmacology: chemical class and MoA: Zosurabalpin (RG6006) is a macrocyclic peptide that disrupts Gram-negative bacterial cell membranes by inhibiting the transport of LPS *(1)*.

Spectrum of activity and potential resistance: In vitro poster data show that zosurabalpin is active against *Acinetobacter* spp., including carbapenem-resistant *A. baumannii-calcoaceticus* complex organisms *(2)*. Its activity was not affected by colistin or meropenem resistance in vitro. Zosurabalpin shows no activity against other Gram-negative or Gram-positive species *(3)*. In January 2024, after the deadline for inclusion in the present pipeline, most of the above in vitro data and in vivo data showing activity in mouse models of *A. baumannii* infection were published in the journal *Nature* by Zampaloni et al. (2024).

Sought therapeutic indication: The drug is being studied for treatment of HABP, VABP and bacteraemia caused by CRAB.

Route of administration: Intravenous.

Phase of clinical development: Phase 1 (NCT05614895).

Clinical trial(s): A Phase 1 trial to investigate the safety, tolerability and PK of RO7223280 following iv administration in healthy participants is complete. It consisted of three parts: part 1 (a single iv dose of RO7223280 administered over 1 h, single ascending dose), part 2 (multiple ascending doses) and part 3 (safety, tolerability and PK of a single iv dose of RO7223280 in healthy elderly participants), starting with 124 healthy participants 18 years and older between December 2020 and March 2023. The primary end-point was the percentage of participants with adverse events. No results have yet been published.

Preclinical PK and safety: An unpublished release claims that in in vivo studies, zosurabalpin may be efficacious with improved iv tolerability and no organ toxicity *(1)*.

References

1. Mattei P. Discovery of RG6006, a tethered macrocyclic peptide targeting *Acinetobacter baumannii*. Presented at the 15th Winter Conference on Medicinal and Bioorganic Chemistry, Steamboat Springs Resort, CO, USA, 30 January – 3 February 2022 (https://mbcfconference.com/wp-content/uploads/2022/04/Patrizio-Mattei-2023-MBCF-abstract.pdf, accessed 19 January 2024).
2. Zampaloni C, Mattei P, Bleicher K, Winther L, Thäte C, Bucher C et al. A novel antibiotic class targeting the lipopolysaccharide transporter. Nature. 2024;625(7995):566–71 (https://doi.org/10.1038/s41586-023-06873-0, accessed 28 February 2024).
3. Shortridge D, Rhomberg P, Huband M, Castanheira M, Louvel S, Zampaloni C. In vitro activity of novel compound RG6006 against clinical isolates of *Acinetobacter baumannii*-calcoaceticus complex in the presence of 20% human serum. Presented at ECCMID, Copenhagen, Denmark, 15–18 April 2023; Poster P2173 (https://www.jmilabs.com/data/posters/ECCMID2023_RG6OO6.pdf, accessed 18 January 2024).

Annex 7. Protein synthesis inhibitors – tetracyclines

Product name (INN or company code): zifanocycline (KBP-7072)

Pharmacology: chemical class and MoA: Zifanocycline (KBP-7072) is a third-generation aminomethylcycline *(1)*.

Spectrum of activity and potential resistance: In vitro, KBP-7072 has displayed activity against both Gram-positive and Gram-negative pathogens, including MRSA, geographically diverse *A. baumannii* (including activity against carbapenem-resistant ESBL- and MBL-producing isolates) and ESBL-producing Enterobacterales *(2,3,4)*. KBP-7072 was found to be minimally affected by the presence of acquired tetracycline genes *(3)*. It also showed similar or slightly higher MIC values for tetracycline-susceptible and -resistant *S. aureus* strains compared with tigecycline and omadacycline *(2)*. In vivo data show activity against an MRSA neutropenic murine pneumonia model *(2)* and against *A. baumannii* in a neutropenic murine thigh infection model *(6)*.

Sought therapeutic indication: ABSSSI, CABP and cIAI *(2)*.

Route of administration: Intravenous/oral.

Phase of clinical development: 1

Clinical trial(s):

- Three Phase 1 clinical trials have been reported, completed in 2015 (NCT02454361), in 2016 (NCT02654626) and in October 2020 (NCT04532957), respectively. No results have been published as yet.

KBP-7072 is currently being evaluated in another Phase 1 trial: a double-blind, placebo-controlled, single and multiple iv dose, safety, tolerability and PK study in 56 healthy male and female subjects between August 2022 and 30 June 2023 (NCT05507463, completed June 2023). The study's primary end-point is adverse events and relevant laboratory and vital/physiological abnormalities.

Preclinical PK/PD: Bactericidal activity was noted at ≥ 1 mg/kg/6 h for both methicillin-susceptible *S. aureus* (MSSA) and MRSA; a 3 log10 kill was achieved for all strains tested *(5)*. MICs of zifanocycline against *A. baumannii* ranged from 0.06 mg/L to 0.5 mg/L, with significant activity against all eight strains. Average daily doses of zifanocycline to achieve a static, 1 log10 kill and 2 log10 kill effect were projected to be 6.92, 9.63 and 13.22 mg/kg, and the mean free drug area under the concentration–time curve (fAUC)/MIC ratios were 6.91, 9.10 and 12.60, respectively *(6)*.

References

1. Kaminishi T, Schedlbauer A, Ochoa-L, Benn V, Liu Q, Tan X et al. The third-generation tetracycline KBP-7072 exploits and reveals a new potential of the primary tetracycline binding pocket. bioRxiv. 2018;508218 (https://doi.org/10.1101/508218, accessed 18 January 2024).
2. Huband MD, Thompson JD, Gurung ND, Liu Q, Li L, Zhang J et al. Activity of the novel aminomethylcycline KBP-7072 and comparators against 1,057 geographically diverse recent clinical isolates from the SENTRY surveillance program, 2019. Antimicrob Agents Chemother. 2022;66(1):e0139721 (https://doi.org/10.1128/AAC.01397-21, accessed 28 February 2024).
3. Pfaller MA, Li L, Liu Q, Zhang J, Huband MD, Lindley JM et al. In vitro activity of a novel aminomethylcycline antibacterial (KBP-7072), a third-generation tetracycline, against clinical isolates with molecularly characterized tetracycline resistance mechanisms. JAC Antimicrob Resist. 2021;3(4):dlab177 (https://pubmed.ncbi.nlm.nih.gov/34917942/, accessed 19 January 2024).
4. Han R, Ding L, Yang Y, Guo Y, Yin D, Wu S et al. In vitro activity of KBP-7072 against 536 *Acinetobacter baumannii* complex isolates collected in China. Microbiol Spectr. 2022 Feb;10(1):e0147121 (https://doi.org/10.1128/spectrum.01471-21, accessed 28 February 2024).
5. Lepak AJ, Zhao M, Liu Q, Wang P, Wang Y, Bader JC et al. Pharmacokinetic/pharmacodynamic evaluation of a novel aminomethylcycline antibiotic, KBP-7072, in the neutropenic murine pneumonia model against *staphylococcus aureus* and *streptococcus pneumoniae*. Antimicrob Agents Chemother. 2019;63(3) (https://doi.org/10.1128/aac.02404-18, accessed 28 February 2024).
6. Li L, Tan X, Zhou T, Chi S, Zhu Y, Liu Q et al. In vivo efficacy and PK/PD analyses of zifanocycline (KBP-7072), an aminomethylcycline antibiotic, against *Acinetobacter baumannii* in a neutropenic murine thigh infection model. J Infect Chemother. 2024;30(1):34–9 (https://doi.org/10.1016/j.jiac.2023.09.010, accessed 28 February 2024).

Annex 8. Protein synthesis inhibitors – aminoglycosides

Product name (INN or company code): apramycin (EBL-1003)

Pharmacology: chemical class and MoA: Apramycin (EBL-1003) is an aminoglycoside that was first licensed in 1980 for oral therapy in animals *(1)*.

Spectrum of activity and potential resistance: In vitro studies of EBL-1003 show activity against 3GCRE, CRE, CRAB and CRPA *(2,3,4,5)*. Apramycin also shows broad-spectrum activity against MDR N. gonorrhoea *(6)*. Apramycin demonstrated in vitro activity against carbapenem-resistant hypervirulent *K. pneumoniae* isolates, including those resistant to amikacin and gentamicin *(5)*. Recent in vitro studies with genotypic analysis report that aminoglycoside-modifying enzymes and rRNA methyltransferases did not render cross-resistance to apramycin *(7)*. In vivo efficacy was measured in a neutropenic mouse pneumonia model for *K. pneumonia*; for two out of five strains studied, a delay in growth (approximately 5 h) was observed in vivo but not in vitro *(8)*.

Sought therapeutic indication: Under development for the treatment of BSI in humans and used to treat or prevent infections caused by Gram-negative bacteria such as *E. coli*, *Salmonella* and *Shigella* in animals.

Route of administration: Intravenous 30 mg/kg (see preclinical PK).

Phase of clinical development: 1

Clinical trial(s): Two Phase 1 trials: An initial Phase 1 trial (NCT04105205) was completed in February 2021. A new Phase 1 trial (NCT055907728), currently recruiting, is a study of a single dose of 30 mg/kg of apramycin administered intravenously over 30 (± 5) min. The completed Phase 1 trial (NCT04105205) was a first-in-human study to assess the safety, tolerability and PK of escalating single doses of apramycin in 40 healthy adults between September 2019 and October 2020. For the ongoing Phase 1 trial (NCT05590728), the primary end-point is to assess the plasma PK profile of apramycin and lung penetration of apramycin in epithelial lining fluid and alveolar macrophages after a single 30 mg/kg iv apramycin dose

Preclinical PK and safety: Apramycin demonstrated good lung penetration and sustained exposure in healthy and lung-infected mice *(8)*. Pharmacometric PK/PD modelling showed that apramycin is expected to be efficacious at 30 mg/kg once daily against Gram-negative lung infections in humans. It is yet to be seen whether this will be effective in human trials *(8)*.

References

1. K Wray C, Hedges RW, Shannon KP, Bradley DE. Apramycin and gentamicin resistance in *Escherichia coli* and *salmonellas* isolated from farm animals. J Hyg (Lond). 1986;97(3):445–56 (https://doi.org/10.1017/S0022172400063622, accessed 28 February 2024).
2. Gysin M, Hon PY, Tan P, Sengduangphachanh A, Simmalavong M, Hinfonthong P et al. Apramycin susceptibility of multidrug-resistant Gram-negative blood culture isolates in five countries in Southeast Asia. Int J Antimicrob Agents. 2022;60(4):106659 (https://doi.org/10.1016/j.ijantimicag.2022.106659, accessed 15 January 2024).
3. Zhao C, Chirkova A, Rosenborg S, Palma Villar R, Lindberg J, Hobbie SN et al. Population pharmacokinetics of apramycin from first-in-human plasma and urine data to support prediction of efficacious dose. J Antimicrob Chemother. 2022;77(10):2718–28 (https://doi.org/10.1093/jac/dkac225, accessed 19 January 2024).
4. Kang AD, Smith KP, Eliopoulos GM, Berg AH, McCoy C, Kirby JE. In vitro apramycin activity against multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Diagn Microbiol Infect Dis. 2017;88(2):188–91 (https://doi.org/10.1016/j.diagmicrobio.2017.03.006, accessed 18 January 2024).
5. Hao M, Shi X, Lv J, Niu S, Cheng S, Du H et al. In vitro activity of apramycin against carbapenem-resistant and hypervirulent *Klebsiella pneumoniae* isolates. Front Microbiol. 2020;11 (https://doi.org/10.3389/fmicb.2020.00425, accessed 15 January 2024).
6. Riedel S, Vijayakumar D, Berg G, Kang AD, Smith KP, Kirby JE. Evaluation of apramycin against spectinomycin-resistant and-susceptible strains of *Neisseria gonorrhoeae*. J Antimicrob Chemother. 2019;74(5):1311–6 (https://doi.org/10.1093/jac/dkz012, accessed 19 January 2024).
7. Juhas M, Widlake E, Teo J, Huseby DL, Tyrrell JM, Polikanov YS et al. In vitro activity of apramycin against multidrug-, carbapenem- and aminoglycoside-resistant Enterobacteriaceae and *Acinetobacter baumannii*. J Antimicrob Chemother. 2019;74(4):944–52 (https://doi.org/10.1093/jac/dky546, accessed 18 January 2024).
8. Aranzana-Climent V, Hughes D, Cao S, Tomczak M, Urbas M, Zabicka D et al. Translational in vitro and in vivo PKPD modelling for apramycin against Gram-negative lung pathogens to facilitate prediction of human efficacious dose in pneumonia. Clin Microbiol Infect. 2022;28(10):1367–74 (https://pubmed.ncbi.nlm.nih.gov/35598857/, accessed 12 January 2024).

Annex 9. Protein synthesis inhibitors – macrolides and ketolides

Product name (INN or company code): nafithromycin (WCK-4873)

Pharmacology: chemical class and MoA: Nafithromycin is an oral lactone-ketolide derived from the macrolide erythromycin A, modified to overcome the problem of macrolide resistance. Nafithromycin is an inhibitor of protein synthesis. Ketolides bind to ribosomes with higher affinity than macrolides do.

Note: From available clinical data: Pharmacodynamically, ketolides display an element of concentration-dependent killing as opposed to macrolides, which are time-dependent killers.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for b-lactam/BLIs: In vitro activity against Gram-positive aerobes and some Gram-negative aerobes *(1,2,3,4)*. Activity against drug-resistant *S. pneumoniae*, including efflux and some ribosomal protein mutation-mediated resistance *(5)*. No in vivo activity data are currently available. No cross-resistance has been reported at present.

Note: Macrolide resistance is mediated through two main mechanisms: drug-efflux pumps encoded by the mef gene and modification of the drug target site in the ribosome brought about by the action of Erm methyltransferases.

Nafithromycin interacts at multiple positions on the ribosome and has been shown to maintain activity against both types of resistance in some bacteria strains *(6)*.

Sought therapeutic indication: Being developed/optimized as a treatment for CABP in adults due to typical and atypical respiratory pathogens, including penicillin- and macrolide-resistant pneumococcal strains. The drug has the potential to provide all the clinical advantages of an oral compliance-friendly 3-day regimen in treatment of CABP while overcoming the macrolide resistance problem.

Pharmaceutical form, route of the administration and proposed posology: In a Phase 3 RCT trial in India, the proposed dose for treatment of CABP in adults is 800 mg (two 400 mg tablets) orally q24h for 3 days.

Route of administration and formulation: Oral (tablets).

Phase of clinical development: 3

Clinical trial(s):

- A **Phase 3**, randomized, multicentre, double-blind, comparative study to determine the efficacy and safety of oral nafithromycin vs oral moxifloxacin in the treatment of CABP in adults. The study has been registered with the clinical trial registry of India (registration no. CTRI/2019/11/021964).

Study population: 488 male and female subjects ≥ 18–90 years of age with a diagnosis of CABP as defined by the study protocol (more details available via this link using keyword trial registration no. CTRI/2019/11/021964 , prospective, interventional, and date of registration: November 2019), were randomized and parallelly assigned to receive either nafithromycin 800 mg (two 400 mg tablets) administered orally every 24 h for 3 days, or moxifloxacin 400 g orally every 24 h for 7 days.

Product name (INN or company code): nafithromycin (WCK-4873) (continued)

- **Time period:** 31 December 2019 to 14 June 2023.
- **Sites:** 40 sites in India.
- **Primary end-point** is defined as the successful outcome of clinical success (symptom resolution and no new symptoms) at the TOC visit (= day 4), in the MITT analysis set. Information on the non-inferiority margin is not available at present.

Adverse events: From a Phase 2 trial (NCT02903836 OBJ) in CABP patients treated with 800 mg for either 3 or 5 days. The most frequent adverse events were gastrointestinal events (3 days/5 days: vomiting 4.5%/1.39%; nausea 4.05%/6.94%; diarrhoea 2.7%/2.78%) and hypertension (4.05%/1.39%). Ketolides hold the potential for liver toxicity. Potential nafithromycin liver toxicity is currently not characterized. Repeat-dose toxicity studies in rats and dogs revealed no adverse haematological, biochemical or histopathological changes suggestive of systemic or hepatobiliary safety concern at exposures 3–8-fold higher than targeted therapeutic exposures. In vitro studies showed that nafithromycin undergoes moderate CYP3A-mediated metabolism, is a weak inhibitor of CYP3A4/5 and does not inhibit other key CYP enzymes. In addition to hepatic clearance, nafithromycin is also eliminated unchanged by the kidneys in a significant amount, thereby minimizing accumulation in the liver *(7)*.

Product name (INN or company code): solithromycin (T-4288)

Pharmacology: chemical class and MoA: Ketolide, inhibitor of protein synthesis.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactams/BLIs: Activity in vitro is similar to that of telithromycin *(8,9)*; however, solithromycin has three binding sites as opposed to two for telithromycin *(9,10)*. Efficacy against *S. pneumoniae* was demonstrated in a murine lung infection model *(11)*. Cross-resistance with telithromycin is not commonly found; no cross-resistance has been reported with macrolides in pneumococci or group A streptococci, but cross-resistance has been reported in staphylococci *(12,13)*.

Sought therapeutic indication: Treatment of ear, nose and throat infections; CABP.

Pharmaceutical form, route of the administration and proposed posology: Intravenous and oral.

Phase of clinical development: 3

Clinical trial(s):

- An NDA was filed but rejected by the FDA and withdrawn from EMA submission because the potential for liver toxicity had not been adequately characterized. To address this deficiency, the FDA recommended a comparative study to evaluate the safety of solithromycin in patients with CABP (study population of approximately 9000 patients exposed to solithromycin to enable exclusion of serious drug-induced liver injury events, occurring at a rate of approximately 1:3000, with 95% probability *(14)*. The company decided to discontinue the adult drug development programme both in the USA and the EU. The NDA was based on two Phase 3 trials for CAP (NCT01756339, NCT01968733) and one Phase 3 trial for treatment of gonorrhoea (NCT02210325). In the NCT01756339 trial comparing 5 days of oral solithromycin versus 7 days of oral moxifloxacin for treatment of CABP in adults, solithromycin was non-inferior to moxifloxacin in both early clinical response and short-term follow-up *(15)*. Similarly, in the NCT01968733 trial, iv-to oral solithromycin was non-inferior to iv-to-oral moxifloxacin in CABP among 863 adults *(16)*. In contrast, in the NCT02210325 trial solithromycin was not non-inferior to ceftriaxone + azithromycin for treatment of gonorrhoea *(17)*. A Phase 2/3 trial in children and adolescents with CABP, which was ongoing at the time of FDA rejection, was prematurely discontinued not due to any specific safety or effectiveness concerns in the enrolled paediatric population *(18)*.
- An NDA was submitted in Japan in April 2019 for treatment of ear, nose and throat infection, following the demonstration of non-inferiority to cephen antibiotics in patients with sinusitis in a Phase 3 trial registered in Japan. No further information is available.

Product name (INN or company code): solithromycin (T-4288) (continued)

- A Phase 3 multicentre, randomized, double-blind, non-inferiority study of oral solithromycin compared to oral azithromycin in the treatment of patients with CABP is currently ongoing in Japan.
  - **Study population:** Adult patients with newly developed infiltrative shadow on either chest x-ray imaging or computed tomography imaging taken within 48 h before the start of study drug administration, and no history of hospitalization within 2 weeks before the development of pneumonia, or no history of hospitalization in a long-term care institution.
  - **Time period:** October 2019 to September 2023.
  - **Primary end-point:** Not specified.

Adverse events: In the two Phase 3 trials submitted in support of the NDA, ALT elevations above the threefold upper limit of normal occurred at a higher frequency than with other macrolide antibiotics, leading the FDA to mandate expanded safety trial data prior to approval. The company declared that currently no cases of severe hepatotoxicity associated with solithromycin had been reported in the previous clinical studies in Japan.

References

1. Rosato A, Vicarini H, Bonnefoy A, Chantot JF, Leclercq R. A new ketolide, HMR 3004, active against streptococci inducibly resistant to erythromycin. Antimicrob Agents Chemother. 1998;42(6):1392–6 (https://doi.org/10.1128/aac.42.6.1392, accessed 28 February 2024).
2. Zhong P, Cao Z, Hammond R, Chen Y, Beyer J, Shortridge VD et al. Induction of ribosome methylation in MLS-resistant *Streptococcus pneumoniae* by macrolides and ketolides. Microb Drug Resist. 1999;5(3):183–8 (https://doi.org/10.1089/mdr.1999.5.183, accessed 28 February 2024).
3. Flamm RK, Rhomberg PR, Sader HS. In vitro activity of the novel lactone ketolide nafithromycin (WCK 4873) against contemporary clinical bacteria from a global surveillance program. Antimicrob Agents Chemother. 2017;61(12):e01230-17 (https://doi.org/10.1128/aac.01230-17, accessed 28 February 2024).
4. Zhou M, Wu L, Kang W, Li Y, Zhang G, Zhang J et al. In vitro activity of lactone ketolide nafithromycin (WCK 4873) against *Streptococcus pneumoniae* isolates enriched with macrolide-resistance phenotype collected from mainland China. JAC Antimicrob Resist. 2022;4(5):dlac103 (https://doi.org/10.1128/aac.01230-17, accessed 28 February 2024).
5. Veeraraghavan B, Varghese R, Saigal K, Balasubramanian S, Bai PSP, Lal YB et al. Activity of novel lactone ketolide nafithromycin against multicentric invasive and non-invasive pneumococcal isolates collected in India. JAC Antimicrob Resist. 2021;3(2):dlab066 (https://doi.org/10.1093/jacamr/dlab066, accessed 28 February 2024).
6. Bhavsar S, Tadiparthi R, Gupta S, Pawar S, Yeole R, Kayastha AK et al. Design and development of efficient synthetic strategies for the chiral synthesis of novel ketolide antibiotic, nafithromycin (WCK 4873). Chem Pap. 2023;77(7):3629–40 (https://doi.org/10.1007/s11696-023-02725-3, accessed 28 February 2024).
7. Chavan R, Zope V, Chavan N, Patil K, Yeole R, Bhagwat S et al. Assessment of the in vitro cytochrome P450 (CYP) inhibition potential of nafithromycin, a next generation lactone ketolide antibiotic. Xenobiotica. 2021;51(3):251–61 (https://doi.org/10.1080/00498254.2020.1839983, accessed 28 February 2024).
8. Farrell DJ, Sader HS, Castanheira M, Biedenbach DJ, Rhomberg PR, Jones RN. Antimicrobial characterisation of CEM-101 activity against respiratory tract pathogens, including multidrug-resistant pneumococcal serogroup 19A isolates. Int J Antimicrob Agents. 2010;35(6):537–43 (https://doi.org/10.1016/j.ijantimicag.2010.01.026, accessed 28 February 2024).
9. Zhanel GG, Walters M, Noreddin A, Vercaigne LM, Wierzbowski A, Embil JM et al. The ketolides: a critical review. Drugs. 2002;62(12):1771–804 (https://doi.org/10.2165/00003495-200262120-00006, accessed 28 February 2024).
10. Buege MJ, Brown JE, Aitken SL. Solithromycin: a novel ketolide antibiotic. Am J Health Syst Pharm. 2017;74(12):875–87 (https://doi.org/10.2146/ajhp160934, accessed 28 February 2024).
11. Okusanya OO, Forrest A, Bhavnani SM, Fernandes P, Ambrose PG, Andes DR. Pharmacokinetic/pharmacodynamic evaluation of solithromycin against *Streptococcus pneumoniae* using data from a neutropenic murine lung infection model. Antimicrob Agents Chemother. 2019;63(8):e02606-18 (https://doi.org/10.1128/aac.02606-18, accessed 28 February 2024).
12. McGhee P, Clark C, Kosowska-Shick KM, Nagai K, Dewasse B, Beachel L et al. In vitro activity of CEM-101 against *Streptococcus pneumoniae* and Streptococcus pyogenes with defined macrolide resistance mechanisms. Antimicrob Agents Chemother. 2010;54(1):230–8 (https://doi.org/10.1128/aac.01123-09, accessed 28 February 2024).
13. Yao W, Xu G, Li D, Bai B, Wang H, Cheng H et al. *Staphylococcus aureus* with an erm-mediated constitutive macrolide-lincosamide-streptogramin B resistance phenotype has reduced susceptibility to the new ketolide, solithromycin. BMC Infect Dis. 2019;19(1):175 (https://doi.org/10.1186/s12879-019-3779-8, accessed 28 February 2024).
14. Solithera FDA approval status. In: Drugs.com/FDA status [website]; 2024 (https://www.drugs.com/history/solithera.html, accessed 28 February 2024).

15. Barrera CM, Mykietiuk A, Metev H, Nitu MF, Karimjee N, Doreski PA et al. Efficacy and safety of oral solithromycin versus oral moxifloxacin for treatment of community-acquired bacterial pneumonia: a global, double-blind, multicentre, randomised, active-controlled, non-inferiority trial (Solitaire-ORAL). Lancet Infect Dis. 2016;16(4):421-30 (https://doi.org/10.1016/S1473-3099(16)00017-7, accessed 2 March 2024).

16. File TM Jr, Rewerska B, Vucinic-Mihailovic V, Gonong JRV, Das AF, Keedy K et al. SOLITAIRE-IV: a randomized, double-blind, multicenter study comparing the efficacy and safety of intravenous-to-oral solithromycin to intravenous-to-oral moxifloxacin for treatment of community-acquired bacterial pneumonia. Clin Infect Dis. 2016;63(8):1007–16 (https://doi.org/10.1093/cid/ciw490, accessed 2 March 2024).

17. Chen MY, McNulty A, Avery A, Whiley D, Tabrizi SN, Hardy D et al. Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (Solitaire-U): a randomised phase 3 non-inferiority trial. Lancet Infect Dis. 2019;19(8):833–42 (https://doi.org/10.1093/cid/ciw490, accessed 2 March 2024).

18. Lang JE, Hornik CP, Elliott C, Silverstein A, Hornik C, Al-Uzri A et al. Solithromycin in children and adolescents with community-acquired bacterial pneumonia. Pediatr Infect Dis J. 2022;41(7):556–62 (https://doi.org/10.1097/INF.0000000000003559, accessed 2 March 2024).

Annex 10. NBTIs

Product name (INN or company code): BWC0977

Pharmacology: chemical class and MoA: BWC0977 is an NBTI, with similar activity against DNA gyrase GyrA and topoisomerase IV. BWC0977 triggers an SOS response in bacterial cells similar to ciprofloxacin through the induction of recA, recN, sulA and lexA promoters *(1,2,3)*.

Spectrum of activity and potential resistance: Currently, no peer reviewed data are available. BWC0977 has shown activity in MDR Gram-negative pathogens such as *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, *E. coli*, and Enterobacteriaceae expressing an ESBL phenotype *(4)*, and in *S.* typhi and *S. aureus (5)*. BWC0977 is claimed to lack cross-resistance to current antibiotics. In vitro, the resistance frequency of BWC0977 at 4× MIC was found to be $< 10^{-9}$ in *E. coli* and *P. aeruginosa*, and $2.5 \cdot 10^{-9}$ in *A. baumannii (6,7)*. In vivo, BWC0977 produced a significant impact on bacteriuria and tissue burden in normal and diabetic mice and eradicated detectable bacteria (quantitative polymerase chain reaction) in the urine of diabetic mice *(8)*.

Sought therapeutic indication: BWC0977 is being developed as a treatment in critical care Gram-negative infections, including Enterobacterales (ESBL phenotype), and non-fermenter infections, including *A. baumannii* (oral step-down administration).

Phase of clinical development: 1

Clinical trial(s): A Phase 1 trial to assess the safety, tolerability and PK of single and multiple iv doses of BWC0977 when administered to healthy adult volunteers. Recently completed (28 May 2023, NCT05088421). No published results as yet.

Preclinical PK and safety: BWC0977 was tolerated well, with no observable irreversible adverse signs in any treated diabetic mice *(9)*. The defined PK/PD index for efficacy is fAUC/MIC *(10)*

Product name (INN or company code): zoliflodacin (ETX0914)

Pharmacology: chemical class and MoA: NBTI (spiropyrimidenetrione scaffold). Utilizes a distinct DNA gyrase binding site in GyrB compared with fluoroquinolones (GyrA)

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactams/BLIs: Activity against *N. gonorrhoeae* and Gram-positive cocci (in vitro and in vivo data) *(11)*. Early findings indicated no cross-resistance with fluoroquinolones (or other topoisomerase inhibitors) *(12,13,14)*. However, recent observations showed that the GyrB D429N substitution reduces susceptibility to zoliflodacin. The GyrB D429N substitution can be acquired by *N. gonorrhoeae* in the presence of ciprofloxacin, resulting in increased ciprofloxacin MIC, at least in some backgrounds *(15)*.

Sought therapeutic indication: Uncomplicated gonorrhoea. Potential to be effective against *N. gonorrhoeae* infections caused by fluoroquinolone-resistant strains *(16)*.

Pharmaceutical form, route of the administration and proposed posology: Oral, 3 g single-dose formulation.

Phase of clinical development: 3

Product name (INN or company code): zoliflodacin (ETX0914) (continued)

Clinical trial(s):

- **Phase 3:** A Phase 3 multicentre, explanatory, open label, randomized, non-inferiority clinical trial comparing a single 3 g oral dose of zoliflodacin with a combination of ceftriaxone (500 mg, IM) and azithromycin (1 g, PO) in the treatment of 1092 adult patients with uncomplicated gonorrhoea (NCT03959527).
  - **Study population:** Patients with urogenital infections caused by *N. gonorrhoeae*.
  - **Time period:** 27 September 2019 to 31 July 2023. Recruitment completed on 23 May 2023. Topline results have been published showing non-inferiority of microbiological respect to IM ceftriaxone and oral azithromycin *(17)*.
  - **Sites:** 17 sites located in Belgium, Netherlands (Kingdom of the), South Africa, Thailand, USA.
  - **Primary end-point:** Microbiological cure as determined by culture at urethral or cervical sites at the TOC visit.
  - **Primary efficacy evaluation** will be performed in micro-MITT patients with uncomplicated urogenital infection due to any *N. gonorrhoeae* strain that is non-resistant to the intervention.
- **Phase 2:** Early results from a small Phase 2 RCT (141 patients in the micro-MITT population) indicated potential for comparable action in various infection sites with some variation. Specifically, the study reported a cure rate of 96% in participants with urogenital infections (n = 113) and 100% cure for rectal infections (12 participants), while pharyngeal infections were cured in four of eight participants (50%) receiving 2 g of zoliflodacin and in nine of 11 participants (82%) who received 3 g of zoliflodacin.

Adverse events: A Phase 2 RCT study (NCT02257918) in approximately 180 adult male and female subjects, aged 18–55, reported a total of 84 adverse events in 59 participants, 21 of which were attributed to zoliflodacin and were generally mild, self-limiting GI tract-related events.

Product name (INN or company code): gepotidacin (GSK2140944)

Pharmacology: chemical class and MoA: Novel dual bacterial topoisomerase II inhibitor (triazaacenaphthylene). Selectively inhibits bacterial DNA replication by interacting at a unique site on the GyrA subunit of bacterial DNA gyrase and the ParC subunit of bacterial topoisomerase IV *(18)*.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: Inhibitory activity against *N. gonorrhoeae* *(19)*. Non-clinical data and a small Phase 2 clinical trial in uUTI also showed activity against ESBL-producing *E. coli* *(20,21,22,23)*. In vitro activity against MRSA has been reported *(16,17)*, as well as some cross-resistance with fluoroquinolones (potentially overlapping/close binding sites).

Sought therapeutic indication: uUTI and uncomplicated urogenital gonorrhoea in adults and adolescents ≥ 12 years of age.

Pharmaceutical form, route of the administration and proposed posology: uUTI (tested in adult females only): oral, 1500 mg (two 750 mg tablets) of gepotidacin bid; every q12h for 5 days. Uncomplicated urogenital gonorrhoea: 3000 mg oral dose (four 750 mg tablets) bid, q12h.

Note: Oral dose is high due to poor absorption. Fifty-three per cent of the oral dose is eliminated through the fecal route due to poor GIT absorption (59% of the iv dose is eliminated through urine). A higher dose, for urogenital gonorrhoea infection compared to cUTI, is needed to suppress resistance development to gepotidacin in N. gonorrhoeae (24).

Phase of clinical development: 3

Product name (INN or company code): gepotidacin (GSK2140944) (continued)

Clinical trial(s):

- **EAGLE-1** trial in urogenital gonorrhoea (NCT04010539): Interventional, randomized, multicentre, open-label study in adolescent and adult participants comparing the efficacy and safety of gepotidacin with ceftriaxone + azithromycin in the treatment of uncomplicated urogenital gonorrhoea caused by *N. gonorrhoeae*. Completed October 2023
  - **Study population** 600 adolescents and adults (≥ 12 years of age), with > 45 kg weight, presenting uncomplicated urogenital gonococcal infection with or without pharyngeal and/or rectal gonococcal infection and one of the following: prior *N. gonorrhoeae*-positive culture or presumptive for Gram-negative intracellular diplococci from up to 5 days before screening (without treatment) or a positive Gram stain (urogenital specimens only), or a positive nucleic acid amplification assay for *N. gonorrhoeae* from up to 7 days before screening (without treatment).The study population were randomized/parallelly assigned to receive either oral gepotidacin (single dose at baseline, i.e., day 1 site visit, followed by a self-administered second oral dose as an outpatient 6–12 h after the first dose) OR a single IM dose of ceftriaxone plus a single oral dose of azithromycin at the baseline, day 1 visit.
  - *Note: the study started prior to the change in SOC recommended by the Centers for Disease Control and Prevention in the USA, and as such uses ceftriaxone + azithromycin, rather than ceftriaxone alone (25).*
  - **Time period:** 21 October 2019 to 31 October 2023.
  - **Sites:** The study is being conducted at 47 locations in five countries (Australia, Germany, Spain, United Kingdom, USA).
  - **Primary end-point:** Number of participants with culture-confirmed bacterial eradication of *N. gonorrhoeae* from the urogenital site at the TOC (time frame: from day 4 to day 8).
  - Pre-treatment urogenital swab specimen will be obtained for bacteriological culture for *N. gonorrhoeae*. TOC is defined by urogenital site as culture-confirmed bacterial eradication of *N. gonorrhoeae* observed 4–8 days post-treatment.
- **EAGLE-2 and EAGLE-3** are near-identical Phase 3, randomized, multicentre, parallel-group, double-blind, double-dummy, comparator-controlled, non-inferiority studies in adolescent and adult female participants, comparing the efficacy and safety of gepotidacin (1500 mg bid for 5 days) with nitrofurantoin (100 mg bid for 5 days) for treatment of uUTI (NCT04020341, NCT04187144). Both studies are completed.
  - **Study population:** 1533 + 1605 female patients (> 12 years) with acute symptomatic cystitis with onset < 96 h prior to study entry, and with nitrite or pyuria from a pre-treatment clean-catch midstream urine sample based on local laboratory procedures were randomized 1:1 to receive either treatment. For the long list of exclusion criteria see: NCT04020341.
  - **Time period:** October 2019 to November 2022.
  - **Sites:** EAGLE-2 was conducted across approximately 95 sites in Bulgaria, Czechia, Germany, Greece, Hungary, India, Mexico, Poland, Romania, Slovakia, Spain, the United Kingdom and the USA. EAGLE-3 was conducted across approximately 110 sites in Australia, Bulgaria, India, Poland, South Korea and the USA. Participating sites in both studies were community-based outpatient clinics.
  - **Primary end-points:** Primary end-points were two:
    - Number of participants with therapeutic response (combined per participant clinical and microbiological response) at the TOC visit (days 9–16). A therapeutic response was referred to participants who had been deemed both a “microbiological success” (reduction of all qualifying bacterial uropathogens (> 105 CFU/mL recovered at baseline to < 103 CFU/mL as observed on quantitative urine culture without the participant receiving other systemic antimicrobials before the TOC visit) and a “clinical success” (resolution of signs and symptoms of acute cystitis present at baseline (and no new signs and symptoms) without the participant receiving other systemic antimicrobials before the TOC visit). Lack of clinical or microbiological success (including missing outcome assessments) was considered as therapeutic failure.
    - Number of participants who had been deemed both a microbiological success (reduction of all qualifying bacterial uropathogens recovered at baseline to < 103 CFU/mL without receiving other antimicrobials before the TOC visit) and a clinical success (resolution of symptoms of acute cystitis present at baseline and no new symptoms without receiving other antimicrobials before the TOC visit (or antimicrobials for uUTI on day of TOC visit)). Lack of clinical or microbiological success (including missing outcome assessments) was considered as therapeutic failure.

Product name (INN or company code): gepotidacin (GSK2140944) (continued)

- Primary efficacy evaluation was performed in two populations:
  - The MITT NTF-S population, defined as all participants in the MITT population whose baseline qualifying uropathogens (105 CFU/mL) are all susceptible to nitrofurantoin (NCT04187144: 292 gepoptidacin/275 nitrofurantoin; NCT04020341: 336 gepoptidacin/298 nitrofurantoin.

The MITT NTF-S (IA Set) population included participants in the MITT NTF-S group who per the interim analysis data had the opportunity to reach their TOC visit, or had not yet reached their TOC visit but were already known to be failures (NCT04187144: 277 gepotidacin/264 nitrofurantoin; NCT04020341: 320 gepotidacin/287 nitrofurantoin). The noninferiority margin was set at –10% .

Phase 3 trial results: EAGLE-2 and EAGLE-3 Phase 3 trials met the primary end-point of non-inferiority to nitrofurantoin; both trials were stopped for non-inferiority based on predefined non-inferiority success boundaries. In addition, EAGLE-3 demonstrated statistical superiority. Results were published in abstract form by Wagenlehner et al. (2023) *(26)*. **EAGLE-2** (IA Set): 162 (50.6%) vs 135 (47%), 4.3% treatment difference (CI 95%: –3.6%, 12.1%). **EAGLE-3** (IA Set): 162 (58.5%) vs 115 (43.6%), 14.6% treatment difference (CI 95%: –3.5% to –12.3%).

Adverse events *(22)***:** The most commonly reported adverse events in gepotidacin subjects were GI: diarrhoea (16% of subjects), followed by nausea (9%). The maximum severity grades of most subjects were mild (69% grade 1) and moderate (28% grade 2). Grade 3 GI events were 3% of the total GI events and occurred in <1% of subjects. There was one drug-related serious adverse event in each treatment arm (gepotidacin and NTF-S) across the two trials.

References

1. Zaslaver A, Bren A, Ronen M, Itzkovitz S, Kikoin I, Shavit S et al. A comprehensive library of fluorescent transcriptional reporters for *Escherichia coli*. 2006;3(8):623–8 (https://doi.org/10.1038/nmeth895, accessed 28 February 2024).
2. Fan J, de Jonge BL, MacCormack K, Sriram S, McLaughlin RE, Plant H et al. A novel high-throughput cell-based assay aimed at identifying inhibitors of DNA metabolism in bacteria. Antimicrob Agents Chemother. 2014;58(12):7264–72 (https://doi.org/10.1128/aac.03475-14, accessed 28 February 2024).
3. Nandishaiah R, Katagihallimath N, Bharatham N, Datta S, Hamee S. Molecular interactions of BWC0977; a dual inhibitor of DNA gyrase and topoisomerase IV. Presented at ECCMID, Copenhagen, Denmark, 15–18 April 2023; Poster P2170. In: ESCMID eLibrary [website]. Basel: ESCMID; 2023 (https://elibrary.escmid.org, accessed 28 February 2024).
4. Wiederhold NP, McElmeel M, Patterson TF, Slayden RA, Cummings JE, Ramachandran V et al. In vitro activity of BWC0977, a novel bacterial topoisomerase inhibitor, against molecularly characterized Enterobacteriaceae and non-fermenter isolates of the CDC collection and key biodefense pathogens. Presented at ECCMID, Amsterdam, Netherlands (Kingdom of the), 13–16 April 2019; Poster P1846) (https://bugworksresearch.com/wp-content/uploads/2021/11/c-20190415_ECCMID_P1846.pdf, accessed 19 January 2024).
5. Raveendran S, Thomas T, Sharma M, Rajagopal S, Prabhumurthy S, Nagaraj S et al. In vitro activity of BWC0977 (a novel bacterial topoisomerase inhibitor) and comparators against recent clinical Enterobacteriaceae and non-fermenter Isolates from two hospitals in Bengaluru, India. Presented at ECCMID, Amsterdam, Netherlands (Kingdom of the), 13–16 April 2019; Poster P1845 (https://bugworksresearch.com/wp-content/uploads/2021/11/d-20190415_ECCMID_P1845.pdf, accessed 19 January 2024).
6. Sharma S, Banerjee T, Yadav G, Kumar A. Susceptibility profile of blaOXA-23 and metallo-β-lactamases co-harbouring isolates of carbapenem resistant *Acinetobacter baumannii* (CRAB) against standard drugs and combinations. Front Cell Infect Microbiol. 2022;12:1068840. doi: 10.3389/fcimb.2022.1068840, PMID 36683677.
7. Mathur T., Hackel M., Sahm D., Balasubramanian V., Ramachandran V. Minimum inhibitory concentration evaluation of BWC0977, a novel bacterial topoisomerase inhibitor, against recent drug resistant clinical isolates. Poster P2166 (https://www.ihma.com/app/uploads/P2166_Bugworks.pdf, accessed 28 February 2024)
8. Pyles R, Greenberg M, Bourne N, Vasanthi Ramachandran VB. Efficacy of oral BWC0977 against drug resistant *Escherichia coli* ST131-H30 in normal and diabetic murine model of ascending UTI infection. Presented at ECCMID, Copenhagen, Denmark, 15–18 April 2023. In: ESCMID eLibrary [website]. Basel: ESCMID; 2023; Poster P2194 (https://elibrary.escmid.org, accessed 28 February 2024).
9. Hameed S., Sharma S., Nandishaiah R., Katagihallimath N., Bharatham N., Shanbag A., Rajagopal S., Bhowmik P., Amar P., Najari R., Ramachandran V., Datta S., Balasubramanian V.. BWC0977, a novel dual target topoisomerase inhibitor: antimicrobial potency, spectrum, and mechanism of action; 29th European Congress on Clinical Microbiology and Infectious Diseases, Amsterdam, Netherlands (Kingdom of the); 2019; P1844.
10. McEntee L., Farrington N., Johnson A., Stevenson A., Horner I., Jimenez-Valverde A. et al. PK-PD of new broad-spectrum agent BWC0977. Presented at ECCMID, Copenhagen, Denmark, 15–18 April 2023; Poster P2191.
11. Bradford PA, Miller AA, O'Donnell J, Mueller JP. Zoliflodacin: an oral spiropyrimidinetrione antibiotic for the treatment of *Neisseria gonorrheae*, including multi-drug-resistant isolates. ACS Infect Dis. 2020;6(6):1332–45 (https://doi.org/10.1021/acsinfecdis.0c00021, accessed 28 February 2024).
12. Jacobsson S, Golparian D, Oxelbark J, Franceschi F, Brown D, Louie A et al. Pharmacodynamic evaluation of zoliflodacin treatment of *Neisseria gonorrhoeae* Strains With amino acid substitutions in the zoliflodacin target GyrB using a dynamic hollow fiber infection model. Front Pharmacol. 2022;13:874176 (https://doi.org/10.3389/fphar.2022.874176, accessed 28 February 2024).

13. Alm RA, Lahiri SD, Kutschke A, Otterson LG, McLaughlin RE, Whiteaker JD et al. Characterization of the novel DNA gyrase inhibitor AZD0914: low resistance potential and lack of cross-resistance in *Neisseria gonorrhoeae*. Antimicrob Agents Chemother. 2015;59(3):1478–86 (https://doi.org/10.1128/aac.04456-14, accessed 28 February 2024).

14. Unemo M, Ringlander J, Wiggins C, Fredlund H, Jacobsson S, Cole M. High in vitro susceptibility to the novel spiropyrimidinetrione ETX0914 (AZD0914) among 873 contemporary clinical *Neisseria gonorrhoeae* isolates from 21 European countries from 2012 to 2014. Antimicrob Agents Chemother. 2015;59(9):5220–5 (https://doi.org/10.1128/aac.00786-15, accessed 28 February 2024).

15. Grad YH, Rubin DHF, Mortimer TD. *Neisseria gonorrhoeae* diagnostic escape from a gyrA-based test for ciprofloxacin susceptibility and the effect on zoliflodacin resistance: a bacterial genetics and experimental evolution study. Lancet Microbe. 2023;4:247–54 (https://doi.org/10.1016/S2666-5247(22)00356-1, accessed 28 February 2024).

16. Taylor SN, Marrazzo J, Batteiger BE, Hook EW, Seña AC, Long J et al. Single-dose zoliflodacin (ETX0914) for treatment of urogenital gonorrhea. N Engl J Med. 2018;379(19):1835–45 (https://www.nejm.org/doi/10.1056/NEJMoa1706988, accessed 28 February 2024).

17. Callaway E. "Groundbreaking": first treatment targeting "super-gonorrhoea" passes trial. Nature. 2023;623:236 (https://doi.org/10.1038/d41586-023-03448-x, accessed 2 March 2024).

18. Bax BD, Chan PF, Eggleston DS, Fosberry A, Gentry DR, Gorrec F et al. Type IIA topoisomerase inhibition by a new class of antibacterial agents. Nature. 2010;466(7309):935–40 (https://doi.org/10.1038/nature09197, accessed 28 February 2024).

19. Farrell DJ, Sader HS, Rhomberg PR, Scangarella-Oman NE, Flamm RK. In vitro activity of gepotidacin (GSK2140944) against *Neisseria gonorrhoeae*. Antimicrob Agents Chemother. 2017;61(3) (https://doi.org/10.1128/aac.02047-16, accessed 28 February 2024).

20. Biedenbach DJ, Bouchillon SK, Hackel M, Miller LA, Scangarella-Oman NE, Jakielaszek C et al. In vitro activity of gepotidacin, a novel triazaacenaphthylene bacterial topoisomerase inhibitor, against a broad spectrum of bacterial pathogens. Antimicrob Agents Chemother. 2016;60(3):1918–23 (https://doi.org/10.1128/aac.02820-15, accessed 28 February 2024).

21. Flamm RK, Farrell DJ, Rhomberg PR, Scangarella-Oman NE, Sader HS. Gepotidacin (GSK2140944) in vitro activity against gram-positive and gram-negative bacteria. Antimicrob Agents Chemother. 2017;61(7) (https://doi.org/10.1128/AAC.00468-17, accessed 28 February 2024).

22. Kresken M, Wohlfarth E, Weikel C, Butler D, Pfeifer Y, Werner G et al. In vitro activity of gepotidacin against urine isolates of *Escherichia coli* from outpatient departments in Germany. J Antimicrob Chemother. 2022;78:418–22 (https://doi.org/10.1093/jac/dkac406, accessed 28 February 2024).

23. Overcash JS, Tiffany CA, Scangarella-Oman NE, Perry CR, Tao Y, Hossain M et al. Phase 2a pharmacokinetic, safety, and exploratory efficacy evaluation of oral gepotidacin (GSK2140944) in female participants with uncomplicated urinary tract infection (acute uncomplicated cystitis). Antimicrob Agents Chemother. 2020;64(7) (https://doi.org/10.1128/aac.00199-20, accessed 28 February 2024).

24. Scangarella-Oman NE, Hossain M, Perry CR, Tiffany C, Powell M, Swift B et al. Dose selection for a Phase III study evaluating gepotidacin (GSK2140944) in the treatment of uncomplicated urogenital gonorrhoea. Sex Transm Infect. 2023;99(1):64–9 (https://doi.org/10.1136/sextrans-2022-055518, accessed 28 February 2024).

25. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1–187 (http://dx.doi.org/10.15585/mmwr.rr7004a1, accessed 28 February 2024).

26. Wagenlehner F, Perry CR, Hooton TM, Scangarella-Oman NE, Millns H, (Ed) Feng H et al. P31 Efficacy and safety of oral gepotidacin in the treatment of uncomplicated urinary tract infection: results of two randomized, multicentre Phase 3 trials (EAGLE-2 and EAGLE-3). JAC-Antimicrob Resist. 2023;5(Suppl 3) (https://dx.doi.org/10.1093/jacamr/dlad077.035, accessed 28 February 2024).

Annex 11. FabI inhibitors – pyrido-enamides

Product name (INN or company code):
afabicin (Debio 1450) prodrug of Debio 1452 (previously AFN-1252)

Pharmacology: chemical class and MoA: Afabicin (Debio 1450) is a pyridoenamide and a selective enoyl-ACP reductase (FabI) inhibitor, a key enzyme in bacterial fatty acid biosynthesis *(1)*.

Spectrum of activity and potential resistance: Afabicin activity in vitro is comparable to that of rifampicin, active against extra- and intracellular *S. aureus* (MRSA S186) independent of resistance patterns *(2)*. The risk of emergence of high-level resistance may be offset by high affinity for its target *(3)*. AFN-1252 was efficacious in in vivo data of murine acute lethal septicaemia models *(4)*.

Sought therapeutic indication: Afabicin is being studied in the treatment of ABSSSI and bone and joint infection due to drug-resistant *S. aureus (5)*.

Route of administration and proposed posology: High-dose and low-dose iv formulation with oral switch given as described below.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2** (NCT03723551, currently recruiting).
  - **Summary:** A randomized, active-controlled, open-label study to assess the safety, tolerability and efficacy of afabicin in the treatment of participants with bone or joint infection due to *S. aureus* (both MSSA and MRSA and/or coagulase-negative staphylococci (CoNS) and to compare it to SOC in two arms:
    - iv at a dose 160 mg bid for a minimum of 1 day (two doses) and up to a maximum of 14 days (2 weeks), followed by a switch to oral afabicin at a dose of 240 mg bid; and
    - iv at a dose of 55 mg bid for a minimum of 1 day (two doses) and up to a maximum of 14 days (2 weeks) followed by a switch to oral afabicin at a dose of 80 mg bid for the remaining treatment duration (with a conditional higher dose of 80 mg bid for a minimum of 1 day (two doses) and up to a maximum of 14 days (2 weeks) followed by a switch to oral afabicin at a dose of 120 mg bid for the remaining treatment duration.
  - **Patient population:** 18 years and older with a diagnosis of bone or joint infection which fulfils the following conditions: (i) infection is due to *S. aureus* (MSSA or MRSA) and/or CoNS only; and (ii) participants had received no more than 7 days of empiric antibiotics prior to initiating treatment with the study drug unless the pathogen isolated was resistant to the administered empiric antibiotics; and (iii) biofilm is not considered to be yet established and/or has been mechanically eradicated; and (iv) infection is not associated with a diabetic foot; and (v) Infection can involve periosteal or soft tissue.

Product name (INN or company code): afabicin (Debio 1450) prodrug of Debio 1452 (previously AFN-1252) (continued)

Primary end-point: Number of participants with adverse events and serious adverse events based on nature, incidence, severity, and outcome, and change from baseline in number of participants with incidence of laboratory abnormalities.

- **Phase 2** completed September 2016 (NCT02426918).
  - **Summary:** The efficacy, safety and tolerability of afabicin were compared with that of vancomycin/linezolid in the treatment of ABSSSI due to staphylococci in this multicentre, parallel-group, double-blind, double-dummy Phase 2 study. 330 randomized patients (1:1:1 ratio) received either low-dose afabicin (iv 80 mg, followed by oral 120 mg, bid), high-dose afabicin (iv 160 mg, followed by oral 240 mg, bid), or vancomycin/linezolid (iv vancomycin 1 g or 15 mg/kg, followed by oral linezolid 600 mg, bid).
  - **Patient population:** 18–70 years old with clinically documented infection of the skin or skin structure suspected or documented to be caused by a staphylococcal pathogen.
  - **Primary end-point:** Early clinical response rate: percentage of responders to treatment at 48–72 h from randomization as assessed by the investigator (time frame: at 48–72 h from randomization (day 4)).
  - **Primary efficacy evaluation:** Performed in the micro-MITT population using a non-inferiority margin of 15%.
  - **Study results:** Early clinical response at 48–72 h was comparable among treatment groups (94.6%, 90.1% and 91.1% for low-dose afabicin, high-dose afabicin and vancomycin/linezolid, respectively) in the MITT population *(5)*. Low- and high-dose afabicin were found to be non-inferior to vancomycin/linezolid (difference, −3.5% (95% CI: −10.8 to 3.9) for low-dose afabicin; difference, 1.0% (95% CI: −7.3 to 9.2) for high-dose afabicin)) *(5)*.

Adverse events: Most common TEAEs were mild; headache (9.1% and 16.8%) and nausea (6.4% and 8.4%) with low- and high-dose afabicin, respectively *(5)*.

References

1. Heath RJ, Rock CO. Fatty acid biosynthesis as a target for novel antibacterials. Curr Opin Investig Drugs. 2004;5(2):146–53.
2. Tsuji BT, Harigaya Y, Lesse AJ, Forrest A, Ngo D. Activity of AFN-1252, a novel FabI inhibitor, against *Staphylococcus aureus* in an in vitro pharmacodynamic model simulating human pharmacokinetics. J Chemother. 2013;25(1):32–5 (https://doi.org/10.1179/1973947812Y.0000000060, accessed 28 February 2024).
3. Yao J, Rock CO. Resistance mechanisms and the future of bacterial enoyl-acyl carrier protein reductase (FabI) antibiotics. Cold Spring Harb Perspect Med. 2016;6(3):a027045 (https://doi.org/10.1101/cshperspect.a027045, accessed 28 February 2024).
4. Kaplan N, Albert M, Awrey D, Bardouniotis E, Berman J, Clarke T et al. Mode of action, in vitro activity, and in vivo efficacy of AFN-1252, a selective antistaphylococcal FabI inhibitor. Antimicrob Agents Chemother. 2012;56(11):5865–74 (https://doi.org/10.1128/aac.01411-12, accessed 28 February 2024).
5. Wittke F, Vincent C, Chen J, Heller B, Kabler H, Overcash JS et al. Afabicin, a first-in-class antistaphylococcal antibiotic, in the treatment of acute bacterial skin and skin structure infections: clinical noninferiority to vancomycin/linezolid. Antimicrob Agents Chemother. 2020;64(10):e00250-20 (https://doi.org/10.1128/aac.00250-20, accessed 28 February 2024).

Annex 12. FtsZ inhibitors

Product name (INN or company code): TXA709

Pharmacology: chemical class and MoA: TXA709 is a filamenting temperature-sensitive mutant Z (FtsZ)-targeting benzamide prodrug. Inhibition of FtsZ assembly restrains the cell-division complex known as the divisome, which results in destruction of the cell *(1,2)*.

Spectrum of activity and potential resistance: In vitro, *S. aureus* isolates, including MRSA, demonstrated an MIC of 1 mg/L, with β-lactam resistance showing no impact on TXA707 potency *(3)*. This was in keeping with unpublished in vitro data of a population of over 60 clinical *S. aureus* isolates, where the MIC range was 0.5–2 mg/L *(3)*. TXA709/707 was shown to exhibit dose-dependent in vivo activity against *S. aureus* isolates, including those with β-lactam resistance *(3)*. Kaul et al. (2022) demonstrated recently that oxacillin is efficacious in mouse models of both systemic and tissue infection with MRSA when co-administered with TXA709 at human-equivalent doses below recommended daily dosages *(4)*.

Sought therapeutic indication: Anti-MRSA.

Route of administration: Oral.

Phase of clinical development: 1

Clinical trial(s): First-in-human Phase 1 trial completed according to public information on developer website. Registration and further details unavailable.

Preclinical PK and safety: Maximum TXA707 concentrations (Cmax) ranged from 0.5 to 13.7 mg/L *(3)*. According to unpublished data, Phase 1 clinical trial results showed no serious adverse events *(5)*.

References

1. Tripathy S, Sahu SK. FtsZ inhibitors as a new genera of antibacterial agents. Bioorg Chem. 2019;91:103169 (https://doi.org/10.1016/j.bioorg.2019.103169, accessed 28 February 2024).
2. Bi E, Lutkenhaus J. FtsZ regulates frequency of cell division in *Escherichia coli*. J Bacteriol. 1990;172(5):2765–8 (https://doi.org/10.1128/jb.172.5.2765-2768.1990, accessed 28 February 2024).
3. Lepak AJ, Parhi A, Madison M, Marchillo K, VanHecker J, Andes DR. In vivo pharmacodynamic evaluation of an FtsZ inhibitor, TXA-709, and its active metabolite, TXA-707, in a murine neutropenic thigh infection model. Antimicrob Agents Chemother. 2015;59(10):6568–74 (https://doi.org/10.1128/aac.01464-15, accessed 28 February 2024).
4. Kaul M, Ferrer-González E, Mark L, Parhi AK, LaVoie EJ, Pilch DS. Combination with a FtsZ inhibitor potentiates the in vivo efficacy of oxacillin against methicillin-resistant *Staphylococcus aureus*. Med Chem Res. 2022;31(10):1705–15 (https://doi.org/10.1007/s00044-022-02960-5, accessed 28 February 2024).
5. Our pipeline. In: Taxis/Pipeline [website]. Monmouth Junction (NJ): Taxis Pharmaceuticals; 2024 (https://www.taxispharma.com/research-development/our-pipeline/, accessed 19 January 2024).

Annex 13. ATP production disruptors

Product name (INN or company code):
RECCE 327 (R327)

Pharmacology: chemical class and MoA: RECCE 327 (R327) is a fully synthetic (acrolein) polymer designed to disrupt bacterial energy (ATP) production, cell growth and division.

Spectrum of activity and potential resistance: In vitro (poster) data suggest broad-spectrum antibacterial activity against MDR strains of Gram-positive and Gram-negative bacteria, including *Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter* spp. (Recce Pharmaceuticals, unpublished data, 2021) *(1)*. In vivo (poster) activity in these "ESKAPE" pathogens has also been described in mouse model studies for kidney and UTI bacterial infection (Recce Pharmaceuticals, unpublished data, 2021) *(1)*.

Sought therapeutic indication: RECCE 327 is being studied as a broad-spectrum intervention in infected burn wound care and diabetic foot infection, and in cUTI/urosepsis caused by ESBL-producing Enterobacteriaceae.

Route of administration and proposed posology: Intravenous and topical gel/spray.

Phase of clinical development: Recent completion of a Phase 1 single iv ascending dose safety and PK study with no publications as yet. Commencement of a Phase 1b/2a proof-of-concept trial for topical application of RECCE 327 for mild diabetic foot infections is planned *(2)*.

Clinical trial(s): Four trials are listed in the Australian New Zealand Clinical Trials Registry:

- ACTRN12621001313820: a Phase 1 ascending-dose, randomized, placebo-controlled, parallel, double-blind, single-dose, first-in-human study to evaluate the safety and PK of RECCE 327 in 80 healthy male subjects 18–55 years of age (June 2021 to December 2022, completed);
- ACTRN12623000448640: a Phase 1 open-label, adaptive design evaluation, crossover study of the safety and PK/PD of various RECCE 327 intravenous dose and infusion rates;
- ACTRN12623000056695: a Phase 1/2 proof-of-concept study of RECCE 327 topical anti-infective therapy for mild skin and soft tissue diabetes foot infections; and
- ACTRN12621000412831: a Phase 1 proof-of-concept study of RECCE 327 topical antibiotic therapy for infected burn wounds in adults.

Preclinical PK and safety: In vivo poster data describe no adverse clinical signs in rats treated with RECCE 327, and it achieved broad distribution with particular concentration in urine (Recce Pharmaceuticals, unpublished data, 2021). In tests comparing 50 mg/kg and 500 mg/kg of R327 to vehicle control, the antibacterial effect was dose-dependent ($P < 0.050$) (Recce Pharmaceuticals, unpublished data, 2021) *(1)*.

References

1. Recce® 327 i.v. In: Recce Pharmaceuticals/Clinical candidates/Sepsis [website]. Sydney: Recce Pharmaceuticals; 2024 (https://www.recce.com.au/product-candidates/sepsis, accessed 29 February 2024).

2. Priyan V. Recce obtains safety committee advice for Phase 1 trial of infectious disease asset. In: Clinical Trials Arena/News [website]. London: Clinical Trials Arena; 2022 (https://www.clinicaltrialsarena.com/news/recce-committee-trial-progress/, accessed 29 February 2024).

Annex 14. Antibiotic hybrids

Product name (INN or company code): TNP-2092

Pharmacology: chemical class and MoA: TNP-2092 is a rifamycin-quinolizinone hybrid (lead ABT-719) designed to reduce resistance to rifamycin and analogues. TNP-2092 produces a bactericidal effect by inhibiting the multitarget synergy of RNA polymerase, DNA gyrase and topoisomerase IV, reducing the frequency of drug resistance and influencing biofilm infection *(1)*.

Spectrum of activity and potential resistance: The in vitro activity of TNP-2092 against a panel of urease-producing bacteria was similar to that of rifaximin *(2)*. It has been shown to be active in vitro against planktonic MRSA among other Gram-positives *(3)*. In vivo, TNP-2092 demonstrated potent efficacy in a mouse CDI model, with no relapse observed after treatment *(4)*. TNP-2092 is not a substrate of fluoroquinolone efflux pumps, likely because of steric interference from the rifamycin pharmacophore; this is believed to confer lower propensity for resistance development *(3)*.

Sought therapeutic indication: TNP-2092 is being investigated in patients with PJI and in ABSSSI caused by Gram-positive pathogens.

Route of administration and proposed posology: 300 mg iv every 12 h.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2:** A double-blind, randomized, multicentre, parallel, controlled study to evaluate the safety, tolerability, PK and efficacy of TNP-2092 to treat ABSSSI (NCT03964493).
  - **Study population:** 120 adults 18 years and older with ABSSSI suspected or confirmed to be caused by Gram-positive pathogens, randomly assigned to TNP-2092 300 mg iv every 12 h or vancomycin 1 g iv every 12 h.
  - **Primary end-points:** Three primary end-points were selected:
    - early clinical response at the early assessment visit in the ITT population, all randomized participants;
    - early clinical response at the early assessment visit in the MITT population, all randomized participants in the ITT population excluding those who have Gram-negative pathogens only; and
    - early clinical response at the early assessment visit in the micro-ITT population (all randomized participants in the MITT population with culture evidence of a baseline Gram-positive ABSSSI pathogen (exclude sole Gram-negative and culture-negative participants)).
  - **Time frame:** Screening 48–72 h after the first dose of study treatment. Early clinical response is defined as responder meeting two criteria: (i) the patient has at least a 20% reduction of ABSSSI primary lesion size compared to baseline measurements; and (ii) patient did not die of any cause within 72 h of the first dose of study treatment. An indeterminate classification is used for a response that could not be adequately inferred because study data are unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up, did not attend the early assessment clinic appointment), or if the early assessment visit is out of the 48–72 h window after the iv study treatment starts.
  - T**opline results published online** *(1)*: The early clinical response rates at early assessment point (within 48–72 h after initiation of treatment, primary end-point of FDA guidance) in the ITT population were 76.3% for TNP-2092 and 67.5% for vancomycin *(1)*. The post-treatment success rates in the clinical evaluable population were 96.4% for TNP-2092 and 92.6% for vancomycin *(1)*. MRSA was the most common pathogen isolated, accounting for about 50% of all pathogens isolated. In a subpopulation analysis, TNP-2092 appeared to be equally efficacious against infections caused by MRSA and other pathogens. Incidence of TEAEs were similar between the two treatment groups *(1)*.

Adverse events as assessed by CTCAE (Common Terminology Criteria for Adverse Events) v4.0 (time frame: day 1 to day 40): thrombotic events and local infusion site reactions.

Adverse events: Unpublished reports state that no serious adverse events occurred in the TNP-2092 treatment group nor deaths during the trial *(1)*.

References

1. TenNor Therapeutics reported Phase II top-line results for TNP-2092. In: PR Newswire/News [website]. Chicago (IL): Cision; 2019 (https://www.prnewswire.com/news-releases/tennor-therapeutics-reported-phase-ii-top-line-results-for-tnp-2092-300955216.html, accessed 29 February 2024).
2. Fisher CR, Schmidt-Malan SM, Ma Z, Yuan Y, He S, Patel R. In vitro activity of TNP-2092 against periprosthetic joint infection–associated staphylococci. Diagn Microbiol Infect Dis. 2020;97(3):115040 (https://doi.org/10.1016/J.DIAGMICROBIO.2020.115040, accessed 12 January 2024).
3. Ma Z, Lynch AS. Development of a dual-acting antibacterial agent (TNP-2092) for the treatment of persistent bacterial infections. J Med Chem. 2016;59(14):6645–57 (https://doi.org/10.1021/acs.jmedchem.6b00485, accessed 29 February 2024).
4. Yuan Y, Wang X, Xu X, Liu Y, Li C, Yang M et al. Evaluation of a dual-acting antibacterial agent, TNP-2092, on gut microbiota and potential application in the treatment of gastrointestinal and liver disorders. ACS Infect Dis. 2020;6(5):820-31. doi: 10.1021/acsinfecdis.9b00374, PMID 31849218.

Annex 15. Agents in development for treating drug-resistant TB

Product name (INN or company code): BTZ-043 ✓NCR ✓CC ✓T ✓MoA

Pharmacology: chemical class and MoA: BTZ-043 is a benzothiazinone that inhibits DprE1, a crucial enzyme involved in *M. tuberculosis* cell wall synthesis *(1)*.

Spectrum of activity and potential resistance: BTZ-043 is effective against various strains of *M. tuberculosis*, including those from MDR and XDR patients. In vitro, BTZ-043 shows a MIC range of approximately 0.1–80 ng/mL for fast growers and 1–30 ng/mL for *M. tuberculosis* complex members *(2)*. In mouse models, BTZ-043 exhibits enhanced activity compared to isoniazid (INH), especially after 2 months and synergistic effects are observed when combined with rifampicin and bedaquiline *(2)*.

Sought therapeutic indication: Drug-sensitive and drug-resistant *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2b:** Open-label, randomized controlled dose ranging multicentre trial to evaluate the safety, tolerability, PK and exposure-response relationship of different doses of BTZ-043 in combination with bedaquiline and delamanid in 90 adult subjects with newly diagnosed, uncomplicated, drug-sensitive pulmonary TB (NCT05926466, not yet recruiting).
  - **Study population:** Consented adults, male or female, 18–64 years old with a newly diagnosed, previously untreated current episode of drug-susceptible (DS) pulmonary TB (presence of *M. tuberculosis* complex with rapid molecular test result confirming susceptibility to rifampicin and isoniazid such as GeneXpert and/or Hain MTBDRplus) able to provide sputum of adequate volume regularly and on effective contraceptive (see clinicaltrials.gov for full details).
  - **There will be four study arms:** An active comparator arm with moxifloxacin. Moxifloxacin will be dosed at the licensed dose of 400 mg PO once daily for 16 weeks. Bedaquiline will be dosed at 400 mg PO once daily for the first 2 weeks, followed by 100 mg PO once daily for 14 weeks. Delamanid will be dosed at 300 mg orally once daily for 16 weeks, and three experimental arms with bedaquiline and delamanid dosed as stated + BTZ-043 at either 500, 1000 or 1500 mg PO once daily for 16 weeks.
  - Primary outcome measure: Time to positivity in BD MGIT liquid culture.
- **Phase 1/2:** A prospective Phase 1b/2a, active-controlled, randomized, open-label study to evaluate the safety, tolerability, extended early bactericidal activity (EBA) and PK of multiple PO doses of BTZ-043 tablets in 77 subjects with newly diagnosed, uncomplicated, smear-positive, DS pulmonary TB (NCT04044001, completed May 2022).

Phase 1: A single-centre, open-label study to investigate the mass balance, excretion pathways and metabolites after a single PO dose of 500 mg, 3.7 megabecquerel (MBq), [14C]BTZ-043 in six healthy male volunteers (NCT04874948, completed October 2021).

Product name (INN or company code): BTZ-043 ✓NCR ✓CC ✓T ✓MoA (continued)

- **Phase 1:** A randomized, double-blind, placebo-controlled, single ascending dose study to evaluate safety, tolerability and PK of single doses of BTZ043 in 30 healthy adult volunteers (NCT03590600, completed March 2019).

Adverse events / preclinical PK and safety:

In preclinical toxicology good laboratory practice (GLP) studies, BTZ-043 showed a low toxicologic potential; there was no observed adverse event level (NOAEL) up to 170 mg/kg (NOAEL) in rats and 360 mg/kg in minipigs over 28 days *(2)*. In a safety panel (neurotoxicity, cardiotoxicity and respiratory toxicity) no negative effects were observed. Phototoxicity, genotoxicity and mutagenicity studies were negative *(2)*.

Product name (INN or company code): delpazolid (RMW2001, LCB01-0371)

Pharmacology: chemical class and MoA: Delpazolid is an oxazolidinone with a cyclic amidrazone *(3)* which targets an early step in protein synthesis involving the binding of N-formylmethionyl-tRNA to the ribosome *(4)*.

Spectrum of activity and potential resistance: LCB01-0371 was evaluated for in vitro and in vivo activity against clinical isolates and showed good activity against Gram-positive pathogens, with MIC90 of 2 µg/mL for MSSA and MRSA, and twofold more activity than linezolid against VRE *(3)*.In another study, Linezolid and delpazolid MIC90 values for *M. tuberculosis* isolates were 0.25 mg/L and 0.5 mg/L, respectively *(5)*. In vivo LCB01-0371 was also more active than linezolid against systemic infections in mice and showed bacteriostatic activity against MRSA *(3)*. While no significant difference in resistance rates was observed between linezolid and delpazolid among XDR-TB isolates, a significantly greater proportion of linezolid-resistant isolates than delpazolid-resistant isolates was found within the MDR-TB group *(5)*.

Sought therapeutic indication: Drug-sensitive and drug-resistant *M. tuberculosis*, *Mycobacterioides abscessus*, MRSA bacteraemia.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2b:** An open-label, randomized controlled dose ranging multicentre trial to evaluate the safety, tolerability, PK and exposure–response relationship of different doses of delpazolid in combination with bedaquiline, delamanid and moxifloxacin in 76 adult subjects with newly diagnosed, uncomplicated, smear-positive, drug-sensitive pulmonary TB (NCT04550832, active not recruiting).
  - **Study population:** Consented 18–65-year-olds with newly diagnosed, previously untreated, DS pulmonary TB: presence of MTB complex and rapid molecular tests result confirming susceptibility to rifampin and isoniazid such as GeneXpert and/or Hain MTBDRplus.
  - **Primary efficacy end-point:** Change in sputum mycobacterial load.
  - **Primary safety end-point:** Proportion of patients experiencing adverse events.
- **Phase 2a:** A multicentre, double-blinded, randomized, parallel design, clinical trial to evaluate the efficacy, safety and PK of LCB01-0371 with vancomycin vs vancomycin monotherapy in 100 patients with MRSA bacteraemia (NCT05225558, recruiting).

Study population: Consented male or female 19 years old or older with confirmed positive MRSA in at least one set of blood cultures within 72 h prior to randomization OR subject who has confirmed positive MRSA at least one set of blood cultures within 96 h prior to randomization and treated with vancomycin at least 72 h prior to randomization or with clinical signs of MRSA bacteraemia by investigator judgement.

Product name (INN or company code): delpazolid (RMW2001, LCB01-0371) (continued)

  - **Primary end-point:** Overall cure rate by day 14 (composite response rate: clinical improvement plus clearance of bacteraemia).

- **Phase 2:** A prospective, randomized, open, active-controlled, interventional, exploratory trial to evaluate the EBA, safety and PK of orally administered LCB01-0371 in 79 adult patients with smear-positive pulmonary TB (NCT02836483, completed July 2019).
  - **Study population:** Male or female 19–75-year-old consented Korean patients with a first diagnosis of TB and have not received TB treatment for TB patients.
  - **Primary end-point:** The extended EBA expressed as the change of log CFU of sputum from baseline at day 15 (EBA0-14).

Adverse events / preclinical PK and safety: Lee et al. (2009) report that LCB01-0371 exhibited favourable ADMET (absorption, distribution, metabolism, excretion, toxicity) and PK profiles, including high aqueous solubility and good absorption, distribution, metabolism, excretion and toxicity *(6)*. In the Phase 2 trial completed in 2019 (NCT02836483), the average daily decline in log CFU was 0.044 ± 0.016, 0.053 ± 0.017, 0.043 ± 0.016 and 0.019 ± 0.017 for the delpazolid 800 mg qd, 400 mg bid, 800 mg bid and the 1200 mg qd groups, respectively *(7)*. The average daily decline in log CFU was 0.192 ± 0.028 for the isoniazid + rifampin + pyrazinamide + ethambutol (HRZE) group and 0.154 ± 0.023 for the linezolid 600 mg bid group. Three serious adverse events were assessed as being related to study drugs *(7)*.

Product name (INN or company code): ganfeborole, GSK3036656 (GSK070) NCR ✓CC ✓T ✓MoA

Pharmacology: chemical class and MoA: Ganfeborole, GSK3036656 (GSK070) belongs to a novel class (oxaborole) with a new MoA that inhibits Leu-Rs, thereby blocking protein synthesis *(8)*.

Spectrum of activity and potential resistance: GSK3036656 has shown in vitro antitubercular activity (*M. tuberculosis* H37Rv MIC = 0.08 µM) with high selectivity for *M. tuberculosis* Leu-RS enzyme, good PK profiles and efficacy against *M. tuberculosis* in mouse TB infection models *(7)*.

Sought therapeutic indication: Drug-sensitive and drug-resistant *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2a:** A parallel group, randomized, open-label, four treatment arm study to assess the EBA, safety and tolerability of oral GSK3036656 in combination with either oral delamanid or oral bedaquiline, oral delamanid in combination with oral bedaquiline or SOC (NCT05382312, recruiting).

Study population: In 128 male and female patients aged 18–65 years inclusive with drug-sensitive (rifampicin-susceptible) Pulmonary TB 1 : 1 parallel assignment.

  - **Primary end-point:** Change from baseline in log10 CFU of *M. tuberculosis* (per millilitre of respiratory sputum samples).

- **Phase 2a:** An open-label trial to investigate the EBA, safety and tolerability of GSK3036656 in 76 participants with drug-sensitive pulmonary TB (NCT03557281, completed December 2021).
  - **Study population:** Consented 18–65-year-olds with normal cardiac profile and a new episode of untreated, rifampicin-susceptible pulmonary TB and at least one sputum sample positive on direct microscopy for AFB, willing to be on contraceptives (if child-bearing age) who are relatively well at screening.
  - The study had four cohorts, with 12–20 participants in each cohort. The participants were randomized in a 3 : 1 ratio to receive either GSK3036656 at doses 1, 5, 15 and 30 mg or SOC regimen for drug-sensitive TB.
  - **Primary outcome measure:** Rate of change in log10 CFU per millilitre direct respiratory sputum samples from baseline to day 14.

Product name (INN or company code): ganfeborole, GSK3036656 (GSK070) NCR ✓CC ✓T ✓MoA (continued)

- **Phase 1:** A double-blind, placebo-controlled first-time-in-human study to evaluate the safety, tolerability and PK of single and repeat doses of GSK3036656 in 30 healthy adult volunteers (NCT03075410, completed 2017).

Adverse events, PK and safety: From NCT03557281, Phase 2a study (completed Dec 2021): GSK3036656 doses of 5–30 mg showed bactericidal activity as evidenced by both end-points after 14 days. GSK3036656 30 mg had the highest bactericidal activity *(9,10)*:

- a decline in CFU of –0.138 log10 CFU/mL (95% CI: –0.167, –0.109); and
- an increase in TTP of 0.22 log10 CFU/mL (95% CI: 0.019, 0.024).

GSK3036656 was generally well tolerated with no serious adverse events identified in the study *(9,10)*.

Product name (INN or company code): sutezolid (PF-2341272, PNU-100480)

Pharmacology: chemical class and MoA: Sutezolid (PF-2341272, PNU-100480) is an oxazolidinone which targets an early step in protein synthesis involving the binding of N-formylmethionyl-tRNA to the ribosome *(4)*.

Spectrum of activity and potential resistance: Sutezolid demonstrated MIC90 values of 0.50 mg/mL or less against drug-sensitive and five MDR strains of *M. tuberculosis (11)*. In vivo, oral sutezolid showed efficacy against *M. tuberculosis* and *M. avium* like that of clinical comparators isoniazid and azithromycin, respectively *(11)*. Both in vitro and in vivo studies showed its improved antimycobacterial action and safety profile compared to linezolid. Sutezolid (PNU-100480), TMC207 and SQ109 were predicted to have cumulative activity comparable to standard TB therapy based on a concentration–activity relationship and PK data in a rapid evaluation in whole blood culture *(12)*. The addition of sutezolid to current first-line anti-TB drugs and moxifloxacin improved bactericidal activities, resulting in a significant reduction in lung CFU counts (2.0 log10 unit) during the first 2 months of treatment *(13)*. The combination of PNU-100480, moxifloxacin and pyrazinamide was also more active than rifampin, isoniazid and pyrazinamide *(13)*. In a *M. tuberculosis* murine model, a dose–response study showed that sutezolid was more active than linezolid (both at 25, 50 and 100 mg/kg of body weight) and that its efficacy increased with escalation of the dose *(14)*. *Note: These are reported preclinical data.*

Sought therapeutic indication: Drug-sensitive and drug-resistant *M. tuberculosis* and NTM.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2/3

Clinical trial (s):

- **Phase 2a:** Open-label, randomized study in 59 treatment-naive, sputum smear positive subjects with drug-sensitive pulmonary TB to assess EBA and whole blood activity (WBA) of PNU-100480 (PF-02341272) (NCT01225640, completed December 2011).
  - **Study population:** Adult male or female 18–65 years old, consented and reasonably healthy newly, diagnosed sputum smear-positive pulmonary TB confirmed with AFB smear and chest x-ray. Patients with TB more than 5 years ago who completed treatment, were healthy and met other inclusion criteria were considered for inclusion. Parallel assignment.
  - **Primary end-point:** The primary end-point is rate of change in sputum log CFU/mL count (EBA) from days 0 to 2.

Results: There were no treatment-related serious adverse events, premature discontinuations or dose reductions due to laboratory abnormalities. There was no effect on the QT interval. The mycobactericidal activity of sutezolid 600 mg bid or 1200 mg qd was detected in sputum and blood. Both schedules were generally safe and well tolerated *(15)*.

- **Phase 2b:** Open-label, randomized controlled dose ranging multicentre trial to evaluate the safety, tolerability, PK and exposure-response relationship of different doses of sutezolid in combination with bedaquiline, delamanid and moxifloxacin in adult subjects with newly diagnosed, uncomplicated, smear-positive, drug-sensitive pulmonary TB (NCT03959566, completed September 2022).

Product name (INN or company code): sutezolid (PF-2341272, PNU-100480) (continued)

Study population: A total of 75 male or female subjects, aged between 18 and 65 years with newly diagnosed, drug-sensitive, uncomplicated, smear-positive, pulmonary TB will be included and randomized to one of five arms containing ethionamide-boosting compounds BDM with different doses of sutezolid: (0 mg, 600 mg once daily (od), 1200 mg od, 600 mg bid, 800 mg bid).

- **Primary efficacy end-point:** Change in sputum mycobacterial load over time.
- **Primary safety end-point:** Proportion of patients experiencing adverse events.

- **Phase 2b/c:** A multiple-arm, multiple-stage, open-label, randomized, controlled platform trial to evaluate experimental arms including an increased dose of rifampicin, an optimized dose of pyrazinamide, moxifloxacin and sutezolid, in 360 adult subjects (NCT05807399, recruiting).
  - **Study population**: Patients 18 years and older with newly diagnosed, smear-positive pulmonary TB: In stage 1, participants will be randomly allocated to the control or one of the two rifampicin-containing experimental regimens in the ratio 1 : 1 : 1. In stage 2, the experimental arm 4 containing sutezolid will be added. Participants will be allocated to control or one of the three experimental regimens in the ratio 1 : 1 : 1 : 1. Towards the end of stage 2, when experimental arms 1 and 2 will be fully enrolled, participants will be randomized 1 : 1 to control and experimental arm 4 (from ClinicalTrials.gov).

Primary outcome measure: Time to stable culture conversion to negative in liquid media.

- Results: All doses were safe and well tolerated *(15)*. There were no haematologic or other safety signals during 28 days of dosing at 600 mg bid *(15)*. Cumulative WBA of PNU-100480 at this dose (−0.316 ± 0.04 log) was superior to the activities of all other doses tested ($P < 0.001$) and was significantly augmented by pyrazinamide (−0.420 ± 0.06 log) ($P = 0.002$) *(15)*.

- **Phase 2/3:** A novel 4-month pan-TB regimen targeting both host and microbe (panTB-HM) (NCT05686356, currently recruiting).

Study population: 352 participants; randomized, parallel assignment.

Primary outcome measures: The proportion of patients achieving durable (non-relapsing) cure.

- **Phase 1:** Safety, tolerability, PK and measurement of WBA of PNU-100480 after multiple oral doses in healthy adult volunteers: (NCT00990990, completed May 2010).

Product name (INN or company code): TBA-7371 (AZ 7371) NCR ✓CC ✓T ✓MoA ✓

Pharmacology: chemical class and MoA: TBA-7371 is a substituted 1,4-azaindole that inhibits DprE1, a crucial enzyme involved in *M. tuberculosis* cell wall synthesis *(16)*.

Spectrum of activity and potential resistance: In a comparative analysis of DprE1 inhibitors, TBA-7371, PBTZ169 and OPC-167832 were effective in treating TB in the C3HeB/FeJ mouse model after 2 months of treatment *(17)*. In vitro, TBA-7371 showed an MIC value of 1 µg/mL in a broth microdilution assay, with a twofold shift in the presence of 4% human serum albumin in the same study *(17)*.

Sought therapeutic indication: Drug-sensitive and drug-resistant *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2a:** A dose-escalation, controlled, randomized study to evaluate safety, EBA and PK of TBA-7371 in 93 adult patients with rifampicin-sensitive pulmonary TB (NCT04176250, completed October 2022).

Product name (INN or company code): TBA-7371 (AZ 7371) NCR ✓CC ✓T ✓MoA ✓ (continued)

Study population: 18–60-year-old male or female consented adults with untreated, rifampicin-sensitive pulmonary TB on effective birth control.

Primary outcome: Slope of average change per day, from day 0 to day 14 of the log CFU counts (BAcfu (0–14)), number of participants who experienced one or more severe (≥ grade 3) and/or serious adverse events.

- **Phase 1:** A partially blind, placebo-controlled, randomized, combined single ascending dose with food effect cohort and multiple ascending dose and drug–drug interaction study to evaluate safety, tolerability, PK and PK interactions between TBA-7371 with midazolam and bupropion in 74 healthy subjects (NCT03199339, completed July 2018).

Preclinical PK and safety: TBA-7371 demonstrated safety in vitro without cytotoxicity up to 100 µM and efficacy in both acute and chronic BALB/c mouse models, with a more than 2 log10 CFU reduction in lungs in the acute model and a 1.5 log10 CFU reduction in the chronic model at 100 mg/kg qd dosing *(17)*.

Product name (INN or company code): telacebec (Q203) NCR ✓CC ✓T ✓MoA ✓

Pharmacology: chemical class and MoA: Telacebec (Q203) is an imidazopyridine amide that targets the respiratory cytochrome bc1 complex to inhibit mycobacterial cellular energy production *(18)*.

Spectrum of activity and potential resistance: Telacebec was found to be active in macrophages infected with both pan-susceptible and MDR TB in in vitro studies *(18,19,20)*. In a mouse model of TB, the compound demonstrated efficacy at a dose of less than 1 mg per kg body weight *(18)*.

Sought therapeutic indication: Drug-sensitive and drug-resistant TB.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2:** An open-label randomized study to evaluate the EBA, safety, tolerability and PK of multiple oral doses of telacebec (Q203) in 60 treatment-naive patients with newly diagnosed drug-sensitive sputum smear-positive pulmonary TB (NCT03563599, completed September 2019).

Study population: Consented 18–65-year-old male or female adults with newly positive pulmonary TB testing using effective contraception (or of non-childbearing potential) *(21)*.

Primary outcome: The EBA of telacebec (Q203).

Results: Increasing doses of telacebec were associated with greater reductions in viable mycobacterial sputum load. Daily increase in log10 time to positivity of 0.0036 (95% CI: 0.0013–0.0060), 0.0087 (95% CI: 0.0064–0.0110) and 0.0135 (95% CI: 0.0112–0.0158) for telacebec at a dose of 100, 200 and 300 mg, respectively *(22)*. Telacebec was associated with acceptable adverse event rates, and adverse events were equally distributed among all groups. There were no serious adverse drug reactions and no adverse drug reactions that resulted in early withdrawal from the study *(22)*.

- **Phase 1b:** A randomized, placebo-controlled, double-blind, multiple ascending dose study to evaluate the safety, tolerability and PK of Q203 when administered orally to 47 healthy adult subjects (NCT02858973, completed May 2018).

Results: Multiple oral doses of telacebec up to 320 mg daily for 14 days appeared to be safe and well tolerated by healthy adult subjects in this study *(23)*. There were no deaths, serious adverse events or subject discontinuations due to adverse events. Three potential metabolites of telacebec have been identified, which may be relatively minimal compared to the parent drug *(23)*.

- **Phase 2:** An open-label, randomized controlled trial to evaluate the biomarker change, efficacy, PK, safety and tolerability of telacebec in participants with moderate COVID-19 disease (NCT04847583, terminated).

Product name (INN or company code): quabodepistat (OPC-167832) NCR ✓CC ✓T ✓MoA ✓

Pharmacology: chemical class and MoA: Quabodepistat (OPC-167832) is a 3,4-dihydrocarbostyril derivative that inhibits DprE1, an enzyme crucial to mycobacterium cell wall biosynthesis *(24,25,26)*.

Spectrum of activity and potential resistance: OPC-167832 demonstrated potent bactericidal activity against *M. tuberculosis* with MICs ranging from 0.00024 to 0.002 µg/mL *(24)*. It showed efficacy in reducing bacterial burden and preventing relapse when used in combination with other anti-TB agents, such as delamanid, bedaquiline, levofloxacin, moxifloxacin or linezolid *(24)*. In recent studies using the C3HeB/FeJ mouse model, OPC-167832 treatment resulted in significant reductions in bacterial load in TB lung lesions *(17)*.

Sought therapeutic indication: Drug-sensitive and MDR-TB.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2b/c

Clinical trial(s):

- **Phase 2b/c:** A multi-arm, two-stage, duration randomized trial of the efficacy and safety of 2–4 months of treatment with regimens containing bedaquiline, OPC-167832, and sutezolid, plus either pretomanid or delamanid, in 514 adults with pulmonary TB (NCT05971602, recruiting).

Study population: Stage 1– consented adult 18–65-year-old males or females newly diagnosed within the past 3 weeks prior to informed consent, untreated (≤ 4 days of treatment), DS pulmonary TB based on predetermined criteria, females of child-bearing potential (FOCBP) on appropriate contraception with further criteria for stage 2 based on treatment for confirmed DS- or RR-TB.

Primary outcome:

  - Stage 1: Percentage of participants with DS-TB reporting severe adverse events (≥ grade 3) and/or serious adverse events, by treatment group, percentage of participants with pulmonary DS-TB with unfavourable outcome, by treatment group.
  - Stage 2: Percentage of participants with DS-TB reporting severe adverse events (≥ grade 3) and/or serious adverse events, by treatment group, percentage of participants with pulmonary DS-TB reporting unfavourable outcome, by treatment group.

- **Phase 2b/c:** A multicentre, open-label, randomized, dose-finding trial to evaluate the safety and efficacy of a 4-month regimen of OPC-167832 in combination with delamanid and bedaquiline in 120 subjects with DS pulmonary TB in comparison with standard treatment (NCT05221502, recruiting).

Study population: Consented adults, male or female, 18–65 years old, newly diagnosed with rifampin- and isoniazid-susceptible (on the screening sample) pulmonary TB, and on effective contraception.

Primary outcomes:

  - incidence of TEAEs;
  - incidence of potentially clinically significant changes of laboratory tests from baseline and abnormalities in the vital signs, physical examinations, electrocardiograms assessed at each visit and at end of study;
  - number of participants with a grade 3 or higher adverse event;
  - number of all cause treatment discontinuation; and
  - sputum culture conversion in MGIT tubes.

- **Phase 1/2:** An active-controlled, randomized, open-label trial to evaluate the safety, tolerability, PK and efficacy of multiple oral doses of OPC-167832 tablets in 122 subjects with uncomplicated, smear-positive, DS pulmonary TB (NCT03678688, completed March 2022).

Study population: Consented adults 18–64 years old, newly diagnosed with uncomplicated, DS pulmonary TB able to provide an adequate volume of sputum regularly and on effective contraception.

Product name (INN or company code): quabodepistat (OPC-167832) NCR ✓CC ✓T ✓MoA ✓ (continued)

Primary outcomes (see full trial details on ClinicalTrials.gov):

- change in TB bacterial load in sputum;
- plasma drug levels of OPC-167832 and/or delamanid and/or bedaquiline at specified pre-dose and post-dose time points; and
- incidence of adverse events.

Results: Conference poster data describe OPC 167832 was well tolerated at all single doses up to 480 mg, with no serious adverse events or adverse events leading to discontinuation *(27)*.

PK parameters:

- Median Tmax ranged from 2.5 to 3.5 h.

Cmax increased with dose and appeared to plateau up to 60 mg, then increased dose-proportionally from 90– 480 mg.

- AUC inf increased dose proportionally up to 240 mg.
- Median t½ ranged from 18 to 40 h across cohorts.
- Minimal differences in Cmax and AUC inf were observed following standard or high-fat meals compared to the fasted state.

Results: In the Phase 1 and Phase 1/2a clinical trials completed in March 2022 (NCT03678688), OPC-167832 was well tolerated, with mild and self-limiting adverse events *(28)*. The drug showed bactericidal activity in participants with DS pulmonary TB. In the multiple ascending dose study, mean terminal half-lives ranged from 15.1 to 23.6 h *(28)*. Once-daily OPC-167832 showed 14-day bactericidal activity from 3 mg (log10 CFU mean ± standard deviation change from baseline, –1.69 ± 1.15) to 90 mg (–2.08 ± 0.75), while the EBA of Rifafour e-275 was –2.79 ± 0.96 *(28)*.

Product name (INN or company code): GSK2556286 (GSK286) NCR ✓CC ✓T ✓MoA ✓

Pharmacology: chemical class and MoA: GSK2556286 is a novel small-molecule adenylyl cyclase Rv1625c agonist *(21)* which interferes with cholesterol regulation to reduce bacterial growth intracellularly (within macrophages) and extracellularly (in cholesterol-rich caseum) *(29)*.

Spectrum of activity and potential resistance: GSK2556286 was discovered by screening against *M. tuberculosis* that resides within human (THP-1) macrophage-like differentiated monocytes and had a 50% inhibitory concentration (IC50) of 0.07 µM *(29)*. GSK2556286 required cholesterol to show activity in an axenic culture and resistance mutations were mapped to *M. tuberculosis* adenylyl cyclase (cya) Rv1625c *(21,29,30,31)*, which has been implicated in cholesterol utilization *(21)*.

Sought therapeutic indication: Drug-sensitive, MDR and XDR TB.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 1

Clinical trial(s):

- Phase 1: A first-time-in-human (FTIH) study is to evaluate the safety, tolerability and PK of single and repeated ascending doses to GSK2556286 in healthy adults. Food effect cohorts will investigate the influence of food on the PK (NCT04472897, recruiting).

Adverse events / preclinical PK and safety: Evaluated in single-dose oral toxicity studies in rats, dogs and cynomolgus monkeys and in repeated-dose oral toxicity studies (4 weeks) in Wistar Han rats and cynomolgus monkeys with no adverse respiratory, cardiovascular or neurobehavioural effects.

Product name (INN or company code): macozinone (MCZ, PBTZ-169) NCR ✓CC ✓T ✓MoA ✓

Pharmacology: chemical class and MoA: Macozinone (PBTZ-169) is a piperazine-benzothiazinone that inhibits the enzyme DprE1, which is necessary for the growth and viability of mycobacterium *(25,26,32)*. It is a second-generation analogue of BTZ043 with physicochemical and PK optimization efforts underway *(33)*.

Spectrum of activity and potential resistance: In vitro, piperazine-benzothiazinones (PBTZs) have been shown to reach MICs between 0.19 ng/mL and 0.75 ng/mL for *M. tuberculosis*, and PBTZ169 was shown to be highly active against a panel of nine MDR- and XDR clinical isolates of *M. tuberculosis (1)*. Cross-resistance between BTZ043 and PBTZ169 was confirmed for BTZ-resistant strains of *M. tuberculosis*, *M. bovis* bacillus Calmette-Guérin and *M. smegmatis*, indicating the common MoA *(1)*. The in vivo efficacy of BTZ043 was assessed 4 weeks after a low-dose aerosol infection of BALB/c mice in a chronic (lung and spleen) model of TB. Treatment with BTZ043 reduced the bacterial burden in the lungs and spleens by 1 and 2 logs, respectively, which was time-dependent (rather than dose-dependent) *(34)*. The in vitro and in vivo synergistic effect of PBT169 and TBI-166 showed a reduction of MIC by 6.25%–25.00% and a lower amount of viable *M. tuberculosis* mouse lung tissues with respect to TBI-166 monotherapy *(32,35)*.

Sought therapeutic indication: MDR, XDR *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral tablet, capsule or suspension (extended and immediate release).

Phase of clinical development: 1

Clinical trial(s):

- A **Phase 2a** study in the Russian Federation was terminated in March 2020 due to very slow enrollment (NCT03334734).
- **Phase 1:** A randomized, double-blind, placebo-controlled, multiple ascending dose study conducted at a study centre in Switzerland. (NCT03776500, completed March 2020).
- **Phase 1:** An open-label, prospective, non-comparative, ascending dose randomized cohort study of single and multiple oral administration of PBTZ169 (capsules 80 mg) in healthy volunteers (NCT04150224, completed February 2019).
- **Phase 1:** An open-label, prospective, non-comparative, safety, tolerability and PK ascending dose randomized cohort study of PBTZ169 (capsules 40 mg) in fasted healthy volunteers after single and multiple oral administration (NCT03036163, completed November 2016).
- **Phase 1a:** A safety, tolerability, PK profile and ex vivo antitubercular activity study of PBTZ169 formulated as spray-dried dispersion vs native crystal powder: single ascending doses, randomized, placebo-controlled, crossover Phase 1a trial in healthy volunteers (NCT03423030, completed March 2018).

Adverse events / preclinical PK and safety: Acute (5 g/kg) and chronic (25 and 250 mg/kg) toxicology studies in uninfected mice showed that, even at the highest dose tested, there were no adverse anatomical, behavioural or physiological effects after 1 month *(34)*.

Product name (INN or company code): TBAJ-587

Pharmacology: chemical class and MoA: TBAJ-587 is a diarylquinoline bedaquiline analogue with a reduced cardiotoxicity profile compared to bedaquiline, beneficial in treating drug-resistant TB *(36,37)*.

Spectrum of activity and potential resistance: TBAJ-587 has shown greater potency than bedaquiline in vitro, including against Rv0678 mutants, and may offer a larger safety margin *(36)*. In a mouse model of TB and different doses of bedaquiline and TBAJ-587, TBAJ-587 has greater efficacy against both strains than bedaquiline, whether alone or in combination with pretomanid and either linezolid or moxifloxacin and pyrazinamide *(36)*. TBAJ-587 also reduced the emergence of resistance to diarylquinolines and pretomanid *(36)*.

Sought therapeutic indication: Drug-sensitive and drug-resistant *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral suspension.

Phase of clinical development: 1

Clinical trial(s):

- **Phase 1:** A partially blinded, placebo-controlled, randomized, combined single ascending dose with food effect cohort trial (part 1) and multiple ascending dose trial (part 2) to evaluate the safety, tolerability and PK of TBAJ-587 in 106 healthy adults (NCT04890535, completed February 2023).

Adverse events / preclinical PK and safety: Bedaquiline analogues TBAJ-587 and TBAJ-876 had lower MICs than bedaquiline against clinical isolates of *M. tuberculosis*, and efficacy demonstrated against murine TB at lower exposures than bedaquiline *(37)*. TBAJ-587 and TBAJ-876 had lower potency against hERG (human ether-à-go-go related gene), predicted higher human clearance and an acceptable safety margin, based on safe exposure in rats compared to efficacious exposure in mice *(37)*.

Product name (INN or company code): TBAJ-876

Pharmacology: chemical class and MoA: TBAJ-876 is a diarylquinoline bedaquiline analogue with improved affinity for F-type ATP synthase to inhibit mycobacterial energy production *(38)*.

Spectrum of activity and potential resistance:

TBAJ-876, displays improved in vitro activity and preclinical safety profile compared to bedaquiline *(37,39)*. In a murine model of TB, TBAJ-876 demonstrated lower MIC against an Rv0678 loss-of-function mutant, and doses ≥ 6.25 mg/kg of TBAJ-876 had greater efficacy against both wild-type and mutant strains compared to bedaquiline at 25 mg/kg, with no selective amplification of bedaquiline-resistant bacteria observed *(39)*.

Sought therapeutic indication: Drug-sensitive and drug-resistant *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 1:** A drug–drug interaction study to evaluate the safety, tolerability and induction potential of TBAJ-876 on CYP3A4 and P-glycoprotein and the inhibition potential of TBAJ-876 on P-glycoprotein in 28 healthy adult subjects (NCT05526911, completed August 2022).
- **Phase 1:** A partially blind, placebo-controlled, randomized, combined single ascending dose with a food effect cohort and multiple ascending dose study to evaluate the safety, tolerability and PK of TBAJ-876 in 107 healthy adult subjects (NCT04493671, completed November 2022).

Adverse events / preclinical PK and safety:

3,5-Dialkoxypyridine analogues of bedaquiline are less lipophilic, have higher clearance and display lower cardiotoxic potential *(40,41,42,43)*.

Product name (INN or company code): pyrifazimine (TBI-166)

Pharmacology: chemical class and MoA: Pyrifazimine (TBI-166) is a novel riminophenazine (clofazimine analogue) that inhibits mycobacterial growth and binds preferentially to mycobacterial DNA with improved side effect profile *(44)*.

Spectrum of activity and potential resistance: The in vitro activity of TBI-166 against both drug-sensitive and drug-resistant *M. tuberculosis* was found to be more potent than that of clofazimine *(45)*. The combination of TBI-166 with bedaquiline and pyrazinamide is highly effective, demonstrating sterilizing activity similar to the bedaquiline + pretomanid + linezolid (BPaL) regimen in a mouse model *(46)*. In another study, a TBI-166 + bedaquiline group showed negative lung tissue culture and significantly lower live bacteria count compared to bedaquiline monotherapy 1.49 log10 CFU ($P < 0.01$) in low-dose aerosol infection models of acute and chronic murine TB. Spontaneous resistance to TBI-166 was reported in *M. tuberculosis* wild-type strains *(45)*.

Sought therapeutic indication: MDR *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Completed:** A Phase 1a clinical trial in China in 2018 (ChiCTR 1800018780).
- **Phase 2:** Evaluation of EBA and safety in pulmonary TB with pyrifazimine (TBI-166) (NCT04670120, status unknown).

Study population: 56 consented adults, male or female, 18–65 years old diagnosed with (initial treatment) TB, and the untreated sputum smear is 2+ or 2 times 1+ or more in relative stable condition on effective contraception.

Primary outcome: EBA, counted by daily log (CFU) change.

Adverse events / preclinical PK and safety: TBI-166 causes less skin discolouration than clofazimine (CFZ) and various studies have described its improved PK/PD profile *(45,46)*.

Product name (INN or company code): TBI-223

Pharmacology: chemical class and MoA: TBI-223 is a novel oxazolidinone *(47,48)* which targets an early step in protein synthesis involving the binding of N-formylmethionyl-tRNA to the ribosome *(4)*.

Spectrum of activity and potential resistance: TBI-223 has shown activity against drug-sensitive and drug-resistant TB strains, including clinical strains from all global lineages; activity against MRSA; and efficacy in mouse TB infection *(47,49)*. Gordon et al. (2022) describe additive activity in combination with bedaquiline and pretomanid *(47)*. In mouse models of MRSA bacteraemia, skin wound infection and orthopedic-implant-associated infection, TBI-223 and linezolid had comparable dose-dependent efficacies in reducing bacterial burden and disease severity compared with sham-treated control mice *(47)*.

Sought therapeutic indication: Drug-sensitive and drug-resistant *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral capsule.

Phase of clinical development: 1

Clinical trial(s):

- **Phase 1:** A partially-blinded, placebo-controlled, randomized, multiple ascending dose study to include a single dose food-effect study to evaluate the safety, tolerability and the PK profile of TBI-223 in 28 healthy subjects (NCT04865536, completed March 2022).
- **Phase 1:** A partially-blinded, placebo-controlled, randomized, single ascending dose with a food-effect cohort study to evaluate the safety, tolerability and PK of TBI-223 in 91 healthy adult participants (NCT03758612, completed March 2020).

Adverse events / preclinical PK and safety:

TBI-223 has high oral bioavailability in dogs with moderate clearance (6.6 mL/min/kg) and a reasonable volume of distribution in mice (half-life 3 h) and rats (half-life 8 h; poster data) *(49)*. It has shown reduced myelosuppression and toxicity compared to linezolid and has a projected human efficacious dose of 800 mg qd *(49)*.

Product name (INN or company code): sudapyridine (WX-081)

Pharmacology: chemical class and MoA: Sudapyridine (WX-081) is a bedaquiline analogue with improved non-clinical toxicology profile *(50,51)*.

Spectrum of activity and potential resistance: WX-081 displayed exceptional anti-mycobacterial activity against *M. tuberculosis* H37Rv in vitro and in vivo *(50)*; it has strong antimicrobial activity against different NTM species with low cytotoxicity *(52)*.

Sought therapeutic indication: Isoniazid- and RR (MDR) *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 3

Clinical trial(s):

Phase 3: A multicentre, randomized, double-blind, positive control study to evaluate the efficacy and safety of sudapyridine (WX-081) tablets in approximately 450 patients with RR pulmonary TB (NCT05824871, enrolling by invite).

Study population: Adult male or female 18–65-year-old patients with clinically diagnosed TB whose drug sensitivity test has proved to be at least resistant to rifampicin; phenotypic or molecular drug sensitivity test results within 3 months before the subject signs informed consent can be accepted.

Primary outcome: The percentage of participants with sputum culture conversion.

- **Phase 2:** A multicentre, randomized, positive-controlled clinical trial to evaluate the EBA, safety and tolerability of WX-081 in 99 participants with drug-naive and susceptible or drug-resistant pulmonary TB (NCT04608955, completed April 2022).

Product name (INN or company code): sudapyridine (WX-081) (continued)

Study population: Consented adults 18–65-years-old, male or female, newly treated **drug-sensitive TB:** clinically diagnosed as pulmonary TB, without treatment, sputum smear-positive for AFB at least 1+, and no resistance to rifampicin or isoniazid in the drug sensitivity test. **Drug-resistant TB:** Re-treatment of pulmonary TB patients, diagnosed as RR-TB or isoniazid and rifampicin-resistant (MDR-TB) by molecular biology methods, and sputum smear-positive for AFB. Patients must be willing to discontinue all TB drugs to allow 7 days washout (see ClinicalTrials.gov for full inclusion/exclusion criteria).

Two stages: Core research stage (stage 1) and extended research stage (stage 2):

- During stage 1, a panel of 59 participants with drug-naive and susceptible TB will be randomized to receive either WX-081 (including three groups: 150 mg qd, 300 mg qd, 450 mg qd, *n* = 12 per group) or standard treatment (*n* = 8) for 2 weeks, followed by a follow-up period of 2 weeks.
- A panel of 40 participants with drug-resistant TB will be randomized to receive either WX-081 (400 mg qd, *n* = 20) or bedaquiline (400 mg qd, *n* = 20) for 2 weeks. During stage 2, the 40 participants with drug-resistant TB will receive WX-081(150 mg qd) + *M. tuberculosis* treatment (i.e., multidrug background treatment) and bedaquiline (200 mg three times weekly (tiw)) + *M. tuberculosis* treatment for 6 weeks respectively, followed by a follow-up period of 4 weeks.

Primary outcome: Time-to-positive, EBA of WX-081.

- **Phase 1/2:** A prospective Phase 1b/2a, active-controlled, randomized, open-label study to evaluate the safety, tolerability, extended EBA and PK of multiple oral doses of BTZ-043 tablets in 77 subjects with newly diagnosed, uncomplicated, smear-positive, DS pulmonary TB (NCT04044001, completed May 2022).
- **Phase 1:** A single-centre, open-label study to investigate the mass balance, excretion pathways and metabolites after a single oral dose of 500 mg, 3.7 MBq, [14C]BTZ-043 in six healthy male volunteers (NCT04874948, completed October 2021).
- **Phase 1:** A randomized, double-blind, placebo-controlled, single ascending dose study to evaluate safety, tolerability and PK of single doses of BTZ043 in 30 healthy adult volunteers (NCT03590600, completed March 2019).

Adverse events / preclinical PK and safety: WX-081 improved PK parameters and, more importantly, had no adverse effects on blood pressure, heart rate or qualitative electrocardiogram parameters from non-clinical toxicology studies *(53)*. WX-081 had excellent PK parameters in animals, better lung exposure and lower QTc prolongation potential compared to bedaquiline *(50)*.

Product name (INN or company code): alpibectir (BVL-GSK098) + ethionamide (Eto) / prothionamide

Pharmacology: chemical class and MoA: Alpibectir (BVL-GSK098) inactivates an *M. tuberculosis* TetR-like repressor, EthR2, to reverse ethionamide-acquired resistance and increase Eto efficacy *(54,55)*.

Spectrum of activity and potential resistance:
BVL-GSK098 has shown rapid bactericidal effects against Eto-resistant strains in both laboratory and animal studies. It is expected to reduce the required dose of Eto by at least threefold, potentially minimizing side effects and improving patient compliance *(55)*. The combination of BVL-GSK098 and low-dose Eto/Pto could be a safer and better-tolerated treatment for drug-resistant TB, including MDR, XDR and isoniazid mono-resistant strains *(54,55,56,57)*.

Sought therapeutic indication: Pulmonary (DS- and RR-) *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Product name (INN or company code): alpibectir (BVL-GSK098) + ethionamide (Eto) / prothionamide (continued)

Clinical trial(s):

- **Phase 1:** A double-blind, randomized, placebo-controlled study to investigate the safety, tolerability and PK and food effect of BVL-GSK098 administered as single and multiple oral doses to 80 healthy volunteers (NCT04654143, completed January 2023).
- **Phase 2:** A trial to evaluate the EBA, safety and tolerability of Eto alone and in combination with BVL-GSK098 administered orally to 105 adults with newly diagnosed, rifampicin- and isoniazid-susceptible pulmonary TB (NCT05473195, recruiting).

Study population: Participants randomized 5:1, consented adults, male or female, 18–65 years old with newly diagnosed and untreated pulmonary TB, rifampicin- and isoniazid-susceptible pulmonary TB as determined by molecular testing, able to produce adequate volume of sputum regularly, on effective contraception.

Primary outcome: EBA CFU.

Adverse events / preclinical PK and safety: Not yet publicly available.

Product name (INN or company code): dovramilast (CC-11050, AMG-634)

Pharmacology: chemical class and MoA: Dovramilast (CC-11050, AMG-634) is an isoindole phosphodiesterase type 4 inhibitor which acts by blocking the breakdown of cyclic adenosine monophosphate, decreasing host inflammatory response *(58)*.

Spectrum of activity and potential resistance: Dovramilast shows activity in various models of inflammatory disease *(59,60,61)*. In an in vivo rabbit model with experimental *M. tuberculosis* infection, CC-11050 plus isoniazid therapy reduces bacillary load and lung pathology *(59,61)*. Additionally, expression of host genes associated with tissue remodelling, TNF-α regulation, macrophage activation and lung inflammation networks was dampened in CC-11050-treated rabbits, compared to untreated rabbits *(60)*. Combined treatment with CC-11050 and isoniazid improves bacterial clearance and reduces lung pathology in rabbits with *M. tuberculosis* infection *(59)*.

Sought therapeutic indication: Under development as host-directed therapy (HDT) in drug-sensitive and drug-resistant *M. tuberculosis* and leprosy.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2:** A randomized trial to evaluate the safety, preliminary efficacy and biomarker response of HDTs added to RIF-modified standard therapy in 200 adults with drug-sensitive smear-positive pulmonary TB (NCT02968927, active, not recruiting).

Study population: Consented adults 18–65 years old, male or female, with first episode of pulmonary TB diagnosed by positive sputum acid-fast bacillus (AFB) smear with subsequent culture confirmation OR positive Xpert TB/RIF with count< 20, RIF susceptibility diagnosed by Xpert TB/RIF OR Hain test, chest radiograph meeting criteria for moderate or far advanced pulmonary TB, HIV-1 seronegative and HBsAg (hepatitis B surface antigen) negative. Eligible patients were randomly assigned (1 : 1 : 1 : 1 : 1) to receive one of the four oral HDTs plus standard TB treatment or standard treatment alone (the control group). HDTs were:

- CC-11050 (200 mg twice daily, taken with food; day 1–112);
- everolimus (0.5 mg/day; day 1–112);
- auranofin (3 mg/day for seven doses, then 6 mg/day; day 1–112); and
- ergocalciferol (5 mg on day 1, then 2.5 mg on day 28 and day 56).

Product name (INN or company code): dovramilast (CC-11050, AMG-634) (continued)

Primary outcome: For auranofin, everolimus and vitamin D: the proportion of patients experiencing suspected or unexpected serious adverse reactions. For CC-11050: the proportion of patients experiencing treatment emergent serious adverse events.

Results:

Primary study findings: No treatment-emergent, treatment-attributable serious adverse events occurred in patients receiving CC-11050 or everolimus *(62)*. Patients treated with CC-11050 and everolimus had increased recovery of FEV1 at day 180 relative to the control group (mean difference from control group 6.30% (95% CI: 0.06–12.54; $P = 0.048$); and 6.56% (95% CI: 0.18–12·95; $P = 0.044$), respectively), whereas auranofin and ergocalciferol recipients did not *(62)*. CC-11050 and everolimus were safe and reasonably well tolerated as adjunctive therapies for TB, and analysis of preliminary efficacy suggests they might also enhance the recovery of FEV1, a key measure of lung function and predictor of all-cause mortality *(62)*.

Secondary study findings: Early biomarkers did not predict HDT effects on inflammation or infection consistently, suggesting specific responses related to HDT mechanisms of action *(63)*.

- **Phase 2:** A single-centre, open-label pilot study to evaluate the safety and efficacy of CC-11050 in Nepalese patients with erythema nodosum leprosum (NCT03807362, recruiting).
- **Phase 1:** A study to evaluate the safety, tolerability and PK/PD of a new spray-dried dispersion formulation of CC-11050 after single dose of CC-11050 and to evaluate the PK of CC-11050 under fasted and fed conditions and after co-administration with omeprazole (NCT04139226, completed February 2020).
- **Phase 2:** Pilot, multicentre, sequential, ascending dose study to evaluate the preliminary safety, tolerability, PK/PD and efficacy of CC-11050 in 48 subjects with discoid lupus erythematosus and subacute cutaneous lupus erythematosus (NCT01300208, completed March 2013).
- **Phase 1:** CC-11050 in 38 HIV-1-infected adults with suppressed plasma viraemia on antiretroviral therapy (NCT02652546, completed November 2018).

Product name (INN or company code): TBD09 (MK7762)

Pharmacology: chemical class and MoA: TBD09 (MK7762) is an oxazolidinone which targets an early step in protein synthesis involving the binding of N-formylmethionyl-tRNA to the ribosome *(4)*.

Spectrum of activity and potential resistance: In vitro and in vivo evaluation of MK-7762 and MK-3854 have shown that both candidates have antibacterial activity against *M. tuberculosis*, including some resistant strains *(64)* (website data).

Sought therapeutic indication: Drug-sensitive and drug-resistant *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 1

Clinical trial(s):

- **Phase 1:** A randomized, double-blind, placebo-controlled, single ascending dose and multiple ascending dose trial in 96 healthy adults to evaluate the safety, tolerability and PK of MK-7762 (NCT05824091, recruiting).

Adverse events / preclinical PK and safety: Not yet publicly available.

Product name (INN or company code): SQ109 ?NCR ✓T ✓MoA

Pharmacology: chemical class and MoA: SQ109 is a 1,2-ethylenediamine that specifically targets MmpL3 in *M. tuberculosis (65,66)*. It is currently the only inhibitor of the MmpL3 mycolic acid transporter, which is essential for the incorporation of mycolic acid into the *M. tuberculosis* cell wall, in clinical development *(66,67)*.

Spectrum of activity and potential resistance: SQ109 has shown activity against , Erdman and drug-resistant strains of *M. tuberculosis* with an MIC of 0.7–1.56, an selectivity index (SI) of 16.7 and 99% inhibition activity against intracellular bacteria. It has also demonstrated potency in vivo and limited toxicity in vitro and in vivo *(69)*.

Sought therapeutic indication: Drug-sensitive and drug-resistant *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2:** Multiple-arm, multiple-stage, open-label, randomized, controlled trial to evaluate four treatment regimens of SQ109, increased doses of rifampicin and moxifloxacin in 365 adults with newly diagnosed, smear-positive pulmonary TB (NCT01785186, completed March 2015).

Study population: Consented adults, male or female, 18 years or older with diagnosis of pulmonary TB from a health clinic established by sputum smear and/or GeneXpert MTB/RIF and/or chest x-ray and a valid rapid test result (GeneXpert MTB/RIF) from sputum positive for *M. tuberculosis* complex and indicating susceptibility to rifampicin (see clinicaltrials.gov for full inclusion criteria).

Participants were randomly allocated to control or one of the four experimental intensive phase regimens in the ratio 2 : 1 : 1 : 1 : 1. The control and four experimental regimens were:

Control: HRZE isoniazid, rifampicin standard, pyrazinamide, ethambutol

- arm 1: HRZQlow isoniazid, rifampicin standard, pyrazinamide, SQ109 150 mg;
- arm 2: HRZQhigh isoniazid, rifampicin standard, pyrazinamide, SQ109 300 mg;
- arm 3: HR20ZQhigh isoniazid, rifampicin 20 mg/kg, pyrazinamide, SQ109 300 mg; and
- arm 4: HR20ZM isoniazid, rifampicin 20 mg/kg, pyrazinamide, moxifloxacin 400 mg.

Primary outcome: Sputum culture conversion (two negative cultures) using liquid media.

Results: Time to stable culture conversion in liquid media was faster in the 35 mg/kg rifampicin group than in the control group (median 48 days vs 62 days, adjusted hazard ratio 1.78 (95% CI: 1.22–2.58, $P = 0.003$), but not in other experimental arms *(70)*. 45 (12%) of 365 patients reported grade 3–5 adverse events, with similar proportions in each arm *(70,71)*.

- **Phase 2a:** To evaluate the extended EBA, safety, tolerability and PK of SQ109 in 90 adult subjects with newly diagnosed, uncomplicated, smear-positive, pulmonary TB (NCT01218217, completed May 2012).

Primary outcome measure: The extended EBA of daily 75, 150 and 300 mg SQ109, and of daily 150 or 300 mg SQ109 with daily RIF standard dose in adults with newly diagnosed, uncomplicated, smear-positive, pulmonary TB.

Phase 1a: A randomized, placebo-controlled, single-dose, double-blind, dose-escalation study to evaluate safety, tolerability and PK of SQ109 in 62 normal, healthy male and female volunteers (NCT01585636, completed February 2007).

- **Phase 1b:** A randomized, placebo-controlled, double-blinded, dose-escalation study to evaluate safety, tolerability and PK of single-daily doses of SQ109 in 10 normal, healthy male and female volunteers (NCT00866190, completed November 2009).
- **Phase 1c:** A randomized, placebo-controlled, double-blinded study to evaluate the safety, tolerability and PK of 300 mg of SQ109 given once daily for 14 days in 10 normal, healthy male and female volunteers (NCT01358162, completed April 2011).

Product name (INN or company code): sanfetrinem cilexetil

Pharmacology: chemical class and MoA: Sanfetrinem cilexetil is a first-in-class tricyclic carbapenem (β-lactam) and oral prodrug of sanfetrinem (developed in the 1990s, GSK) *(72)*.

Spectrum of activity and potential resistance: The oral tricyclic carbapenem, sanfetrinem cilexetil was developed in the 1990s and underwent phase 2 clinical trials for upper respiratory infections. Its development was stopped prior to Phase 3 primarily based on commercial considerations *(74)*. Following the unexpected observation of meropenem activity against *M. tuberculosis*, *(75)*, sanfetrinem cilexetil has recently being repurposed as a potential new drug for TB including DS and MDR/XDR clinical isolates from different geographical origins: it was more active and with a narrow spectrum of activity (MIC90 = 1–4 µg/mL) than the clinically active meropenem (MIC90 = 2–64 µg/mL), with these activities enhanced in the presence of clavulanate, although to a lesser extent *(74)*. Mouse studies demonstrated the oral prodrug's effectiveness compared to a combination of meropenem and amoxicillin/clavulanate *(74)*.

Sought therapeutic indication: Repurposed for the treatment of DS and drug-resistant *M. tuberculosis*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2:** To evaluate the EBA, safety and tolerability of sanfetrinem cilexetil administered orally to 105 adults with newly diagnosed, smear-positive, rifampicin-susceptible pulmonary TB (NCT05388448, actively recruiting).

Study population: Consented adults, male or female, 18–65 years old with newly diagnosed, previously untreated, rifampicin-susceptible pulmonary TB, with investigator-confirmed + chest x-ray, able to produce adequate volume of sputum regularly and on effective contraception. Stage 1 will recruit 20 participants followed by a recruitment pause and an interim analysis to determine if sanfetrinem cilexetil has EBA). Should EBA be demonstrated, stage 2 will focus on optimizing sanfetrinem cilexetil (see full trial details at clinicaltrials.gov).

Primary outcome: Rate of change in *M. tuberculosis* load in sputum from pre-treatment to day 14 on treatment, based on CFU count on solid culture media (7H11 agar plates).

References

1. Makarov V, Mikušová K. Development of macozinone for TB treatment: an update. Appl Sci. 2020;10(7):2269 (https://doi.org/10.3390/app10072269 accessed 29 February 2024).
2. BTZ-043. In: New TB Drugs/Pipeline [website]. New York: Working Group for New TB Drugs; 2024 (https://www.newtbdrugs.org/pipeline/compound/btz-043, accessed 29 February 2024).
3. Jeong JW, Jung SJ, Lee HH, Kim YZ, Park TK, Cho YL et al. In vitro and in vivo activities of LCB01-0371, a new oxazolidinone. Antimicrob Agents Chemother. 2010;54(12):5359–62 (https://doi.org/10.1128/aac.00723-10, accessed 29 February 2024).
4. Shinabarger D. Mechanism of action of the oxazolidinone antibacterial agents. Expert Opin Investig Drugs. 1999;8(8):1195–202 (https://doi.org/10.1517/13543784.8.8.1195, accessed 29 February 2024).
5. Zong Z, Jing W, Shi J, Wen S, Zhang T, Huo F et al. Comparison of in vitro activity and MIC distributions between the novel oxazolidinone delpazolid and linezolid against multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis* in China. Antimicrob Agents Chemother. 2018;62(8) (https://doi.org/10.1128/aac.00165-18, accessed 29 February 2024).
6. Lee HS, Cha DS, Kang DH, Oh KM, Cho YL, Kwak JH et al. New oxazolidinones with cyclic amidrazone(III): pharmacokinetics and repeated dose toxicity studies of LCB01-0183 and LCB01-0371. Presented at the 49th Annual Interscience Conference on Agents and Chemotherapy and the 47th Annual Meeting of the Infectious Diseases Society of America, San Francisco, CA, USA, 12–15 September 2009; Abstract F1-1510.
7. Kim JS, Kim YH, Lee SH, Kim YH, Kim JW, Kang JY et al. Early bactericidal activity of delpazolid (LCB01-0371) in patients with pulmonary tuberculosis. Antimicrob Agents Chemother. 2022;66(2):e0168421 (https://doi.org/10.1128/aac.01684-21, accessed 29 February 2024).
8. Li X, Hernandez V, Rock FL, Choi W, Mak YSL, Mohan M et al. Discovery of a potent and specific *M. tuberculosis* leucyl-tRNA synthetase inhibitor: (S)-3-(aminomethyl)-4-chloro-7-(2-hydroxyethoxy) benzo[1,2]oxaborol-1(3H)-ol (GSK656). J Med Chem. 2017;60(19): 8011–26.
9. Tucker R. GSK3036656 demonstrates antibacterial action in pulmonary tuberculosis after two weeks. In: Hospital Pharmacy Europe/News [website]. London: Cogora; 2022 (https://hospitalpharmacyeurope.com/news/editors-pick/gsk3036656-demonstrates-antibacterial-action-in-pulmonary-tuberculosis-after-two-weeks/, accessed 29 February 2024).
10. Tenero D, Derimanov G, Carlton A, Tonkyn J, Davies M, Cozens S et al. First-time-in-human study and prediction of early bactericidal activity for GSK3036656, a potent Leucyl-tRNA synthetase inhibitor for tuberculosis treatment. Antimicrob Agents Chemother. 2019;63(8) (https://doi.org/10.1128/aac.00240-19, accessed 29 February 2024).
11. Barbachyn MR, Hutchinson DK, Brickner SJ, Cynamon MH, Kilburn JO, Klemens SP et al. Identification of a novel oxazolidinone (U-100480) with potent antimycobacterial activity. J Med Chem. 1996;39(3):680–5 (https://doi.org/10.1021/jm950956y, accessed 29 February 2024).
12. Wallis RS, Jakubiec W, Kumar V, Bedarida G, Silvia A, Paige D et al. Biomarker-assisted dose selection for safety and efficacy in early development of PNU-100480 for tuberculosis. Antimicrob Agents Chemother. 2011;55(2):567–74 (https://doi.org/10.1128/AAC.01179-10, accessed 29 February 2024).
13. Williams KN, Stover CK, Zhu T, Tasneen R, Tyagi S, Grosset JH et al. Promising antituberculosis activity of the oxazolidinone PNU-100480 relative to that of linezolid in a murine model. Antimicrob Agents Chemother. 2009;53(4):1314–9 (https://doi.org/10.1128/AAC.01182-08, accessed 29 February 2024).
14. Cynamon MH, Klemens SP, Sharpe CA, Chase S. Activities of several novel oxazolidinones against *Mycobacterium tuberculosis* in a murine model. Antimicrob Agents Chemother. 1999;43(5):1189–91 (https://doi.org/10.1128/AAC.43.5.1189, accessed 29 February 2024).
15. Wallis RS, Dawson R, Friedrich SO, Venter A, Paige D, Zhu T et al. Mycobactericidal activity of sutezolid (PNU-100480) in sputum (EBA) and blood (WBA) of patients with pulmonary tuberculosis. PLoS ONE. 2014;9(4):e94462 (https://doi.org/10.1371/journal.pone.0094462, accessed 29 February 2024).

16. Shirude PS, Shandil RK, Manjunatha MR, Sadler C, Panda M, Panduga V et al. Lead optimization of 1,4-azaindoles as antimycobacterial agents. J Med Chem. 2014;57(13):5728–37 (https://doi.org/10.1021/jm500571f, accessed 29 February 2024).

17. Robertson GT, Ramey ME, Massoudi LM, Carter CL, Zimmerman M, Kaya F et al. Comparative analysis of pharmacodynamics in the C3HeB/FeJ mouse tuberculosis model for DprE1 inhibitors TBA-7371, PBTZ169, and OPC-167832. Antimicrob Agents Chemother. 2021;65(11):e0058321 (https://doi.org/10.1128/AAC.00583-21, accessed 29 February 2024).

18. Pethe K, Bifani P, Jang J, Kang S, Park S, Ahn S et al. Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis. Nat Med. 2013;19(9):1157–60 (https://doi.org/10.1038/nm.3262, accessed 29 February 2024).

19. Lee BS, Kalia NP, Jin XEF, Hasenoehrl EJ, Berney M, Pethe K. Inhibitors of energy metabolism interfere with antibiotic-induced death in mycobacteria. J Biol Chem. 2019;294(6):1936–43 (https://doi.org/10.1074/jbc.RA118.005732, accessed 29 February 2024).

20. Moraski GC, Seeger N, Miller PA, Oliver AG, Boshoff HI, Cho S et al. Arrival of imidazo[2,1-b]thiazole-5-carboxamides: potent anti-tuberculosis agents that target QcrB. ACS Infect Dis. 2016;2(6):393–8 (https://doi.org/10.1021/acsinfecdis.5b00154, accessed 29 February 2024).

21. Brown KL, Wilburn KM, Montague CR, Grigg JC, Sanz O, Pérez-Herrán E et al. Cyclic AMP-mediated inhibition of cholesterol catabolism in *Mycobacterium tuberculosis* by the novel drug candidate GSK2556286. Antimicrob Agents Chemother. 2023;67(1):e0129422 (https://doi.org/10.1128/aac.01294-22, accessed 29 February 2024).

22. de Jager VR, Dawson R, van Niekerk C, Hutchings J, Kim J, Vanker N et al. Telacebec (Q203), a new antituberculosis agent. N Engl J Med. 2020;382(13):1280–1 (https://doi.org/10.1056/NEJMc1913327, accessed 29 February 2024).

23. Kim J, Choi J, Kang H, Ahn J, Hutchings J, van Niekerk C et al. Safety, tolerability, pharmacokinetics, and metabolism of telacebec (Q203) for the treatment of tuberculosis: a randomized, placebo-controlled, multiple ascending dose Phase 1B trial. Antimicrob Agents Chemother. 2023; 67(1):e0112322 (https://doi.org/10.1128/aac.01123-22, accessed 29 February 2024).

24. Hariguchi N, Chen X, Hayashi Y, Kawano Y, Fujiwara M, Matsuba M et al. OPC-167832, a novel carbostyril derivative with potent antituberculosis activity as a DprE1 inhibitor. Antimicrob Agents Chemother. 2020;64(6) (https://doi.org/10.1128/AAC.02020-19, accessed 29 February 2024).

25. Riccardi G, Pasca MR, Chiarelli LR, Manina G, Mattevi A, Binda C. The DprE1 enzyme, one of the most vulnerable targets of *Mycobacterium tuberculosis*. Appl Microbiol Biotechnol. 2013;97(20):8841–8 (https://doi.org/10.1007/s00253-013-5218-x, accessed 29 February 2024).

26. Shetye GS, Franzblau SG, Cho Sanghyun. New tuberculosis drug targets, their inhibitors, and potential therapeutic impact. Transl Res. 2020;220:68–97 (https://doi.org/10.1016/j.trsl.2020.03.007, accessed 29 February 2024).

27. Quabodepistat. In: New TB drugs/Pipeline/Compounds [website. New York: Working Group for New TB Drugs; 2024 (https://www.newtbdrugs.org/pipeline/compound/quabodepistat-opc-167832, accessed 19 January 2024).

28. Dawson R, Diacon AH, Narunsky K, De Jager VR, Stinson KW, Zhang X et al. Phase I single ascending dose and food effect study in healthy adults and Phase I/IIa multiple ascending dose study in patients with pulmonary tuberculosis to assess pharmacokinetics, bactericidal activity, tolerability, and safety of OPC-167832. Antimicrob Agents Chemother. 2023;67(6):e0147722 (https://doi.org/10.1128/aac.01477-22, accessed 29 February 2024).

29. Nuermberger EL, Martínez-Martínez MS, Sanz O, Urones B, Esquivias J, Soni H et al. GSK2556286 is a novel antitubercular drug candidate effective in vivo with the potential to shorten tuberculosis treatment. Antimicrob Agents Chemother. 2022;66(6):e0013222 (https://doi.org/10.1128/aac.00132-22, accessed 29 February 2024).

30. VanderVen BC, Fahey RJ, Lee W, Liu Y, Abramovitch RB, Memmott C et al. Novel inhibitors of cholesterol degradation in *Mycobacterium tuberculosis* reveal how the bacterium's metabolism is constrained by the intracellular environment. PLoS Pathog. 2015;11(2):e1004679 (https://doi.org/10.1371/journal.ppat.1004679, accessed 29 February 2024).

31. Butler MS, Henderson IR, Capon RJ, Blaskovich MA. Antibiotics in the clinical pipeline as of December 2022. J Antibiotics. 2023;76(8):431–73 (https://doi.org/10.1038/s41429-023-00629-8, accessed 12 January 2024).

32. Imran M, Khan SA, Asdaq SMB, Almehmadi M, Abdulaziz O, Kamal M et al. An insight into the discovery, clinical studies, compositions, and patents of macozinone: a drug targeting the DprE1 enzyme of *Mycobacterium tuberculosis*. J Infect Public Health. 2022;15(10):1097–107 (https://doi.org/10.1016/j.jiph.2022.08.016, accessed 29 February 2024).

33. Koryakova A, Shcherbakova V, Riabova O, Kazaishvili Y, Bolgarin R, Makarov V. Antituberculosis macozinone extended-release tablets to enhance bioavailability: a pilot pharmacokinetic study in beagle dogs. Microbiol Spectr. 2023;11(1):e0232722 (https://doi.org/10.1128/spectrum.02327-22, accessed 29 February 2024).

34. Makarov V, Manina G, Mikusova K, Möllmann U, Ryabova O, Saint-Joanis B et al. Benzothiazinones kill *Mycobacterium tuberculosis* by blocking arabinan synthesis. Science. 2009;324(5928):801–4 (https://doi.org/10.1126/science.1171583, accessed 29 February 2024).

35. Liu HT, Fu L, Wang B, Wang N, Li DS, Ding YM et al. Study on the pharmacodynamic activity of combinations with the new anti-tuberculosis drug pyrifazimine in vitro and in vivo in mouse. 2022;45(6):560–6 (in Chinese) (https://doi.org/10.3760/cma.j.cn112147-20211008-00697, accessed 29 February 2024).

36. Xu J, Converse PJ, Upton AM, Mdluli K, Fotouhi N, Nuermberger EL. Comparative efficacy of the novel diarylquinoline TBAJ-587 and bedaquiline against a resistant Rv0678 mutant in a mouse model of tuberculosis. Antimicrob Agents Chemother. 2021;65(4) (https://doi.org/10.1128/AAC.02418-20, accessed 29 February 2024).

37. Sutherland HS, Tong AST, Choi PJ, Blaser A, Conole D, Franzblau SG et al. 3,5-Dialkoxypyridine analogues of bedaquiline are potent antituberculosis agents with minimal inhibition of the hERG channel. Bioorg Med Chem. 2019;27(7):1292–307 (https://doi.org/10.1016/j.bmc.2019.02.026, accessed 29 February 2024).

38. Krah A, Grüber G, Bond PJ. Binding properties of the anti-TB drugs bedaquiline and TBAJ-876 to a mycobacterial F-ATP synthase. Curr Res Struct Biol. 2022;4:278–84 (https://doi.org/10.1016/j.crstbi.2022.09.001, accessed 29 February 2024).

39. Almeida D, Converse PJ, Li SY, Upton AM, Fotouhi N, Nuermberger EL. Comparative efficacy of the novel diarylquinoline TBAJ-876 and bedaquiline against a resistant Rv0678 mutant in a mouse model of tuberculosis. Antimicrob Agents Chemother. 2021;65(12):e0141221 (https://doi.org/10.1128/AAC.01412-21, accessed 29 February 2024).

40. Sarathy JP, Ganapathy US, Zimmerman MD, Dartois V, Gengenbacher M, Dick T. TBAJ-876, a 3,5-dialkoxypyridine analogue of bedaquiline, is active against Mycobacterium abscessus. Antimicrob Agents Chemother. 2020;64(4) (https://doi.org/10.1128/AAC.02404-19, accessed 29 February 2024).

41. Choi PJ, Sutherland HS, Tong AST, Blaser A, Franzblau SG, Cooper CB et al. Synthesis and evaluation of analogues of the tuberculosis drug bedaquiline containing heterocyclic B-ring units. Bioorg Med Chem Lett. 2017;27(23):5190–6 (https://doi.org/10.1016/j.bmcl.2017.10.042, accessed 29 February 2024).

42. Blaser A, Sutherland HS, Tong AST, Choi PJ, Conole D, Franzblau SG et al. Structure-activity relationships for unit C pyridyl analogues of the tuberculosis drug bedaquiline. Bioorg Med Chem. 2019;27(7):1283–91 (https://doi.org/10.1016/j.bmc.2019.02.025, accessed 29 February 2024).

43. Sutherland HS, Tong AST, Choi PJ, Conole D, Blaser A, Franzblau SG et al. Structure-activity relationships for analogs of the tuberculosis drug bedaquiline with the naphthalene unit replaced by bicyclic heterocycles. Bioorg Med Chem. 2018;26(8):1797–809 (https://doi.org/10.1016/j.bmc.2018.02.026, accessed 29 February 2024).

44. Zhang D, Liu Y, Zhang C, Zhang H, Wang B, Xu J et al. Synthesis and biological evaluation of novel 2-methoxypyridylamino-substituted riminophenazine derivatives as antituberculosis agents. Molecules. 2014;19(4):4380–94 (https://doi.org/10.3390/molecules19044380, accessed 29 February 2024).

45. Xu J, Wang B, Fu L, Zhu H, Guo S, Huang H et al. In vitro and in vivo activities of the riminophenazine TBI-166 against *Mycobacterium tuberculosis*. Antimicrob Agents Chemother. 2019;63(5) (https://doi.org/10.1128/AAC.02155-18, accessed 29 February 2024).

46. Ding Y, Zhu H, Fu L, Zhang W, Wang B, Guo S et al. Superior efficacy of a TBI-166, bedaquiline, and pyrazinamide combination regimen in a murine model of tuberculosis. Antimicrob Agents Chemother. 2022;66(9):e0065822 (https://doi.org/10.1128/aac.00658-22, accessed 29 February 2024).

47. Gordon O, Dikeman DA, Ortines RV, Wang Y, Youn C, Mumtaz M et al. The novel oxazolidinone TBI-223 is effective in three preclinical mouse models of methicillin-resistant *Staphylococcus aureus* infection. Microbiol Spectr. 2022;10(5):e0245121 (https://doi.org/10.1128/spectrum.02451-21, accessed 29 February 2024).

48. TBI-223. In: New TB Drugs/Pipeline/Compounds [website]. New York: Working Group for New TB Drugs; 2024 (https://www.newtbdrugs.org/pipeline/compound/tbi-223, accessed 29 February 2024).

49. Mdluli K, Cooper C, Yang T, Lotlikar M, Betoudji F, Pinn M et al. TBI-223: a safer oxazolidinone in preclinical development for tuberculosis. Presented at ASM Microbe 2017, New Orleans, LA, USA, 1–5 June 2017. In: Abstracts Online [website] (https://www.abstractsonline.com/pp8/#!/4358/presentation/6174, accessed 29 February 2024).

50. Huang Z, Luo W, Xu D, Guo F, Yang M, Zhu Y et al. Discovery and preclinical profile of sudapyridine (WX-081), a novel anti-tuberculosis agent. Bioorg Med Chem Lett. 2022;71:128824 (https://doi.org/10.1016/j.bmcl.2022.128824, accessed 29 February 2024).

51. Sudapyridine (WX-081). In: New TB drugs/Pipeline/Compounds [website]. New York: Working Group for New TB Drugs; 2024 (https://www.newtbdrugs.org/pipeline/compound/sudapyridine-wx-081, accessed 19 January 2024).

52. Zhu R, Shang Y, Chen S, Xiao H, Ren R, Wang F et al. In vitro activity of the sudapyridine (WX-081) against non-tuberculous mycobacteria isolated in Beijing, China. Microbiol Spectr. 2022;10(6):e0137222 (https://doi.org/10.1128/spectrum.01372-22, accessed 29 February 2024).

53. Yao R, Wang B, Fu L, Li L, You K, Li YG et al. Sudapyridine (WX-081), a novel compound against *Mycobacterium tuberculosis*. Microbiol Spectr. 2022;10(1):e0247721 (https://doi.org/10.1128/spectrum.02477-21, accessed 29 February 2024).

54. Weber W, Schoenmakers R, Keller B, Gitzinger M, Grau T, Daoud-El Baba M et al. A synthetic mammalian gene circuit reveals antituberculosis compounds. Proc Natl Acad Sci U S A. 2008;105(29):9994–8 (https://doi.org/10.1073/pnas.0800663105, accessed 29 February 2024).

55. Alpibectir (BVL-GSK098). In: New TB drugs/Pipeline/Compounds [website]. New York: Working Group for New TB Drugs; 2024 (https://www.newtbdrugs.org/pipeline/compound/alpibectir-bvl-gsk098, accessed 19 January 2024).

56. Willand N, Dirié B, Carette X, Bifani P, Singhal A, Desroses M et al. Synthetic EthR inhibitors boost antituberculous activity of ethionamide. Nat Med. 2009;15(5):537–44 (https://doi.org/10.1038/nm.1950, accessed 29 February 2024).

57. Guieu B, Jourdan JP, Dreneau A, Willand N, Rochais C, Dallemagne P. Desirable drug-drug interactions or when a matter of concern becomes a renewed therapeutic strategy. Drug Discov Today. 2021;26(2):315–28 (https://doi.org/10.1016/j.drudis.2020.11.026, accessed 29 February 2024).

58. CC-11050. In: New TB drugs/Pipeline/Compounds [website]. New York: Working Group on New TB Drugs; 2024 (https://www.newtbdrugs.org/pipeline/compound/cc-11050, accessed 29 February 2024).

59. Subbian S, Tsenova L, O'Brien P, Yang G, Koo MS, Peixoto B et al. Phosphodiesterase-4 inhibition alters gene expression and improves isoniazid-mediated clearance of *Mycobacterium tuberculosis* in rabbit lungs. PLoS Pathog. 2011;7(9):e1002262 (https://doi.org/10.1371/journal.ppat.1002262, accessed 29 February 2024).

60. Subbian S, Tsenova L, Holloway J, Peixoto B, O'Brien P, Dartois V et al. Adjunctive phosphodiesterase-4 inhibitor therapy improves antibiotic response to pulmonary tuberculosis in a rabbit model. EBiomedicine. 2016;4:104–14 (https://doi.org/10.1016/j.ebiom.2016.01.015, accessed 29 February 2024).

61. Subbian S, Koo MS, Tsenova L, Khetani V, Zeldis JB, Fallows D et al. Pharmacologic inhibition of host Phosphodiesterase-4 improves isoniazid-mediated clearance of *Mycobacterium tuberculosis*. Front Immunol. 2016;7:1 (https://doi.org/10.3389/fimmu.2016.00238, accessed 29 February 2024).

62. Wallis RS, Ginindza S, Beattie T, Arjun N, Likoti M, Edward VA et al. Adjunctive host-directed therapies for pulmonary tuberculosis: a prospective, open-label, Phase 2, randomised controlled trial. *Lancet* Respir Med. 2021;9(8):897–908 (https://doi.org/10.1016/S2213-2600(20)30448-3, accessed 29 February 2024).

63. Wallis RS, Ginindza S, Beattie T, Arjun N, Likoti M, Sebe M et al. Lung and blood early biomarkers for host-directed tuberculosis therapies: secondary outcome measures from a randomized controlled trial. PLoS ONE. 2022;17(2):e0252097 (https://doi.org/10.1371/journal.pone.0252097, accessed 29 February 2024).

64. Merck and the Bill & Melinda Gates Medical Research Institute announce licensing agreement for novel tuberculosis antibiotic candidates. In: Merck/Media/News releases [website]. Rahway (NJ): Merck & Co.; 2022 (https://www.merck.com/news/merck-and-the-bill-melinda-gates-medical-research-institute-announce-licensing-agreement-for-novel-tuberculosis-antibiotic-candidates/, accessed 29 February 2024).

65. Sacksteder KA, Protopopova M, Barry CE, Andries K, Nacy CA. Discovery and development of SQ109: a new antitubercular drug with a novel mechanism of action. Future Microbiol. 2012;7(7):823–37 (https://doi.org/10.2217/fmb.12.56, accessed 29 February 2024).

66. Tahlan K, Wilson R, Kastrinsky DB, Arora K, Nair V, Fischer E et al. SQ109 targets MmpL3, a membrane transporter of trehalose monomycolate involved in mycolic acid donation to the cell wall core of *Mycobacterium tuberculosis*. Antimicrob Agents Chemother. 2012;56(4):1797–809 (https://doi.org/10.1128/AAC.05708-11, accessed 29 February 2024).

67. Grzegorzewicz AE, Pham H, Gundi VA, Scherman MS, North EJ, Hess T et al. Inhibition of mycolic acid transport across the *Mycobacterium tuberculosis* plasma membrane. Nat Chem Biol. 2012;8(4):334–41 (https://doi.org/10.1038/nchembio.794, accessed 29 February 2024).

68. Egbelowo O, Sarathy JP, Gausi K, Zimmerman MD, Wang H, Wijnant GJ et al. Pharmacokinetics and target attainment of SQ109 in plasma and human-like tuberculosis lesions in rabbits. Antimicrob Agents Chemother. 2021;65(9):e0002421 (https://doi.org/10.1128/AAC.00024-21, accessed 29 February 2024).

69. Protopopova M, Hanrahan C, Nikonenko B, Samala R, Chen P, Gearhart J et al. Identification of a new antitubercular drug candidate; SQ109, from a combinatorial library of 1,2-ethylenediamines. J Antimicrob Chemother. 2005;56(5):968–74 (https://doi.org/10.1093/jac/dki319, accessed 29 February 2024).

70. Boeree MJ, Heinrich N, Aarnoutse R, Diacon AH, Dawson R, Rehal S et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet* Infect Dis. 2017;17(1):39–49 (https://doi.org/10.1016/S1473-3099(16)30274-2, accessed 29 February 2024).

71. Infectex announces positive Phase 2b-3 clinical trial results of SQ109 for the treatment of multidrug-resistant pulmonary tuberculosis. In: Working Group on New TB Drugs/News [website]. New York: Working Group for New TB Drugs; 2017 (https://www.newtbdrugs.org/news/press-release-infectex-and-sequella-sq-109-clinical-trial-russia, accessed 14 January 2024).

72. Singh KV, Coque TM, Murray BE. In vitro activity of the trinem sanfetrinem (GV104326) against Gram-positive organisms. Antimicrob Agents Chemother. 1996;40(9):2142–6 (https://doi.org/10.1128/AAC.40.9.2142, accessed 29 February 2024).

73. Tamura S, Miyazaki S, Tateda K, Ohno A, Ishii Y, Matsumoto T et al. In vivo antibacterial activities of sanfetrinem cilexetil, a new oral tricyclic antibiotic. Antimicrob Agents Chemother. 1998;42(7):1858–61 (https://doi.org/10.1128/AAC.42.7.1858, accessed 29 February 2024).

74. Ramón-García S, Bates R, González del Río R, Gamallo P, Mendoza A, Ferrer S et al. Sanfetrinem, repurposing an oral beta-lactam with intracellular activity for the treatment of tuberculosis. Int J Tuberc Lung Dis. 2019;23(10)(Suppl 1):S590.

75. Diacon AH, van der Merwe L, Barnard M, von Groote-Bidlingmaier F, Lange C, García-Basteiro AL, Sevene E, Ballell L, Barros-Aguirre D. β-Lactams against Tuberculosis--New Trick for an Old Dog? N Engl J Med. 2016 Jul 28;375(4):393-4. doi: 10.1056/NEJMc1513236. Epub 2016 Jul 13. PMID: 27433841.

Annex 16. Non-traditionals – antibodies

Product name (INN or company code): tosatuxumab (AR-301)

Pharmacology: chemical class and MoA: Anti-*S. aureus* IgG1 antibody.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: IgG1 monoclonal antibody targeting *S. aureus* α-toxin, an important virulence factor that is secreted by both MRSA and MSSA (1,2,3). The MoA of AR-301 is independent of the antibiotic resistance profile of *S. aureus*, and it is active against infections caused by both MRSA and MSSA.

Sought therapeutic indication: Adjunctive treatment of severe *S. aureus* pneumonia, including HABP, VABP and CABP, treated in the ICU.

Pharmaceutical form, route of the administration and proposed posology: 20 mg/kg administered once intravenously.

Phase of clinical development: 3

Clinical trial(s): Two superiority studies evaluating the efficacy and safety of tosatuxumab for adjunctive therapy of pneumonia caused by *S. aureus* in patients with VABP due to *S. aureus*. In agreement with both the FDA and EMA, results from the first study, NCT03816956, were used to design a second confirmative trial (still not registered) in a restricted patient population (> 65 years old), with the primary efficacy end-point in older adults (≥ 65 years old).

Phase 3 Study: International, multicentre, prospective, randomized, double-blind, placebo-controlled, parallel design protocol in patients with VABP caused by *S. aureus* (NCT03816956).

Study population: 174 adult patients with pneumonia treated in an ICU for a documented infection with *S. aureus*, mechanically ventilated for at least 48 h, and with at least one of the following signs: fever, hypothermia, total peripheral WBC count > 10 000 cells/μL, and leukopenia with total WBC < 4500 cells/μL (mm^3) vs > 15% immature neutrophils (bands) noted on peripheral blood smear. Patients were randomized 1:1 to be treated with placebo plus SOC or AR-301 (20 mg/kg, single iv infusion) plus SOC. The selection of SOC antibiotics is made in accordance with local best practices at the discretion of the investigator.

- **Time period:** May 2019 to October 202; completed.
- **Sites:** 45 locations in Brazil, China, Europe, Georgia, Israel, Mexico, the Russian Federation, South Africa, Türkiye, Ukraine and the USA.
- **Primary end-point:** Clinical cure rates of SOC alone and SOC with AR-301 at day 21 as measured by all-cause mortality, need for mechanical ventilation and signs and symptoms of pneumonia.
- **Study results from the company website (4):** The study did not meet its primary end-point (4). An improvement trend in absolute efficacy in the clinical cure rate at day 21 of 11.3% ($P = 0.23$) was observed in the microbiologically confirmed full analysis data set "mFAS" population ($n = 120$) as compared to placebo. In the prespecified older adult population of 65+ years, the absolute efficacy on day 21 was increased to 33.6% ($P = 0.056$), and to 37.9% ($P = 0.025$) on day 28 vs +11% improvement ($P = 0.24$) in the overall mFAS population. According to the company, the increase in absolute efficacy was driven by the lower efficacy of SOC antibiotics in > 65-year-old adults compared to ≤ 65-year-old adults (30% vs 75%, respectively). In the patients with MRSA, the day 21 absolute efficacy trend was 28% higher than SOC alone ($P = 0.831$). The increase in absolute efficacy was also driven primarily by the lower efficacy of SOC antibiotics in MRSA patients compared with MSSA patients (38% vs 63%, respectively).

Product name (INN or company code): tosatuxumab (AR-301) (continued)

- **Confirmative Phase 3 study:** The study is not yet registered; the following information is available online. Based on FDA and EMA inputs, a larger patient population is planned to be enrolled, including *S. aureus* VABP, HABP and ventilated CAP patients *(5)*.
  - **Primary end-point:** Clinical cure rates of SOC alone and SOC with AR-301 in patients > 65 years old, at day 21 as measured by all-cause mortality, need for mechanical ventilation and signs and symptoms of pneumonia *(5)*.

Product name (INN or company code): suvratoxumab (AR-320)

Pharmacology: chemical class and MoA: Anti-*S. aureus* IgG1 antibody.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: Human monoclonal IgG1 antibody targeting the pore-forming α-toxin of *S. aureus*, an important virulence factor secreted by both MRSA and MSSA *(1,2,3)*. AR-320 has a long half-life and is able to sustain effective toxin neutralizing activities for approximately 3 months post-dose and above baseline level at 1 year post-dose.

Sought therapeutic indication: Pre-emptive treatment in *S. aureus* colonized, mechanically ventilated patients in the ICU.

Pharmaceutical form, route of the administration and proposed posology: Single-dose iv.

Phase of clinical development: 3

Clinical trial(s):

- **Phase 3:** A randomized, double-blind, placebo-controlled study evaluating the efficacy of a single iv dose of suvratoxumab in mechanically ventilated subjects in the ICU who are at high risk for *S. aureus* infection and who are currently free of active *S. aureus*-related disease but are colonized with *S. aureus* in the low respiratory tract (NCT05331885).
  - **Study population:** 564 mechanically ventilated adult patients in the ICU colonized with *S. aureus*, randomly assigned 1:1 to either a single iv dose of suvratoxumab or placebo.
  - **Time period:** September 2022 to June 2024.
  - **Sites:** Not specified.
  - **Primary end-point:** Incidence of nosocomial all-cause pneumonia through 30 days post-dose (time frame: 30 days). All-cause pneumonia is based on clinical, radiographic and microbiologic criteria.
- **Phase 2:** A randomized, double-blind, placebo-controlled, single-dose, dose-ranging superiority study of the efficacy and safety of MEDI4893 in mechanically ventilated adult subjects (NCT02296320).
  - **Study population:** 213 adult patients with confirmed *S. aureus* colonization of the lower respiratory tract were randomly assigned (1:1:1) to receive either a single iv infusion of suvratoxumab 2000 mg, suvratoxumab 5000 mg or placebo. At an interim analysis, the suvratoxumab 2000 mg group was discontinued on the basis of predefined PK criteria. The study design was modified, and approximately 206 patients were randomly assigned (1:1) to either the suvratoxumab 5000 mg group or the placebo group. The power of the study was reduced to 70% for this exploratory proof-of-concept study to provide data for a future confirmatory efficacy trial.
  - **Time period:** October 2014 to October 2018.
  - **Sites:** 49 locations in the USA and the EU.
  - **Primary end-point:** The incidence of *S. aureus* pneumonia at 30 days after treatment.
  - **Primary efficacy evaluation** was performed in the MITT population and included all participants who received any dose of study drug and analysed according to their randomized treatment group.
  - **Phase 2 clinical trial results:** The study did not meet its primary end-point. At 30 days after treatment, 17 (18%) of 96 patients in the suvratoxumab 5000 mg group and 26 (26%) of 100 patients in the placebo group had developed *S. aureus* pneumonia (relative risk reduction 31·9% (90% CI: –7·5 to 56·8), $P = 0{\cdot}17$). The study was underpowered to identify a significant difference between the suvratoxumab 5000 mg group and the placebo group. No inferences regarding the potential benefits of suvratoxumab in patients colonized with MRSA could be made, due to the insufficient sample size (only 12 (6%) of 196 patients were MRSA colonized) *(6,7)*.

Product name (INN or company code): 9MW1411

Pharmacology: chemical class and MoA: 9MW1411 is an anti-*S. aureus* α-toxin IgG1 antibody. It binds to the pore-forming α-toxin (α-haemolysin) protein monomer, which inhibits its binding to the ADAM10 receptor on the cell membrane *(8)*.

Spectrum of activity: ADAM10 receptor binding reduces the toxicity of α-toxin and its detrimental effect in *S. aureus* infection by modulating the functional activities of pro-inflammatory macrophages *(9)*.

Sought therapeutic indication: Under investigation as therapy for ABSSSI caused by *S. aureus*.

Pharmaceutical form, route of the administration: Intravenous.

Phase of clinical development: 2

Clinical trial(s): 9MW1411 has been evaluated in two trials:

- **Phase 1a** clinical study to evaluate the safety, tolerability, PK characteristics and immunogenicity of a single dose of MW14 injection in healthy subjects (NCT04784312, completed August 2021).
- **Phase 2** multicentre, randomized, double-blind, placebo-controlled trial design used to evaluate the efficacy and safety of two doses of 9MW1411 injection in patients with ABSSSI caused by *S. aureus*. The Phase 2 dose (RP2D) of 9MW1411 injection for this placebo-controlled study will be selected based on the results of Phase 1 clinical trials and preclinical PK/PD analysis.
  - **Study population:** 90 consented male/female participants between the ages of 18 and 75 with ABSSSI + systemic response and positive *S. aureus* lab findings.
  - **Time period:** February 2022 start. Currently recruiting.
  - **Primary end-point:**
    - Efficacy: Clinical cure in the MITT population at the TOC visit (time frame: TOC: 14 days after the last day of linezolid therapy.)
  - **Safety:**
    - Incidence and severity of adverse events, serious adverse events (time frame: from day 1 to day 57 (± 7) after administration).
    - Incidence of abnormal clinical laboratory findings in 12-lead ECG parameters, vital signs, physical examination (time frame: screening (within 48 h prior to the first dose of test article) to follow-up (day 57 ± 7)).
    - PK profile: Cmax (time frame: from day 1 to day 57 (±7) after administration).
    - Immunogenicity: Incidence of anti-drug antibodies (time frame: from day 1 to day 57 (± 7) after administration).
  - **Trial results:** Not yet publicly available.
  - **Adverse events:** Not yet publicly available.

Product name (INN or company code): calpurbatug (TRL1068)

Pharmacology: chemical class and MoA: TRL1068 is a monoclonal antibody that binds to DNABII homologues produced by Gram-positive and Gram-negative bacterial pathogens, disrupting biofilm formation *(10,11)*.

Spectrum of activity: In vitro, TRL1068 has been shown to disrupt biofilm thereby releasing bacteria that revert to the antibiotic sensitive planktonic state *(11,12)*. In vivo activity is described in three animal model experiments: In the murine infectious implant model, TRL1068 in combination with daptomycin (DAP) reduced both planktonic and residual adherent MRSA bacteria *(10)*. In the infective endocarditis rat model, TRL1068 in combination with vancomycin reduced MRSA densities in biofilm vegetation relative to controls, as well as reducing the propensity for septic metastases and mortality *(13)*. In the murine soft tissue infection model the increased exposure to imipenem in combination with TRL1068 showed a significant improvement in efficacy as compared to untreated and imipenem plus isotype control monoclonal antibody (–1.8 and –1.6 log10 CFU/catheter, respectively; $P < 0.001$) *(14)*.

Product name (INN or company code): calpurbatug (TRL1068) (continued)

Sought therapeutic indication: Being investigated as adjunctive therapy in bacterial biofilm pathogens such as MRSA, *Enterobacter*, *Enterococcus, Streptococcus* and *Pseudomonas (15)*.

Pharmaceutical form, route of administration: Intravenous.

Phase of clinical development: 1

Clinical trial(s):

A **Phase 1** trial is designed to assess overall safety and PK of TRL1068 (NCT04763759, not recruiting).

- **Study population:** 18 patients with PJI between 18 and 85 years of age (male and female) planned/scheduled for primary two-stage exchange arthroplasty, with identified pathogen(s) susceptible to an antibiotic regimen.
- **Preclinical PK and safety:** N/A.
- **Trial results** (webpage data): In a preliminary report, 75% (n = 8) of chronic PJI patients treated with a single dose of TRL1068 and standard antibiotics had a bacterial biofilm burden below 100 CFU/mL sonication fluid after 7 days of treatment. In a quarter of the TRL1068-treated patients, biofilm was removed below the limit of detection after only 7 days of treatment *(15)*.
- **Adverse events:** TRL1068 was well tolerated across both dose groups with no drug-related adverse events *(15)*.

Product name (INN or company code): CMTX-101

Pharmacology: chemical class and MoA: CMTX-101 is a humanized biofilm-disrupting anti-DNABII monoclonal antibody. Biofilm collapse combats pathogens through three methods: making bacteria sensitive to antibiotics, boosting the immune system and reducing inflammation in targeted areas *(16)*.

Spectrum of activity: In unpublished data, CMTX-101 has shown activity against biofilms formed by MRSA and other non-BPPL drug-resistant pathogens *(16)*.

Sought therapeutic indication: CMTX-101 is being investigated in the treatment of biofilm-producing MDR bacteria as in moderate-to-severe pneumonia *(17)*.

Pharmaceutical form, route of administration: Intravenous.

Phase of clinical development: 1b/2

Clinical trial(s):

Phase 1/2: A two-part first-in-human study to evaluate the safety, tolerability, PK and immunogenicity of CMTX-101 is currently recruiting (NCT05629741).

- **Study population:** 36 consented adults > 18 years old; healthy (part 1) and hospitalized participants with suspected or confirmed CABP of moderate severity (Part 2).

Preclinical PK and safety: Preliminary (webpage) results of the Phase 1 trials are that no drug-related safety events were observed, no anti-drug antibodies were detected, and preliminary PK results aligned with animal modelling for CMTX-101 *(18)*.

Product name (INN or company code): LMN-101

Pharmacology: chemical class and MoA: LMN-101 is a variable heavy-chain-derived protein designed to bind and inhibit *C. jejuni* and *E. coli* FlaA, a flagellin filament protein. LMN-101 is delivered via whole spray-dried spirulina biomass *(19,20)*.

Spectrum of activity: In vivo, spirulina biomass (SP526) decreased *Campylobacter* fecal shedding and lowered markers of intestinal inflammation in mouse models *(20)*.

Sought therapeutic indication: LMN-101 is currently being investigated as therapy in traveller's diarrhoea caused by *C. jejuni* and enterotoxigenic *E. coli*.

Pharmaceutical form, route of the administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2:** A randomized, double-blind, placebo-controlled, single-dose regimen study of LMN-101 in healthy volunteers challenged with *C. jejuni* (NCT04182490, completed October 2022).
  - **Study population:** 1:1 parallel assignment of 42 consented male/female participants of generally good health 18–50 years of age, with active comparator group receiving LMN-101, six 500 mg capsules orally three times daily for 14 days.
  - **Time period:** February to October 2022.
  - **Primary end-point:** Frequency of solicited or unsolicited adverse events (time frame: 14 days).
  - **Primary efficacy evaluation:** Not yet available.
  - **Trial results and adverse effects:** Not yet available.
- **Phase 1:** A safety and tolerability trial in healthy volunteers aged 18–50 years. 20 subjects were randomized to active or placebo treatment with doses up to 3000 mg of biomass three times daily (NCT04098263, completed June 2020).

Adverse events: No significant adverse events reported during the trial of LMN-101 in healthy volunteers. Minor side effects were similar in frequency between experimental and placebo groups *(20)*.

Product name (INN or company code): RESP-X (INFEX702)

Pharmacology: chemical class and MoA: RESP-X (INFEX702) is a novel humanized monoclonal antibody with anti-virulence activity against *P. aeruginosa (21)*.

Spectrum of activity: MDR *P. aeruginosa*.

Sought therapeutic indication: RESP-X (INFEX702) is being investigated as therapy in chronic *P. aeruginosa* infection in NCFB patients.

Pharmaceutical form, route of the administration: Intravenous.

Phase of clinical development: 1

Clinical trial(s): The Phase 1 trial is a double-blind, placebo-controlled, ascending single iv dose, safety, tolerability PK/PD study in healthy participants and NCFB patients colonized with *P. aeruginosa* administered INFEX702 (ISRCTN17978477, recruiting) The first cohort consisted of eight healthy volunteers who received doses of RESP-X at 1 mg/kg. Dosing of the second cohort of healthy volunteers at 3 mg/kg is reportedly underway as of April 2023.

Preclinical PK and safety: Not yet available.

Trial results (webpage data): Preliminary results show no serious adverse events were reported, and there were no treatment-related trends in vital signs, ECG, clinical laboratory evaluations or physical evaluations, and no local tolerability concerns were reported at the infusion site. A first-in-patient study (Phase 2a dose-ranging study) will consist of two cohorts of NCFB patients to determine the optimal dose ahead of a wider Phase 2 efficacy study *(21)*.

References

1. Gordon RJ, Lowy FD. Pathogenesis of methicillin-resistant *Staphylococcus aureus* infection. Clin Infect Dis. 2008;46(Suppl 5):S350–9 (https://doi.org/10.1086/533591, accessed 29 February 2024).
2. Le VT, Tkaczyk C, Chau S, Rao RL, Dip EC, Pereira-Franchi EP et al. Critical role of alpha-toxin and protective effects of its neutralization by a human antibody in acute bacterial skin and skin structure infections. Antimicrob Agents Chemother. 2016;60(10):5640–8 (https://doi.org/10.1128/AAC.00710-16, accessed 29 February 2024).
3. Hilliard JJ, Datta V, Tkaczyk C, Hamilton M, Sadowska A, Jones-Nelson O et al. Anti-alpha-toxin monoclonal antibody and antibiotic combination therapy improves disease outcome and accelerates healing in a *Staphylococcus aureus* dermonecrosis model. Antimicrob Agents Chemother. 2015;59(1):299–309 (https://doi.org/10.1128/AAC.03918-14, accessed 29 February 2024).
4. AR-301 (Tosatoxumab). In: Aridis Pharmaceuticals/Pipeline [website]. Los Gatos (CA): Aridis Pharmaceuticals; 2022 (https://www.aridispharma.com/ar-301/, accessed 29 February 2024).
5. Aridis receives agreement from the European medicines from the European Medicines Agency (EMA) on the clinical study design and a single confirmatory Phase 3 study of AR-301. In: GlobeNewswire/Newsroom [website]. Los Angeles: GlobeNewswire; 2023 (https://www.globenewswire.com/en/news-release/2023/07/17/2705972/0/en/Aridis-Receives-Agreement-from-the-European-Medicines-Agency-EMA-on-the-Clinical-Study-Design-and-a-Single-Confirmatory-Phase-3-Study-of-AR-301.html, accessed 29 February 2024).
6. Kollef MH, Betthauser KD. Monoclonal antibodies as antibacterial therapies: thinking outside of the box. Lancet Infect Dis. 2021;21(9):1201–2 (https://doi.org/10.1016/S1473-3099(21)00062-1, accessed 29 February 2024).
7. François B, Jafri HS, Chastre J, Sánchez-García M, Eggimann P, Dequin PF et al. Efficacy and safety of suvratoxumab for prevention of *Staphylococcus aureus* ventilator-associated pneumonia (SAATELLITE): a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 2 pilot trial. Lancet Infect Dis:. 2021;21(9):1313–23 (https://doi.org/10.1016/S1473-3099(20)30995-6, accessed 29 February 2024).
8. Pipeline. In: Mabwell/R&D [website]. Shanghai (PRC): Mabwell; 2024 (https://mabwell.com/en/rd.html, accessed 29 February 2024).
9. von Hoven G, Rivas AJ, Neukirch C, Klein S, Hamm C, Qin Q et al. Dissecting the role of ADAM10 as a mediator of *Staphylococcus aureus* α-toxin action. Biochem J. 2016;473(13):1929–40 (https://doi.org/10.1042/bcj20160062, accessed 29 February 2024).
10. Estellés A, Woischnig AK, Liu K, Stephenson R, Lomongsod E, Nguyen D et al. A high-affinity native human antibody disrupts biofilm from *Staphylococcus aureus* bacteria and potentiates antibiotic efficacy in a mouse implant infection model. Antimicrob Agents Chemother. 2016;60(4):2292–30 (https://doi.org/10.1128/AAC.02588-15, accessed 29 February 2024).
11. Ryser S, Tenorio E, Estellés A, Kauvar LM. Human antibody repertoire frequently includes antibodies to a bacterial biofilm associated protein. PLOS ONE. 2019;14(7):e0219256 (https://doi.org/10.1371/journal.pone.0219256, accessed 29 February 2024).
12. Brockson ME, Novotny LA, Mokrzan EM, Malhotra S, Jurcisek JA, Akbar R et al. Evaluation of the kinetics and mechanism of action of anti-integration host factor-mediated disruption of bacterial biofilms. Mol Microbiol. 2014;93(6):1246–58 (https://doi.org/10.1111/mmi.12735, accessed 29 February 2024).
13. Abdelhady W, Bayer AS, Seidl K, Nast CC, Kiedrowski MR, Horswill AR et al. Reduced vancomycin susceptibility in an in vitro catheter-related biofilm model correlates with poor therapeutic outcomes in experimental endocarditis due to methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2013;57(3):1447–54 (https://doi.org/10.1128/AAC.02073-12, accessed 29 February 2024).

14. Xiong YQ, Estellés A, Li L, Abdelhady W, Gonzales R, Bayer AS et al. A human biofilm-disrupting monoclonal antibody potentiates antibiotic efficacy in rodent models of both *Staphylococcus aureus* and *Acinetobacter baumannii* infections. Antimicrob Agents Chemother. 2017;61(10):e00904-17 (https://doi.org/10.1128/AAC.00904-17, accessed 29 February 2024).

15. Trellis bioscience announces positive interim Phase 1 results for TRL1068, a novel native human monoclonal antibody which reduces bacterial biofilm burden in chronic prosthetic joint infections. In: BioSpace/News [website]. West Des Moines (IA): BioSpace; 2023 (https://www.biospace.com/article/releases/trellis-bioscience-announces-positive-interim-phase-1-results-for-trl1068-a-novel-native-human-monoclonal-antibody-which-reduces-bacterial-biofilm-burden-in-chronic-prosthetic-joint-infections/, accessed 19 January 2024).

16. Rogers JV, Hall VL, McOsker CC. Crumbling the castle: targeting DNABII proteins for collapsing bacterial biofilms as a therapeutic approach to treat disease and combat antimicrobial resistance Antibiotics. 2022;11(1):104 (https://www.mdpi.com/2079-6382/11/1/104, accessed 18 January 2024).

17. A 2-part first-in-human study to evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of CMTX-101. In: ClinicalTrials.gov/NCT05629741 [website]. Bethesda (MD): US National Library of Medicine; 2024 (https://clinicaltrials.gov/ct2/show/NCT05629741, accessed 29 February 2024).

18. Clarametyx announces positive early Phase 1 safety findings on CMTX-101, immune-enabling antibody therapy. In: Clarametyx/In news [website]. Columbus (OH): Clarametyx; 2023 (https://clarametyx.com/clarametyx-announces-positive-early-phase-1-safety-findings-on-cmtx-101-immune-enabling-antibody-therapy/, accessed 12 January 2024).

19. Lumen Bioscience receives fast track designation from U.S. FDA for LMN-201. In: Lumen Bioscience/News [website]. Seattle (WA): Lumen Bioscience; 2023 (https://www.lumen.bio/news/lumen-bioscience-receives-fast-track-designation-us-fda-lmn-201, accessed 19 January 2024).

20. Jester BW, Zhao H, Gewe M, Adame T, Perruzza L, Bolick DT et al. Development of spirulina for the manufacture and oral delivery of protein therapeutics. Nat Biotechnol. 2022;40(6):956–64 (https://doi.org/10.1038/s41587-022-01249-7, accessed 18 January 2024).

21. Discovery and development pipeline. In: Infex Therapeutics/Pipeline [website]. Chester: Infex Therapeutics; 2024 (https://www.infextx.com/pipeline/, accessed 19 January 2024).

Annex 17. Non-traditional – anti-virulence agents

Product name (INN or company code): ftortiazinon (fluorothyazinone) + cefepime

Pharmacology: chemical class and MoA: Ftortiazinon (fluorothyazinone) + cefepime is a combination bacterial T3SS inhibitor (anti-virulence) and a β-lactam (fourthßgeneration cephalosporin). Gram-negative bacteria commonly use T3SSs to invade host cells *(1,2)*.

Spectrum of activity: In vitro ftortiazinon + cefepime was shown to inhibit the secretion of T3SS effectors ExoT and ExoY, reduce bacteria cytotoxicity and increase bacteria internalization *(3)*. It was active against resistant *P. aeruginosa* and *Salmonella enterica* serovar Typhimurium in vivo in murine models *(3,4,5)*.

Sought therapeutic indication: Being investigated in cUTI caused by *P. aeruginosa*.

Pharmaceutical form, route of the administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

The **Phase 2** trial evaluated the safety and efficacy of ftortiazinon + cefepime in comparison with placebo in the treatment of hospitalized adult patients with cUTI caused by *P. aeruginosa* (NCT03638830, pending status update on clinicaltrials.gov).

- **Study population:** 777 patients 18–80 years of age hospitalized with suspected cUTI requiring antibiotic therapy.
- **Time period:** October 2018 to January 2022.
- **Primary end-point:** Clinical cure and microbiological eradication.

- The **Phase 1** trial assessed the safety and tolerability of fluorothyazinone used as a single-dose administration and a treatment course in 25 healthy volunteers (NCT03205462, completed July 2018).

Primary efficacy: Not yet publicly available

Trial results: Not yet publicly available.

Adverse effects: Not yet publicly available

Product name (INN or company code): GSK3882347

Pharmacology: chemical class and MoA: GSK3882347 is a type 1 fimbrin D-mannose-specific adhesin (FimH) inhibitor, present in *E. coli*, which stops it from attaching and infecting the bladder wall (antivirulence) *(6)*. Its structure is undisclosed.

Spectrum of activity: No publicly available non-clinical data accessed.

Sought therapeutic indication: Being developed in the treatment of MDR uropathogenic *E. coli*.

Pharmaceutical form, route of the administration: Oral.

Phase of clinical development: Completed a Phase 1 trial, currently in a Phase 1b trial.

Product name (INN or company code): GSK3882347 (continued)

Clinical trial(s):

- The **Phase 1b** trial is a double-blind, double dummy, randomized, Phase 1b, nitrofurantoin controlled, repeat oral dose study to investigate the safety, tolerability, PK and microbiological response of GSK3882347 in 80 female participants with acute uUTI (NCT05138822). Suspended to allow analysis of data from a supplementary non-clinical study.
- Another **Phase 1** trial was a double-blind randomized, placebo-controlled, single and repeated oral dose escalation study to investigate the safety, tolerability, PK (including food effect) of GSK3882347 in 61 healthy participants (NCT04488770, completed May 2021).

Preclinical PK and safety: Not yet publicly available for GSK3882347.

PK and adverse effects: Not yet publicly available for GSK3882347.

Product name (INN or company code): ALS-4

Pharmacology: chemical class and MoA: ALS-4 is a small molecule antivirulence agent that inhibits a key enzyme in the biosynthesis of the carotenoid pigment staphyloxanthin *(7)*.

Spectrum of activity: Studies have indicated that inhibiting pigment synthesis may reduce pathogenicity both in vitro and in vivo *(8,9,10)*. Unpublished in vitro data have shown that in the absence of staphyloxanthin, antibacterial activity of antibiotics such as vancomycin may be enhanced *(11)*. In the same data ALS-4 was shown to inhibit staphyloxanthin in MRSA and vancomycin-resistant *S. aureus* strains, reducing virulence with no activity on bacterial growth *(11)*.

Sought therapeutic indication: ALS-4 is being studied in the treatment of MRSA-related bacterial infection *(5,6)*.

Pharmaceutical form, route of the administration: Oral.

Phase of clinical development: 1

Clinical trial(s):

- **Phase 1:** To evaluate the safety, tolerability and PK of ALS-4 (IM032) in a single ascending dose and multiple ascending dose in healthy adult subjects (NCT05274802, completed 2021, *(7)*). Phase 2 under planning *(1)*.
  - **Study population:** 72 healthy volunteers 18–60 years old.
  - **Primary end-point:** Number of participants with adverse events.
  - **Primary efficacy:** Not yet publicly available.
  - **Trial results:** Not yet publicly available.

Adverse events: Not yet publicly available.

References

1. Lv C, Li Y, Wei Y, Wang J, Yu H, Gao F et al. Research progress on small molecular inhibitors of the Type 3 secretion system. Molecules. 2022;27(23):8348 (https://doi.org/10.3390/molecules27238348, accessed 19 January 2024).
2. Butler MS, Henderson IR, Capon RJ, Blaskovich MAT. Antibiotics in the clinical pipeline as of December 2022. J Antibiot. 2023;76(8):431–73 (https://doi.org/10.1038/s41429-023-00629-8, accessed 12 January 2024).
3. Sheremet AB, Zigangirova NA, Zayakin ES, Luyksaar SI, Kapotina LN, Nesterenko LN et al. Small molecule inhibitor of type three secretion system belonging to a class 2,4-disubstituted-4H-[1,3,4]-thiadiazine-5-ones improves survival and decreases bacterial loads in an airway *Pseudomonas aeruginosa* infection in mice. BioMed Res Int. 2018;2018:(5810767) (https://doi.org/10.1155/2018/5810767, accessed 29 February 2024).
4. Walesch S, Birkelbach J, Jézéquel G, Haeckl FPJ, Hegemann JD, Hesterkamp T et al. Fighting antibiotic resistance – strategies and (pre)clinical developments to find new antibacterials. EMBO Rep. 2023;24(1):e56033 (https://doi.org/10.15252/embr.202256033, accessed 29 February 2024).
5. Zigangirova NA, Nesterenko LN, Sheremet AB, Soloveva AV, Luyksaar SI, Zayakin ES et al. Fluorothiazinon, a small-molecular inhibitor of T3SS, suppresses *salmonella* oral infection in mice. J Antibiot. 2021;74(4):244–54 (https://doi.org/10.1038/s41429-020-00396-w, accessed 29 February 2024).
6. Werneburg GT, Nguyen A, Henderson NS, Rackley RR, Shoskes DA, Le Sueur AL et al. The natural history and composition of urinary catheter biofilms: early uropathogen colonization with intraluminal and distal predominance. J Urol. 2020;203(2):357–64 (https://doi.org/10.1097/JU.0000000000000492, accessed 29 February 2024).
7. Aptorum pipeline. In: Aptorum/pipeline [website]. London: Aptorum; 2024 (http://www.aptorumgroup.com/pipeline, accessed 12 January 2024).
8. Liu CI, Liu GY, Song Y, Yin F, Hensler ME, Jeng WY et al. A cholesterol biosynthesis inhibitor blocks *Staphylococcus aureus* virulence. Science. 2008;319(5868):1391–4 (https://doi.org/10.1126/science.1153018, accessed 29 February 2024).
9. Liu GY, Essex A, Buchanan JT, Datta V, Hoffman HM, Bastian JF et al. *Staphylococcus aureus* golden pigment impairs neutrophil killing and promotes virulence through its antioxidant activity. J Exp Med. 2005;202(2):209–15 (https://doi.org/10.1084/jem.20050846, accessed 29 February 2024).
10. Gao P, Davies J, Kao RYT. Dehydrosqualene desaturase as a novel target for anti-virulence therapy against *Staphylococcus aureus*. mBio. 2017;8(5):8 (https://doi.org/10.1128/mBio.01224-17, accessed 29 February 2024).
11. *Aptorum:* ALS-4 nonconfidential overview. 2022 [cited Jan 31 2024]. Available from: https://www.aptorumgroup.com/ALS_Jun2022.pdf

Annex 18. Non-traditionals – bacteriophages and phage-derived enzymes

Product Name (INN or company code): exebacase (CF-301)

Pharmacology: chemical class and MoA: Exebacase is a recombinantly produced anti-staphylococcal phage endolysin (PlySs2), encoded within a prophage of the *Streptococcus suis* genome *(1)*.

Spectrum of activity: Preclinical studies highlight exebacase's ability to eliminate MRSA biofilm biomass. In an in vitro study by Schuch et al. (2017), biofilm was reduced by more than 5 log10 CFU/mL after 1 h of treatment with CF-301 at a concentration of 32 µg/mL *(2)*. Gilmer et al. (2013) report that the endolysin PlySs2 at 128 µg/mL reduced MRSA and *S. pyogenes* growth by 5 logs and 3 logs within 1 h, respectively, and exhibited a MIC of 16 µg/mL for MRSA *(1)*. In vivo, a single, 2 mg dose of PlySs2 protected 92% (22/24) of the mice in a bacteraemia model of mixed MRSA and *S. pyogenes* infection *(1)*. It has been described as showing synergy with antibiotics *(3)*, low propensity for resistance *(3)* and the potential to suppress antibiotic resistance when used together with antibiotics *(4)*.There is no evidence of inherent underlying biological differences in the activity of exebacase against MRSA and MSSA *(5,6,7)*.

Sought therapeutic indication: Exebacase was previously investigated in BSI and infective endocarditis caused by MDR *S. aureus* and is currently being studied in chronic PJI *(8)*.

Pharmaceutical form, route of administration: Intra-articular.

Phase of clinical development: 1b/2

Clinical trial(s): Five trials for exebacase (CF-301) have been registered.

- **Phase 2:** A multicentre, double-blind, randomized, comparative study of the safety, tolerability, efficacy and PK of CF-301 vs placebo in addition to SOC antibacterial therapy for treatment of adult patients with *S. aureus* BSI, including endocarditis (NCT03163446, Phase 2 results, completed March 2019).
  - **Study population:** 121 participants male or female, 18 years or older, blood culture positive for *S. aureus* with at least one sign or symptom attributable to *S. aureus* bacteraemia, known or suspected complicated *S. aureus* BSI and/or endocarditis by Modified Duke Criteria and not pregnant or breastfeeding or of reproductive potential/agreed to use contraception if of reproductive potential.
  - **Time period:** May 2017 to March 2019.
  - **Primary efficacy** evaluation was performed in the micro-MITT population. Non-inferiority margin 10%.
  - **Trial results:** Rates of adverse events were similar in both groups. No adverse events of hypersensitivity to exebacase were reported. 30-day all-cause mortality rates were 9.7% and 12.8% in the exebacase + antibiotics and antibiotics-alone groups, respectively, with a notable difference in MRSA patients (3.7% vs 25.0%, difference = –21.3 (90% CI: –45.1, 2.5, ad hoc ($P = 0.06$) *(7)*. Among MRSA patients in the USA, median length of stay was 4 days shorter and 30-day hospital readmission rates were 48% lower in the exebacase-treated group compared with antibiotics alone *(7)*.
- **Phase 1b/2** (currently recruiting): A randomized, double-blind, placebo-controlled clinical study conducted in France to assess the safety, PK and efficacy of intra-articularly administered exebacase in patients with chronic PJI of the knee due to *S. aureus* or CoNS. The study will be conducted in two parts. Part 1 will assess efficacy at an early, 6-week time point in addition to safety and PK. Part 2 will be a long-term clinical safety and efficacy follow-up for a period of up to 2 years. Patients entering the study will be randomized 3 : 1 to either exebacase or placebo, with all patients receiving the study drug in the setting of a DAIR procedure *(9)*.

Product Name (INN or company code): exebacase (CF-301) (continued)

A **Phase 3** trial (DISRUPT) was terminated as the independent Data and Safety Monitoring Board recommended that the study be stopped for futility following interim efficacy analysis. (NCT04160468, last update September 2022).

- **Phase 1:** A placebo-controlled, dose-escalating study to examine the safety and tolerability of single iv doses of CF-301 in healthy subjects (NCT02439359, completed December 2015).
- An **expanded access study** of exebacase in COVID-19 patients with persistent MRSA bacteraemia (NCT04597242, no longer available).

Preclinical PK and safety: CF-301 is 26 kDa, has only one catalytic domain (an endopeptidase) and is limited to a single-dose regimen based on preclinical toxicology studies (dose-limiting toxicity leading to vasculitis and hypersensitivity) *(10,11)*.

Product name (INN or company code): LSVT-1701, N-Rephasin (SAL200, tonabacase)

Pharmacology: chemical class and MoA: LSVT-1701 (N-Rephasin, SAL200, tonabacase) is a recombinant phage anti-staphylococcal endolysin that hydrolyses bacterial cell walls.

Spectrum of activity: LSVT-1701 (N-Rephasin) has shown bacteriolytic activity, with a narrow MIC range against a wide range of MDR *S. aureus* isolates *(10,12)*. It has antibiofilm activity *(10,12)*; in vitro studies have shown its synergy with SOC antistaphylococcal antibiotics such as vancomycin and daptomycin *(10,13)*. LSVT-1701 (N-Rephasin) combined with daptomycin in a 4-day regimen microbiologically sterilized all target organs in an in vivo rabbit model of single-strain MRSA aortic valve infective endocarditis *(10)*.

Sought therapeutic indication: It is under development for the treatment of drug-resistant *S. aureus* bacteraemia and infective endocarditis.

Pharmaceutical form, route of administration: Intravenous.

Phase of clinical development: 1

Clinical trial(s): Three trials are registered:

- A **Phase 2a** trial, terminated by the sponsor for strategic reasons, was supposed to test a single iv dose of LSVT-1701 in addition to the standard treatment for persistent *S. aureus* bacteraemia (NCT03089697, last update October 2021).
- A **Phase 2** trial (ERASE), withdrawn as a business decision before FPFV (first patient first visit) not related to any safety concerns, aimed at evaluating the safety and tolerability of endolysin-derived LSVT-1701 (tonabacase) as an add-on to SOC antibiotic therapy for treatment of patients with complicated *S. aureus* bacteraemia, including left- and right-sided infective endocarditis (NCT05329168, last update June 2022).
- A **Phase 1** trial to evaluate the safety, PK/PD and immunogenicity of N-Rephasin following single and multiple ascending doses in healthy male volunteers after continuous iv infusion over 60 min (NCT03446053, completed February 2019).

Preclinical PK and safety: LSVT-1701 showed minimal toxicity in single- and repeated-dose toxicity studies of both rodent and non-human primates, with no significant effects on central nervous or respiratory system function tests or sensitivity *(10,14)*.

Product name (INN or company code): AP-PA02

Pharmacology: chemical class and MoA: AP-PA02 is a therapeutic phage cocktail that targets *P. aeruginosa* (15).

Spectrum of activity: AP-PA02 is reported to reduce *P. aeruginosa* biofilm mass by acting synergistically with *E. coli* HU2117 (16). Other preclinical unpublished reports are that therapy shows limited organ distribution, stability in biological fluids, compatibility with standard antibiotics and efficacy with other CF therapies (15).

In vivo, in an acute murine lung infection model with *P. aeruginosa*, phages reduced infective burden and all phage-treated mice cleared *P. aeruginosa* infection at 24 h, whereas infection persisted in all control mice (median, 1305 CFU/mL (range, 190–4700 CFU/mL), $P < 0.01$) (17).

Sought therapeutic indication: AP-PA02 is being investigated in the treatment of respiratory *P. aeruginosa* infection in patients with CF and in NCFB.

Pharmaceutical form, route of the administration: Inhalation.

Phase of clinical development: 2

Clinical trial(s): AP-PA02 is being investigated in a Phase 2 trial (Tailwind) and a Phase 1b/2 trial (SWARM-Pa).

- **Tailwind:** A Phase 2, multicentre, double-blind, randomized, placebo-controlled study to evaluate the safety, phage kinetics and efficacy of inhaled AP-PA02 multi-phage therapeutic in 60 subjects with NCFB and chronic pulmonary *P. aeruginosa* Infection (NCT05616221, recruiting).

Study population: 1 : 1 parallel assignment consented male/female participants 18 years or older, with evidence of chronic pulmonary *P. aeruginosa* infection and bronchiectasis per computed tomography. Patients are separated into cohorts based on their exposure to chronic inhaled antipseudomonal antibiotics.

  - **Time period:** Currently recruiting; estimated completion February 2024.
  - **Primary end-point:** *P. aeruginosa* recovery in sputum following multiple doses of AP-PA02 administered by inhalation.
  - **Trial results and adverse events:** Not yet available.

- **SWARM-Pa:** A Phase 1b/2a, multicentre, double-blind, randomized, placebo-controlled, single and multiple ascending dose study to evaluate the safety and tolerability of AP-PA02 multi-phage therapeutic candidate for inhalation in subjects with CF and chronic pulmonary *P. aeruginosa* infection (NCT04596319, completed December 2022).

Preclinical PK and safety: No safety concerns were noted in vivo (18).

Product name (INN or company code): YPT-01

Pharmacology: chemical class and MoA: Yale Phage Therapy 01, or YPT-01, is a bacteriophage therapy that targets MDR *P. aeruginosa* (19).

Spectrum of activity: An in vitro study showed that phage selection causes a trade-off in MDR *P. aeruginosa*, leading to increased sensitivity to drugs from multiple antibiotic classes (20).

Sought therapeutic indication: Being investigated as a potential treatment for chronic (MDR) *P. aeruginosa* in CF patients.

Pharmaceutical form, route of administration: Inhalation.

Phase of clinical development: 1/2

Clinical trial(s) information: The Phase 1/2 trial is a prospective, randomized, placebo-controlled, double-blinded, single-site study to determine the safety and efficacy of YPT-01 in CF subjects with chronic *P. aeruginosa* airway infections. The study has two parallel arms of phage therapy and placebo (CYPHY, NCT04684641, active, not recruiting). As of November 2022 the double-blind, randomized portion of the study was closed and the open-label extension was opened.

Product name (INN or company code): YPT-01 (continued)

- **Study population:** Clinically stable subjects who have confirmed diagnosis of CF with *P. aeruginosa* in sputum cultures on at least two occasions within the past year, and in sputum at screening visit (eight currently enrolled).
- **Primary end-point:** Reduction in sputum bacterial culture (14 days).
- **Primary efficacy:** Not yet publicly available.
- **Trial results:** Not yet publicly available.
- **Adverse events:** Not yet publicly available.

Product name (INN or company code): BX004-A

Pharmacology: chemical class and MoA: BX004-A are bacteriophages directed at *P. aeruginosa (21)*.

Spectrum of activity: MDR *P. aeruginosa*.

Sought therapeutic indication: Being investigated as a potential treatment for chronic (MDR) *P. aeruginosa* in CF patients.

Pharmaceutical form, route of administration: Inhalation.

Phase of clinical development: 1b/2a

Clinical trial(s): The Phase 1b/2a study's primary objective is to determine whether BX004-A is safe and tolerable. Exploratory objectives include whether BX004-A reduces sputum *P. aeruginosa* bacterial load in CF subjects with chronic *P. aeruginosa* pulmonary infection (NCT05010577, recruiting).

The study is divided into two parts, a single ascending and multiple-dose phase (part 1) and a multiple-dose phase (part 2).

Study population: 32 participants were randomized to receive the standard dose of nebulized bacteriophage vs nebulized placebo (parallel assignment). CF patients with chronic *P. aeruginosa* pulmonary infection receiving SOC CF medications, ≥ 18 years with clinically stable lung disease.

Trial results: Unpublished (website) data reported. No safety issues were reported in part 1 of the Phase 1b/2a study of BX004 in relation to the treatment received with BX004. Mean *P. aeruginosa* CFU at day 15 (compared to baseline): –1.42 log10 CFU/g (BX004) vs –0.28 log10 CFU/g (placebo). There was no emerging resistance to BX004 during or after treatment with BX004, and no detectable effect on per cent predicted FEV1 (forced expiratory volume in 1 second) *(22)*.

Preclinical PK and safety: Not yet publicly available.

Product name (INN or company code): LBP-EC01

Pharmacology: chemical class and MoA: LBP-EC01 is a bacteriophage cocktail engineered with CRISPR technology targeting the *E. coli* genome. The cocktail combines phagelytic activity with the DNA-targeting activity of Cas3 *(23)*.

Spectrum of activity: Unpublished in vitro and in vivo UTI animal models show increased LBP-EC01 activity against *E. coli* compared to corresponding natural bacteriophages (website data) *(23)*.

Sought therapeutic indication: It is under development for the treatment of uUTI and other infections caused by MDR *E. coli*.

Pharmaceutical form, route of administration: Intraurethral irrigation and iv.

Product name (INN or company code): LBP-EC01 (continued)

Phase of clinical development: 2/3

Clinical trial(s):

- A **Phase 2/3 study** (ELIMINATE, NCT05488340, recruiting) is a double-blind, randomized, active-controlled evaluation of the safety, tolerability, PK and efficacy of LBP-EC01 in the treatment of acute uUTI caused by MDR *E. coli* intervention:
  - **Part 1:**

Arm 4 IU LBP-EC01 on D1 and D2 with iv LBP-EC01 ($1 \cdot 10^{11}$ PFU) and oral trimethoprim + sulfamethoxazole (TMP/SMX) on D1 through D3.

  - Arm 5 IU LBP-EC01 on D1 and D2 with iv LBP-EC01 ($1 \cdot 10^{10}$ PFU) and oral TMP/SMX on D1 through D3.
  - Arm 6 IU LBP-EC01 on D1 and D2 with iv LBP-EC01 infusion ($1 \cdot 10^{12}$ PFU) and oral TMP/SMX on D1 through D3.
  - **Part 2:** LBP-EC01 given by dose regimen selected from Part 1 and oral TMP/SMX.
    - **Study population:** With an initial three-arm PK lead-in portion of 30 patients to evaluate the optimal dosing regimen to be used in the subsequent 550 patient portion of the study, which will be randomized 1 : 1 comparing LBP-EC01 + antibiotic vs placebo + antibiotic in patients with a history of prior UTI caused by *E. coli*. All patients will be required to have an active acute uUTI at baseline.
    - **Time period:** Start July 2022, recruiting.

Primary end-point: Part 1: Levels of LBP-EC01 in urine and blood measured by quantitative plaquing assay across the treatment period and over 48 h after the last dose. Part 2: Proportion of patients with resolution of clinical symptoms of a uUTI and microbiologic response of uUTI caused by MDR *E. coli* as defined at day 10.

  - **Primary efficacy evaluation:** The efficacy of LBP-EC01 when used concomitantly with TMP/SMX compared to placebo when used concomitantly with TMP/SMX on resolution of acute uUTI symptoms and demonstration of microbiologic response of acute uUTI caused by MDR *E. coli* will be assessed.

- A **Phase 1** trial to evaluate the safety, tolerability and PK/PD of LBP-EC01 in patients with lower-tract *E. coli* colonization (NCT04191148, completed November 2020).

Trial results: LBP-EC01 was found safe and well-tolerated in the Phase 1b study. It showed proof of mechanism by amplifying phage in patients with sensitive *E. coli* isolates. There was an apparent difference in PD effect between LBP-EC01 and placebo regardless of MDR status *(24)*. The placebo arm showed increased levels of *E. coli* and higher variability over the treatment period. An average difference of 2–3 log (100× to 1000×) existed in urine *E. coli* concentration (CFU/mL) between the LBP-EC01 and placebo arms across the duration of the treatment period *(24)*.

Adverse events: No drug-related TEAEs were observed. All non-drug-related TEAEs were grade 2 or below, and there were no tolerability signals associated with LBP-EC01 *(24)*.

Product name (INN or company code): SNIPR001

Pharmacology: chemical class and MoA: SNIPR001 is a cocktail of four CRISPR-armed phages that selectively target fluoroquinolone-resistant *E. coli* *(25)*.

Spectrum of activity: SNIPR001 has been shown to target bacteria in biofilms such as carbapenem-resistant, ESBL-producing or MDR and fluoroquinolone-resistant *E. coli* in vitro *(26)*. As a complementary bacteriophage cocktail, it is more effective in reducing *E. coli* load in mice and minipigs compared to its constituents *(26)*.

Sought therapeutic indication: SNIPR001 is being developed to treat infections caused by *E. coli* in patients with haematological cancer.

Pharmaceutical form, route of administration: Oral.

Product name (INN or company code): SNIPR001 (continued)

Phase of clinical development: 1

Clinical trial(s): Phase 1 is a randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study in healthy participants investigating the safety, tolerability, recovery and PD of multiple oral administrations of SNIPR001 (NCT05277350, complete and planning for Phase 2).

Study population: 36 healthy participants 18–65 years old with *E. coli* present in faeces sample.

Preclinical PK and safety: SNIPR001 was studied in female Göttingen minipigs; there were no adverse effects on health or immune cells compared to the vehicle treatment *(26)*.

Product name (INN or company code): APT PhageBank

Pharmacology: chemical class and MoA: APT PhageBank consists of numerous phages against clinically relevant bacteria *(27)*.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs: Website data: The empiric phage cocktails are developed based on epidemiologic data in a number of clinical indications and directed against clinical syndromes caused by MRSA and *P. aeruginosa (27)*.

Sought therapeutic indication: Treatment of PJI, diabetic foot osteomyelitis and *P. aeruginosa* colonization in CF.

Pharmaceutical form, route of the administration: Intravenous, intra-articular.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 1b/2 trial**: A multicentre, randomized, placebo-controlled, double-blind study in subjects diagnosed with CF to evaluate the safety and microbiological activity of a single dose of iv bacteriophage administered over 30 min (NCT05453578).

Study population: 72 subjects with confirmed CF diagnosis based on a compatible clinical syndrome confirmed by either an abnormal sweat chloride testing or CF transmembrane conductance regulator gene variations. Stage 1: 2 subjects in each of the three dose arms: $4 \cdot 10^7$ plaque-forming units (PFU), $4 \cdot 10^8$ PFU and $4 \cdot 10^9$ PFU. Stage 2a: 4 arms (placebo iv, $4 \cdot 10^7$ PFU, $4 \cdot 10^8$ PFU and $4 \cdot 10^9$ PFU) in a 1 : 1 : 1 : 1 allocation. Stage 2b: Bacteriophage or placebo.

  - **Primary end-point:** (i) Describe the safety of a single dose of iv bacteriophage therapy in clinically stable CF subjects with *P. aeruginosa* in expectorated sputum; (ii) describe the microbiological activity of a single dose of iv bacteriophage therapy in clinically stable CF subjects with *P. aeruginosa* in expectorated sputum; (iii) describe the benefit-to-risk profile of a single dose of iv bacteriophage therapy in clinically stable CF subjects with *P. aeruginosa* in expectorated sputum.

- **Phase 2b (DANCE):** A randomized, parallel, double-blind, placebo-controlled, repeat-dose, multi-site study for safety, tolerability and efficacy of personalized phage treatment and SOC for subjects with diabetic foot osteomyelitis due to *S. aureus* (NCT05177107, recruiting).

  - **Study population:** 2 : 1 (phage : placebo) parallel assignment of 126 consented adults, male or female, 18–85 years old with diabetes, meeting clinical criteria for intervention in DFO (see full inclusion criteria at clinicaltrials.gov).
  - **Primary outcome measure:** Percent area reduction of study ulcer through week 13.

Product name (INN or company code): APT PhageBank (continued)

Phase 1/2 (ACTIVE1): An open-label, multicentre study to evaluate the safety and efficacy of PhageBank phage therapy in conjunction with DAIR for patients with first-time culture-proven chronic PJI (NCT05269121, not yet recruiting).

Phase 2 (ACTIVE2): A randomized, double-blind, placebo-controlled, multicentre study to evaluate the safety and efficacy of APT PhageBank phage therapy vs placebo in conjunction with DAIR in subjects with chronic PJI (NCT05269134, now withdrawn based on sponsor decision as of November 2023.

Trial results: Not yet publicly available.

Adverse events: Not yet publicly available

Product name (INN or company code): Phages: PP1493 and PP1815

Pharmacology: chemical class and MoA: Two-phage cocktail.

Spectrum of activity: Designed to target *S. aureus* (28,29,30).

Pharmaceutical form, route of the administration: Intra-articular.

Sought therapeutic indication: It is being investigated in the treatment of staph-related PJI.

Phase of clinical development: 2

Clinical trial(s): Phase 2 is a pilot non-comparative study assessing the clinical control of infection of DAIR + suppressive antibiotic therapy (SAT) + NaCl and DAIR + SAT + anti-*S. aureus* phages in patients with *S. aureus* PJI with an indication of DAIR + SAT (NCT05369104, currently recruiting).

- **Study population:** 64 consented male/female participants ≥ 18 years (non-pregnant, on contraceptives) with life expectancy > 2 years and no concomitant superinfection with known:
  - *S. aureus* monomicrobial knee or hip PJI > 3 months after prosthesis implantation with clinical signs of infection and with indication of DAIR with direct closure and SAT.
  - *S. aureus* only in joint fluid within 6 months before randomization or in case of relapse of infection under antibiotic therapy after a DAIR performed within 6 months before the pre-inclusion visit.
- **Primary outcome measures:** Clinical control of infection at week 12 visit.
- **Primary efficacy:** Not yet publicly available.
- **Adverse events:** Not yet publicly available.

Product name (INN or company code): EcoActive

Pharmacology: chemical class and MoA: EcoActive is a bacteriophage cocktail.

Spectrum of activity: In vitro, EcoActive showed activity against clinical AIEC strains *(31)*. In the murine model of induced colitis of animals with AIEC strain LF82, clinical and microscopic AIEC manifestations improved *(31)*.

Sought therapeutic indication: It is being investigated as therapy targeting adherent invasive AIEC in Crohn's disease patients.

Pharmaceutical form, route of the administration: Oral.

Phase of clinical development: 1/2a

Clinical trial(s): The **Phase 1/2a trial** is a double-blind, randomized, placebo-controlled study evaluating the safety of oral administration of EcoActive to patients with inactive Crohn's disease and how it affects the levels of AIEC in stool (NCT03808103, currently recruiting).

- **Study population:** 30 consented participants (male and non-pregnant females on contraception) ≥ 18 years old with inactive Crohn's disease history and AIEC detected in stool, by parallel assignment. The experimental intervention dosed at 1 mL of bacteriophage preparation given PO twice a day for 15 days compared to oral placebo.
- **Primary end-point:** Incidence and severity of TEAEs and inflammatory parameters related to Crohn's disease.
- **Primary efficacy evaluation:** Not yet publicly available.
- **Trial results:** Not yet publicly available.
- **Adverse events:** Not yet publicly available.

Product name (INN or company code): ShigActive

Pharmacology: chemical class and MoA: ShigActive is a phage cocktail composed of five lytic bacteriophages.

Spectrum of activity: In vitro ShigActive showed activity against resistant *S. flexneri* strains *(32)*. In a mouse model the treatment regimen elicited a 10- to 100-fold reduction in CFU of the challenge strain in faecal and caecum specimens compared to untreated control mice ($P < 0.05$) *(32)*.

Sought therapeutic indication: It is being investigated in the treatment of *Shigellosis*.

Pharmaceutical form, route of the administration: Oral.

Phase of clinical development: 1/2a

Clinical trial(s): The Phase 1/2a trial is a first-in-human, randomized, double-blind, placebo-controlled trial to assess the clinical safety and efficacy of ShigActive in healthy adults with experimental *Shigella* challenge (NCT05182749, active, currently recruiting).

- **Study population:** 52 healthy consented participants (male and non-pregnant females on contraception) 18–50 years old, parallel assignment. The experimental intervention dosed at 1 mL of bacteriophage preparation given orally three times a day for 7 days (Phase 1) or 6 days (Phase 2a).
- **Primary end-point:** Solicited or unsolicited adverse reactions and onset of shigellosis post-challenge (Phase 2a only).
- **Primary efficacy evaluation:** Not yet available.
- **Trial results:** Not yet available.

Preclinical PK and safety: In the mouse model, no toxic side effects of phage administration were observed during the studies, and the phage cocktail showed less impact on the normal gut microbiota than treatment with a commonly prescribed antibiotic *(32)*. Long-term safety studies did not identify any side effects or distortions in overall gut microbiota associated with bacteriophage administration *(32)*.

Product name (INN or company code): VRELysin

Pharmacology: chemical class and MoA: VRELysin comprises bacteriophages designed to combat VRE.

Spectrum of activity: VRELysin is designed to decrease VRE quantities in the human GI tract *(33)*. Lysis in Gram negative bacteria involves three proteins: holins, endolysins and spanins, which work on different parts of the cell envelope, i.e., the inner membrane, peptidoglycan and outer membrane *(34)*.

Sought therapeutic indication: It is being studied as a decolonizing agent for VRE-colonized patients to prevent associated bacteraemia.

Pharmaceutical form, route of the administration: Oral.

Phase of clinical development: 1/2a

Clinical trial(s): A Phase 1/2a trial is a double-blind, randomized, placebo-controlled trial to assess the safety and efficacy of oral VRELysin in 80 healthy and VRE-colonized subjects. A cocktail of lytic enterococcus-specific bacteriophages will be orally administered with sodium bicarbonate solution (NCT05715619, currently recruiting).

- **Primary end-point:** Phase 1: number and severity of solicited and unsolicited adverse reactions; Phase 2a: number and severity of solicited and unsolicited adverse reactions.
- **Primary efficacy:** Not yet publicly available.
- **Trial results:** Not yet publicly available.
- **Adverse events:** Not yet publicly available.

Product name (INN or company code): AP-SA02

Pharmacology: chemical class and MoA: AP-SA02 is a lytic bacteriophage compound.

Spectrum of activity: Targets methicillin-resistant *S. aureus* and vancomycin-resistant *S. aureus* in non-clinical studies (website data) *(35)*.

Sought therapeutic indication: Being developed for the treatment of complicated *S. aureus* bacteraemia *(35)*.

Pharmaceutical form, route of the administration: iv.

Phase of clinical development: 1b/2a

Clinical trial(s): Phase 1b/2a (diSArm) trial (NCT05184764) currently recruiting to study the safety, tolerability and efficacy of iv AP-SA02 as an adjunct to best-available antibiotic therapy compared to best-available antibiotic therapy alone for treatment of adults with bacteraemia due to *S. aureus*.

- **Study population:** 50 hospitalized patients (male and female) ≥ 18 years old with a positive blood culture for *S. aureus*.
  - Phase 1b will evaluate the safety and tolerability of multiple ascending intravenous *(4)* doses of AP-SA02 or placebo as an adjunct to best-available therapy compared to best-available therapy alone in subjects with *S. aureus* bacteraemia.
  - Phase 2a will evaluate the efficacy, safety and tolerability of multiple doses of AP-SA02 or placebo as an adjunct to best-available therapy compared to best-available therapy alone in subjects with complicated *S. aureus* bacteraemia.
- **Primary end-point:** Incidence of TEAEs (safety and tolerability) of multiple doses of iv AP-SA02.
- **Primary efficacy evaluation:** Not yet publicly available.
- **Trial results:** Not publicly yet available.
- **Adverse events:** Not publicly yet available.

References

1. Gilmer DB, Schmitz JE, Euler CW, Fischetti VA. Novel bacteriophage lysin with broad lytic activity protects against mixed infection by Streptococcus pyogenes and methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2013;57(6):2743–50 (https://doi.org/10.1128/AAC.02526-12, accessed 12 January 2024).
2. Schuch R, Khan BK, Raz A, Rotolo JA, Wittekind M. Bacteriophage lysin CF-301, a potent antistaphylococcal biofilm agent. Antimicrob Agents Chemother. 2017;61(7):e02666-16 (https://doi.org/10.1128/AAC.02666-16, accessed 19 January 2024).
3. Schuch R, Lee HM, Schneider BC, Sauve KL, Law C, Khan BK et al. Combination therapy with lysin CF-301 and antibiotic is superior to antibiotic alone for treating methicillin-resistant *Staphylococcus aureus*-induced murine bacteremia. J Infect Dis. 2014;209(9):1469–78 (https://doi.org/10.1093/infdis/jit637, accessed 19 January 2024).
4. Xiong YQ, Abdelhady W, PharmD, Li L, Schuch R, Cassino C et al. 671. Impact of dose-administration strategies of the antistaphylococcal lysin exebacase, (CF-301), in addition to daptomycin (DAP) in an experimental infective endocarditis (IE) model due to methicillin-resistant *Staphylococcus aureus* (MRSA). Open Forum Infect Dis. 2019;6(Suppl 2):S307 (https://doi.org/10.1093/ofid/ofz360.739, accessed 29 February 2024).
5. Watson A, Oh JT, Sauve K, Bradford PA, Cassino C, Schuch R. Antimicrobial activity of exebacase (lysin CF-301) against the most common causes of infective endocarditis. Antimicrob Agents Chemother. 2019;63(10) (https://doi.org/10.1128/AAC.01078-19, accessed 29 February 2024).
6. Traczewski M, Oh J, Cassino C, Schuch R. In vitro activity of Exebacase (CF-301) against clinical *Staphylococcus aureus* surveillance isolates from the United States, Europe, and Latin America, 2015–2017. Diagn Microbiol Infect Dis. 2019;95(4):114879 (https://doi.org/10.1016/j.diagmicrobio.2019.114879, accessed 29 February 2024).
7. Fowler VG, Das AF, Lipka-Diamond J, Schuch R, Pomerantz R, Jáuregui-Peredo L et al. Exebacase for patients with *Staphylococcus aureus* bloodstream infection and endocarditis. J Clin Invest. 2020;130(7):3750–60 (https://doi.org/10.1172/JCI136577, accessed 29 February 2024).
8. Ferry T, Batailler C, Souche A, Cassino C, Chidiac C, Perpoint T et al. Arthroscopic "debridement and implant retention" with local administration of exebacase (Lysin CF-301) followed by suppressive tedizolid as salvage therapy in elderly patients for relapsing multidrug-resistant S. epidermidis prosthetic knee Infection. Front Med. 2021;8:550853 (https://doi.org/10.3389/fmed.2021.550853, accessed 12 January 2024).
9. ContraFect begins Phase Ib/II clinical trial of exebacase. In: Clinical Trials Arena/News [website]. London: Clinical Trials Arena; 2023 (https://www.clinicaltrialsarena.com/news/contrafect-begins-clinical-trial-exebacase/, accessed 29 February 2024).
10. Huang DB, Gaukel E, Kerzee N, Borroto-Esoda K, Lowry S, Xiong YQ et al. Efficacy of antistaphylococcal lysin LSVT-1701 in combination with daptomycin in experimental left-sided infective endocarditis due to methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2021;65(8):e0050821 (https://doi.org/10.1128/AAC.00508-21, accessed 15 January 2024).
11. Immunomodulator/enhancers product development. Silver Spring (MD): US Food and Drug Administration; 2018 (https://www.fda.gov/media/115771/download, accessed 29 February 2024).
12. Jun SY, Jung GM, Yoon SJ, Oh MD, Choi YJ, Lee WJ et al. Antibacterial properties of a pre-formulated recombinant phage endolysin, SAL-1. Int J Antimicrob Agents. 2013;41(2):156–61 (https://doi.org/10.1016/j.ijantimicag.2012.10.011, accessed 18 January 2024).
13. Kim H, Park WB, Cho JE, Choi YJ, Choi SJ, Jun SY et al. Effects of phage endolysin SAL200 combined with antibiotics on *Staphylococcus aureus* infection. Antimicrob Agents Chemother. 2018;62(10) (https://doi.org/10.1128/AAC.00731-18, accessed 18 January 2024).
14. Jun SY, Jung GM, Yoon SJ, Choi YJ, Koh WS, Moon KS et al. Preclinical safety evaluation of intravenously administered SAL200 containing the recombinant phage endolysin SAL-1 as a pharmaceutical ingredient. Antimicrob Agents Chemother. 2014;58(4):2084–8 (https://doi.org/10.1128/AAC.02232-13, accessed 18 January 2024).

15. AP-PA02. In: Armata Pharma/Pipeline [website]. Los Angeles: Armata Pharmaceuticals; 2024 (https://www.armatapharma.com/pipeline/ap-pa02/, accessed 29 February 2024).

16. Liao KS, Lehman SM, Tweardy DJ, Donlan RM, Trautner BW. Bacteriophages are synergistic with bacterial interference for the prevention of *Pseudomonas aeruginosa* biofilm formation on urinary catheters. J Appl Microbiol. 2012;113(6):1530–9 (https://doi.org/10.1111/j.1365-2672.2012.05432.x, accessed 29 February 2024).

17. Pabary R, Singh C, Morales S, Bush A, Alshafi K, Bilton D et al. Antipseudomonal bacteriophage reduces infective burden and inflammatory response in murine lung. Antimicrob Agents Chemother. 2016;60(2):744–51 (https://doi.org/10.1128/AAC.01426-15, accessed 29 February 2024).

18. Fong SA, Drilling AJ, Ooi ML, Paramasivan S, Finnie JW, Morales S et al. Safety and efficacy of a bacteriophage cocktail in an in vivo model of *Pseudomonas aeruginosa* sinusitis. Transl Res. 2019;206:41–56 (https://doi.org/10.1016/j.trsl.2018.12.002, accessed 29 February 2024).

19. Our approach. In: Felix/Platform [website]. San Francisco (CA): Felix Biotechnology; 2024 (https://www.felixbt.com/platform, accessed 29 February 2024).

20. Chan BK, Sistrom M, Wertz JE, Kortright KE, Narayan D, Turner PE. Phage selection restores antibiotic sensitivity in MDR *Pseudomonas aeruginosa*. Sci Rep. 2016;6(1):26717 (https://doi.org/10.1038/srep26717, accessed 29 February 2024).

21. Our pipeline – Biomx [internet] [cited Jan 30 2024]. Available from: https://www.biomx.com/our-pipeline/.

22. BiomX announces positive results from part 1 of the Phase 1b/2a study evaluating BX004 for treatment of chronic pulmonary infections in patients with cystic fibrosis. In: BiomX/News and events [website]. Ness Ziona (Israel): BiomX; 2023 (https://ir.biomx.com/news-events/press-releases/detail/81/biomx-announces-positive-results-from-part-1-of-the-phase, accessed 15 January 2024).

23. Locus Biosciences initiates world's first controlled clinical trial for a CRISPR enhanced bacteriophage therapy. In: Locus Biosciences/Media [website]. Morrisville (NC): Locus Biosciences; 2020 (https://www.locus-bio.com/locus-biosciences-initiates-worlds-first-controlled-clinical-trial/, accessed 29 February 2024).

24. Kim P, Sanchez A, Kime J, Ousterout D. 1083. Phase 1b results of pharmacokinetics, pharmacodynamics, and safety for LBP-EC01, a CRISPR-Cas3 enhanced bacteriophage cocktail targeting *Escherichia coli* that cause urinary tract infections. Open Forum Infect Dis. 2021;8(Suppl 1):S633 (https://doi.org/10.1093/ofid/ofab466.1277, accessed 18 January 2024).

25. Snipr Biome [website]. Copenhagen: Snipr Biome; 2022 (https://www.sniprbiome.com/, accessed 19 January 2024).

26. Allegretti JR, Mullish BH, Kelly C, Fischer M. The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. Lancet. 2019;394(10196):420–31 (https://doi.org/10.1016/S0140-6736(19)31266-8, accessed 29 February 2024).

27. APT's phage bank therapeutics. In: Aphage/Science/Pipeline [website]. Gaithersburg (MD): Adaptive Phage Therapeutics; 2024 (https://aphage.com/science/pipeline/, accessed 12 January 2024).

28. Plumet L, Ahmad-Mansour N, Dunyach-Remy C, Kissa K, Sotto A, Lavigne JP et al. Bacteriophage therapy for *Staphylococcus aureus* infections: a review of animal models, treatments, and clinical trials. Front Cell Infect Microbiol. 2022;12:907314 (https://doi.org/10.3389/fcimb.2022.907314, accessed 19 January 2024).

29. Ferry T, Kolenda C, Batailler C, Gustave A, Lustig S, Malatray M et al. Phage therapy as adjuvant to conservative surgery and antibiotics to salvage patients with relapsing *S. aureus* prosthetic knee infection. Front Med. 2019;7 (https://doi.org/10.3389/fmed.2020.570572, accessed 12 January 2024).

30. Albac S, Medina M, Labrousse D, Hayez D, Bonnot D, Anzala N et al. Efficacy of bacteriophages in a *Staphylococcus aureus* nondiabetic or diabetic foot infection murine model. Antimicrob Agents Chemother. 2020;64(2):e01870-19 (https://doi.org/10.1128/AAC.01870-19, accessed 29 February 2024).

31. Titécat M, Rousseaux C, Dubuquoy C, Foligné B, Rahmouni O, Mahieux S et al. Safety and efficacy of an AIEC-targeted bacteriophage cocktail in a mice colitis model. J Crohns Colitis. 2022;16(10):1617–27 (https://doi.org/10.1093/ecco-jcc/jjac064, accessed 29 February 2024).

32. Mai V, Ukhanova M, Reinhard MK, Li M, Sulakvelidze A. Bacteriophage administration significantly reduces *Shigella* colonization and shedding by *Shigella*-challenged mice without deleterious side effects and distortions in the gut microbiota. Bacteriophage. 2015;5(4):e1088124 (https://doi.org/10.1080/21597081.2015.1088124, accessed 29 February 2024).

33. Human therapeutics. In: Intralytix/Our pipeline [website]. Columbia (MD): Intralytix: 2024 (https://intralytix.com/human-therapeutics#pipeline, accessed 18 January 2024).

34. Cahill J, Young R. Phage lysis: multiple genes for multiple barriers. Adv Virus Res. 2019;103:33–70 (https://doi.org/10.1016/bs.aivir.2018.09.003, accessed 29 February 2024).

35. AP_SA02. In: Armata Pharma/Pipeline [website]. Los Angeles: Armata Pharmaceuticals; 2024 (https://www.armatapharma.com/pipeline/ap-sa02/, accessed 19 January 2024).

Annex 19. Non-traditionals – immunomodulating agents

Product name (INN or company code): reltecimod (AB103)

Pharmacology: chemical class and MoA: Reltecimod is a synthetic octapeptide with homology to the T-lymphocyte receptor CD28 (CD 28 T-lymphocyte receptor mimetic). It blocks binding of superantigens from Gram-positive organisms to CD28 (*1*,*2*,*3*). and also impairs endotoxin-mediated activation of T-cells in Gram-negative infections (*4*). As such, it is supposed to be pathogen agnostic.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)): Activity against Gram-positive pathogens shown in mice lethally challenged with streptococcal exotoxin A, and in a murine model of *Streptococcus pyogenes* necrotizing soft-tissue infection (NSTI) (*3*). Activity against Gram-negative pathogens shown in mouse models of severe bacterial sepsis and Gram-negative bacterial peritonitis (*4*).

Sought therapeutic indication: Treatment of suspected organ dysfunction or failure in patients ≥ 12 years of age with NSTI, in conjunction with surgical debridement, antibiotic therapy and supportive care.

Pharmaceutical form, route of the administration and proposed posology: Single iv infusion of 0.5 mg/kg (at a concentration of 1 mg/mL) over approximately 10 min.

Phase of clinical development: 3

Clinical trial(s): Two Phase 3 trials are listed: NCT02469857 in patients with NSTI and NCT03403751 in patients with sepsis-associated acute kidney injury, early terminated.

- **ACCUTE** (NCT02469857)**:** A Phase 3, randomized, double-blind, placebo-controlled, parallel group, study of AB103 as compared to placebo in patients with NSTI.
  - **Study population:** 290 patients aged ≥ 12 years with surgical confirmation of NSTI, and a modified sequential organ failure assessment (mSOFA) score before debridement of ≥ 3 with at least one of the five components having a score of at least 2. The mSOFA score included the five components: cardiovascular, neurologic, respiratory, renal and coagulation. Patients were randomized 1:1 to either reltecimod or placebo (reltecimod 142, placebo 148).
  - **Time period:** December 2015 to October 2019.
  - **Sites:** 71 sites in France and the USA.
  - **Primary end-point:** The necrotizing infection clinical composite endpoint using a responder analysis such that a successful outcome required that a patient meet all components of the composite score. These included: alive at day 28, ≤ 3 debridements by day 14, no amputation beyond the first operation and resolution of organ dysfunction (mSOFA ≤ 1 on day 14 and a reduction of ≥ 3 points from baseline to day 14). mSOFA total scores range from 0 to 20, with higher scores reflecting a worse clinical status or outcome. An mSOFA total score of 0 or 1 reflects resolution of organ dysfunction/failure.
  - **Primary efficacy evaluation** was performed in the MITT responder population.
  - **Results:** From Bulger et al. (2020) (*5*): 42.4% of the 290 patients were diabetic and 28.6% had perineal infection. The screening mSOFA mean was 5.5 ± 2.4. 28-day mortality was 15% in both groups. The study did not meet its primary end-point: In the MITT population, the necrotizing infection clinical composite end-point success was 48.6% in the reltecimod-treated group vs 39.9% in the placebo group, $P = 0.135$. In the per protocol patient population, which excluded patients who failed to meet the inclusion criteria for organ dysfunction at admission (three patients in each arm) and patients who met exclusion criteria (11 patients), there were 54.3% responders in the reltecimod group compared to 40.3% responders in the placebo group (P value = 0.021). Resolution of organ dysfunction was 65.1% reltecimod vs 52.6% placebo, $P = 0.041$, in the MITT population, and 70.9% vs 53.4%, $P = 0.005$, in the per protocol population.

Product name (INN or company code): reltecimod (AB103) (continued)

- *Note: Based on these data, an NDA was submitted to FDA under the accelerated approval pathway with resolution of organ dysfunction being the basis for this approval pathway. The FDA decision (PDUFA date) was 30 September 2021. No further update is available.*
- **Adverse events from the Phase 3 trial:** There were no significant differences in adverse events or secondary infections between the groups. 21% of patients in each arm developed at least one secondary infection, with the most common being pneumonia, skin and soft tissue infections, and UTI. In the reltecimod group, 29/143 (20.3%) patients had a serious adverse event vs 25/147 (17%) in the placebo group (relative risk 1.2, 95% CI: 0.7–1.9).

- A **Phase 3** randomized, double-blind study (NCT03403751) to evaluate the safety and efficacy of reltecimod as compared to placebo in addition to SOC in patients with sepsis-associated acute kidney injury.
  - **Study population:** 58 adult patients with suspected or confirmed abdominal sepsis (planned or completed surgical (laparotomy or laparoscopy) or interventional radiologic procedures for control of underlying abdominal infection within 24 h of evaluation by medical personnel) or patients with surgically confirmed NSTI, requiring ICU or step down unit admission and in whom the diagnosis of stage 2/3 AKI (as defined by Kidney Disease Improving Global Outcomes criteria) is established at initial presentation for medical evaluation or up to 48 h from the suspected diagnosis of abdominal sepsis or from surgically confirmed diagnosis of NSTI. 58 patients were randomized 1:1 to either single iv infusion of 0.5 mg/kg reltecimod (at a concentration of 1 mg/mL; 28 patients) or placebo (30 patients).
  - **Time period:** May 2018 to December 2019; the study was terminated earlier due to slow enrolment.
  - **Sites:** In France (16 sites) and the USA (40 sites).
  - **Primary end-point:** Freedom from durable loss of renal function at day 28 (time frame: 28 days). Freedom from durable loss of renal function at day 28 required all of the following three components: alive at day 28, free of dialysis at day 28 and less than 37% loss of estimated glomerular filtration rate (eGFR) at day 28 from patient reference eGFR (measured by the modification of diet in renal disease formula). The primary end-point was changed during the course of the study. The previous primary end-point was complete recovery from stage 2/3 AKI at day 14 (time frame: 14 days).
  - **Primary efficacy evaluation** was performed in the MITT population, which included all randomized patients who were exposed to the study drug and who had a suspected or confirmed diagnosis of abdominal sepsis or confirmed NSTI and stage 2 or stage 3 AKI, with patients analysed according to the treatment actually received.
  - **Phase 3 clinical trial results:** Of 58 patients, 77.6% had stage 2 AKI and 22.4% had stage 3 AKI; 29.6% had diabetes and 22.4% had cardiovascular disease. Sepsis presentation was cardiovascular organ failure in 50% and respiratory organ failure in 8.6%. The screening mSOFA mean was 5.1 ± 2.8. The primary end-point was met by 71.4% of patients in the reltecimod group vs 76.7% in the placebo group ($P = 0.649$).
  - **Adverse events from the Phase 3 trial:** There were more secondary infections in the reltecimod group vs the placebo group. The most common were sepsis: 2 vs 0; septic shock: 2 vs 0; and post-operative wound infection: 1 vs 0.

Product name (INN or company code): Rhu-pGSN

Pharmacology: chemical class and MoA: Rhu-pGSN (recombinantly produced human plasma protein gelosin) regulates inflammatory homeostasis by binding to extracellular actin.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)): In vivo, researchers found that using Rhu-pGSN to treat mice with Gram-negative sepsis caused by *P. aeruginosa* resulted in decreased inflammation and bacterial growth (6). In a mouse model of pneumococcal pneumonia, Rhu-pGSN without antibiotics increased survival and reduced morbidity and weight loss after infection with either penicillin-susceptible or penicillin-resistant *S. pneumoniae* (7).

Sought therapeutic indication: Researchers are currently studying the potential of Rhu-pGSN as an adjunctive treatment in acute CABP, sepsis and acute respiratory distress syndrome (ARDS).

Product name (INN or company code): Rhu-pGSN (continued)

Pharmaceutical form, route of the administration: Intravenous.

Phase of clinical development: 1b/2a

Clinical trial(s): Rhu-pGSN is registered in five trials:

- A **Phase 2** randomized double-blind placebo-controlled study to evaluate the efficacy and safety of adjunctive Rhu-pGSN with standard care for moderate-to-severe ARDS due to pneumonia or other infection. Subjects will receive Rhu-pGSN 24 mg/kg once, followed by five daily doses of 12 mg/kg based on actual body weight in addition to SOC (NCT05947955).
  - **Study population:** 520 consented male/female patients ≥ 18 years old diagnosed with ARDS.
  - **Time frame:** Not yet recruiting.
  - **Primary end-point:** All-cause mortality rate at study day 60, incidence of significant adverse events.
  - **Primary efficacy evaluation:** Not yet available
- A **Phase 1b/2a**, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and PK/PD of Rhu-pGSN added to SOC in subjects hospitalized for acute CABP; 33 participants (NCT03466073, completed April 2019).
- **Phase 2** for severe COVID-19 pneumonia (NCT04358406, completed January 2022).
- **Phase 1** to evaluate plasma gelsolin in healthy volunteers (NCT05789745, BTI-101, completed May 2023).
- **Phase 1** ascending single-dose study of Rhu-pGSN in patients with decreased gelsolin levels (NCT00671307, completed May 2010).

Primary efficacy evaluation: Not yet publicly available.

Adverse effects: In the Phase 1b/2a study (NCT03466073) both treatment groups reported mild adverse events. In the 18 Rhu-pGSN recipients, there were no serious or drug-related adverse events, but two reported nausea and increased blood pressure *(8)*.

References

1. Arad G, Levy R, Nasie I, Hillman D, Rotfogel Z, Barash U et al. Binding of superantigen toxins into the CD28 homodimer interface is essential for induction of cytokine genes that mediate lethal shock. PLoS Biol. 2011;9(9):e1001149 (https://doi.org/10.1371/journal.pbio.1001149, accessed 29 February 2024).
2. Kaempfer R, Arad G, Levy R, Hillman D, Nasie I, Rotfogel Z. CD28: direct and critical receptor for superantigen toxins. Toxins. 2013 Sep;5(9):1531-42 (https://doi.org/10.3390/toxins5091531, accessed 29 February 2024).
3. Ramachandran G, Tulapurkar ME, Harris KM, Arad G, Shirvan A, Shemesh R et al. A peptide antagonist of CD28 signaling attenuates toxic shock and necrotizing soft-tissue infection induced by Streptococcus pyogenes. J Infect Dis. 2013;207(12):1869–77 (https://doi.org/10.1093/infdis/jit104, accessed 29 February 2024).
4. Ramachandran G, Kaempfer R, Chung CS, Shirvan A, Chahin AB, Palardy JE et al. CD28 homodimer interface mimetic peptide acts as a preventive and therapeutic agent in models of severe bacterial sepsis and gram-negative bacterial peritonitis. J Infect Dis. 2015;211(6):995–1003 (https://doi.org/10.1093/infdis/jiu556, accessed 29 February 2024).
5. Bulger EM, May AK, Robinson BRH, Evans DC, Henry S, Green JM et al. A novel immune modulator for patients with necrotizing soft tissue infections (NSTI): results of a multicenter, Phase 3 randomized controlled trial of Reltecimod (AB 103). Ann Surg. 2020;272(3):469–78 (https://doi.org/10.1097/SLA.0000000000004102, accessed 29 February 2024).
6. Piktel E, Wnorowska U, Cieśluk M, Deptuła P, Prasad SV, Król G et al. Recombinant human plasma gelsolin stimulates phagocytosis while diminishing excessive inflammatory responses in mice with *Pseudomonas aeruginosa* sepsis. Int J Mol Sci. 2020;21(7):2551 (https://doi.org/10.3390/ijms21072551, accessed 19 January 2024).
7. Yang Z, Bedugnis A, Levinson S, Dinubile M, Stossel T, Lu Q et al. Delayed administration of recombinant plasma gelsolin improves survival in a murine model of penicillin-susceptible and penicillin-resistant pneumococcal pneumonia. J Infect Dis. 2019;220(9):1498–502 (https://doi.org/10.1093/infdis/jiz353, accessed 29 February 2024).
8. Tannous A, Levinson SL, Bolognese J, Opal SM, DiNubile MJ. Safety and pharmacokinetics of recombinant human plasma gelsolin in patients hospitalized for nonsevere community-acquired pneumonia. Antimicrob Agents Chemother. 2020;64(10):e00579-20 (https://doi.org/10.1128/AAC.00579-20, accessed 29 February 2024).

Annex 20. Non-traditionals – microbiome-modulating agents

Product name (INN or company code):
SER-155

Pharmacology: chemical class and MoA: SER-155 is a fermented microbiome therapeutic composed of cultivated spores and vegetative bacterial strains *(1)*.

Spectrum of activity: Preclinical in vitro and in vivo data indicate potential to reduce infection caused by CREs and VRE *(1)*. In vivo studies suggest SER-155 may decolonize VRE and CRE, and further modulate epithelial barrier integrity and T-cell biology with relevance to graft vs host disease (GvHD) *(1,2)*.

Sought therapeutic indication: Being developed to reduce the risk of bacteraemia and GvHD in allo-HSCT recipients by decolonizing potential pathogens and restoring GI colonization resistance *(3)*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 1b

Clinical trial(s): A multiple-dose Phase 1b study to evaluate the safety, tolerability, PK and efficacy of SER-155 in 75 adults undergoing HSCT to reduce the risk of infection and GvHD (NCT04995653) is currently recruiting.

Preclinical PK and safety: Not yet publicly available.

References

1. Halvorsen E, Vulic M, O'Brien JE, Byrant J, Lombardo MJ, Ford C et al. 130. Design and preclinical characterization of SER-155, an investigational cultivated microbiome therapeutic to restore colonization resistance and prevent infection in patients undergoing hematopoietic stem cell transplantation. Open Forum Infect Dis. 2021;8(Suppl 1):S79–80 (https://doi.org/10.1093/ofid/ofab466.130, accessed 15 January 2024).

2. Seres Therapeutics reports SER-155 Phase 1b cohort 1 results showing successful drug bacteria engraftment and substantial reduction in pathogen domination in the gastrointestinal microbiome. In: Seres Therapeutics/News and events [website]. Cambridge (MA): Seres Therapeutics; 2023 (https://ir.serestherapeutics.com/news-releases/news-release-details/seres-therapeutics-reports-ser-155-phase-1b-cohort-1-results, accessed 19 January 2024).

3. Markey KA. Toward optimizing the microbiome for transplant patients. Hematologist. 2022;19(5) (https://doi.org/10.1182/hem.V19.5.2022512, accessed 16 January 2024).

Annex 21. Non-traditionals – miscellaneous

Product name (INN or company code): OligoG (CF-5/20)

Pharmacology: chemical class and MoA: OligoG is an alginate oligosaccharide (G-block) fragment extracted and purified from the marine algae *Laminaria hyperborea (1)*.

Spectrum of activity: OligoG shows anti-biofilm activity, and inhibition of bacterial growth normalizes CF mucus by chelating calcium *(2)*. In a study using atomic force microscopy, OligoG CF-5/20 was shown to modify the surface charge of MDR *P. aeruginosa*, resulting in cell aggregation and a reduction in motility *(3)*. In vitro, OligoG treatment reduced (by up to 512-fold) the MICs of a range of antibiotics, such as ceftazidime and macrolides, against MDR *P. aeruginosa (1)*.

Sought therapeutic indication: It is currently being investigated in studies related to the treatment of *P. aeruginosa* lung infection in patients with CF.

Pharmaceutical form, route of the administration: Inhalation.

Phase of clinical development: 2b

Clinical trial(s): OligoG has been studied in six clinical trials:

- **Phase 2/3:** A randomized, double-blind, placebo-controlled study. The study has two parts: a dose-finding part, followed by longer-term follow-up (6 months) (NCT03698448, withdrawn, determined not feasible).
- **Phase 2b:** A randomized, double-blind, parallel-group study of OligoG dry powder inhalation in addition to SOC compared to placebo in addition to SOC in 20 patients with CF (NCT03822455, status unknown as of May 2020).
- **Phase 2:** A double-blind, randomized, placebo-controlled crossover study of inhaled OligoG administered for 28 days in subjects with CF (NCT02157922, completed September 2017).
  - **Study population:** 65 consented male/females (on contraceptive) with confirmed CF and positive microbiological finding of *P. aeruginosa*
  - **Time period:** 10/2014-09/2017
  - **Primary end-point:** An improvement in FEV1 during treatment with OligoG as compared to placebo (28 days)

Primary efficacy evaluation: Not yet available

- **Phase 2**, completed September 2014 (NCT01991028).
- **Phase 1/2**, completed November 2013 (NCT01465529).
- **Phase 1**, completed November 2009 (NCT00970346).

Preclinical PK and safety: The preclinical toxicity and PK studies from unpublished data were reported to demonstrate that doses at which OligoG is effective in vitro may be safely attainable in the lung in vivo *(1)*.

Product name (INN or company code): PLG0206 (WLBU2)

Pharmacology: chemical class and MoA: PLG0206 (WLBU2) is a 24-amino-acid engineered cationic antibiotic peptide *(4)*.

Spectrum of activity: Broad-spectrum against bacteria that cause biofilm-related infections, including MDR and XDR *S. aureus*, *Enterococcus* spp., and aerobic Gram-negative bacilli *(4,5)*. As a systemic (UTI) and local (PJI) agent, PLG0206 exhibits activity in a variety of animal infection models *(5)*.

Pharmaceutical form, route of the administration: Irrigation.

Sought therapeutic indication: Treatment of a PJI occurring after TKA (total knee athroplasty).

Phase of clinical development: 1

Clinical trial(s): The current Phase 1 study is in 14 participants undergoing DAIR for treatment of a PJI occurring after TKA (NCT05137314, recruiting).

PK and adverse events: In the now completed Phase 1 study of 47 healthy participants, single iv infusion of PLG0206 resulted in linear PK at doses ranging from 0.05 mg/kg to 1 mg/kg and was safe and well tolerated *(5)*. Most of the adverse events related to PLG0206 treatment were mild and similar between the PLG0206 treatment and placebo groups *(5)*. No severe adverse events, life-threatening events or deaths occurred during the study.

Product name (INN or company code): CAL02

Pharmacology: chemical class and MoA: CAL02 is an antitoxin agent made up of liposomes. These liposomes create stable liquid-ordered lipid microdomains that function as docking sites for a range of bacterial virulence effectors (toxins) *(6)*.

Spectrum of activity: In vitro, artificial liposomes have been shown to protect mammalian cells against bacterial toxins during infection *(7)*. CAL02 proved to be efficacious in in vivo acute models of infection caused by Gram-positive (*S. aureus* and *S. pneumoniae*) *(7)*. When administered within 10 h, it rescued mice with invasive pneumococcal pneumonia from septicaemia caused by *S. aureus* and *S. pneumoniae* in vivo *(7)*.

Sought therapeutic indication: Severe CABP.

Pharmaceutical form, route of the administration: Intravenous.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 1:** A randomized, double-blind, multicentre, placebo-controlled trial done in patients with severe CABP who required ICU admission and had been identified as being infected with *S. pneumoniae* (NCT02583373, completed February 2018).
  - **Study population:** 19 consented adults male or female patients ≥ 18 years and ≤ 80 years of age with confirmed severe pneumonia caused by *S. pneumoniae* managed in an ICU.
  - Time period: March 2018 to February 2019.
  - **Primary end-point:** Frequency, severity and characteristics of adverse events after two iv administrations of CAL02.
- **Phase 2:** A randomized, double-blind, placebo-controlled multicentre study to evaluate the efficacy and safety of CAL02 administered intravenously in addition to SOC in subjects with severe CABP (NCT05776004, recruiting).
  - **Study population:** 276 participants with severe CABP will receive either two iv infusions of CAL02 (13.7–24 mg/kg bracketed dose by weight), administered 24–26 h apart or two iv infusions of placebo by a parallel assignment.
  - **Time period:** Recruiting.
  - **Primary end-point:** Efficacy – clinical recovery, incidence of TEAEs.

Product name (INN or company code): CAL02 (continued)

Trial results: During the Phase 1 clinical trial, the group receiving a high dose of CAL02 showed better patient outcomes than the placebo group, shown in the initial stages of the infection when the level of bacteria is high *(8)*.

Adverse events (from Phase 1 trial): Adverse events occurred in 12 (86%) of 14 patients in the CAL02 treatment groups combined and all five (100%) patients in the placebo group *(9)*. Serious adverse events occurred in four (29%) of 14 patients in the CAL02 treatment groups combined and two (40%) of five patients in the placebo group. No adverse events were linked to local tolerability events *(9)*.

Product name (INN or company code): AR501 (Panaecin)

Pharmacology: chemical class and MoA: Gallium citrate, which acts as an iron analogue to starve bacteria of iron. The inhibitory activity of AR-501 reaches bacteria growing in mature biofilms *(10)*.

Spectrum of activity: The target bacterium in the Phase 2a clinical study is *P. aeruginosa*. However, AR-501 has broad antibacterial activity against Gram-negative and Gram-positive bacteria in vitro, including antibiotic-resistant strains *(10)*. In mouse models of bacterial lung infections reported (webpage data), a single inhalation exposure of aerosolized AR-501 protected the animal from morbidity and mortality. AR-501 was also protective when used in combination with antibiotics *(11)*.

Sought therapeutic indication: Treatment of bacterial lung infections in patients with CF.

Pharmaceutical form, route of the administration: Inhalation, to be given once a week.

Phase of clinical development: 1/2a

Clinical trial(s): Randomized, double-blind, two-part (Phase 1 and 2a), single and multiple dose ascending, multicentre study of the safety and PK of inhaled AR-501 in healthy adults and *P. aeruginosa*-infected CF subjects. CF multiple ascending dose cohort to evaluate four different dose levels: once-per-week administration at 6.4 mg (low-dose cohort), 20 mg (mid-dose cohort) and 40 mg (high-dose cohort), 80 mg Ga dose (top dose) (NCT0366614, ongoing).

- **Study population:** 48 subjects in healthy volunteer cohort, 54 subjects with CF and confirmed *P. aeruginosa* bacterial colonization. single and multiple ascending dose healthy volunteer cohorts: 3:1 randomization. The CF multiple ascending dose cohort: sentinel subjects 2:1 ratio, expanded cohort 2:3:3:2 ratio, then top dose 2:1 ratio.
- **Time period:** 28 days for healthy volunteer cohorts and 42 days for CF cohorts.
- **Primary end-point:** Evaluation of adverse events in healthy volunteer and CF subjects.
- **Primary efficacy evaluation:** N/A.

Trial results: Topline results published online state that AR-501 was well tolerated with no serious adverse events and achieved high concentrations (50-fold higher than that required for inhibition of *P. aeruginosa*) in the respiratory tract *(11)*.

References

1. Khan S, Tøndervik A, Sletta H, Klinkenberg G, Emanuel C, Onsøyen E et al. Overcoming drug resistance with alginate oligosaccharides able to potentiate the action of selected antibiotics. Antimicrob Agents Chemother. 2012;56(10):5134–41 (https://doi.org/10.1128/AAC.00525-12, accessed 29 February 2024).
2. Ermund A, Recktenwald CV, Skjåk-Braek G, Meiss LN, Onsøyen E, Rye PD et al. OligoG CF-5/20 normalizes cystic fibrosis mucus by chelating calcium. Clin Exp Pharmacol Physiol. 2017;44(6):639–47 (https://doi.org/10.1111/1440-1681.12744, accessed 29 February 2024).
3. Powell LC, Pritchard MF, Emanuel C, Onsøyen E, Rye PD, Wright CJ et al. A nanoscale characterization of the interaction of a novel alginate oligomer with the cell surface and motility of *Pseudomonas aeruginosa*. Am J Respir Cell Mol Biol. 2014;50(3):483–92 (https://doi.org/10.1165/rcmb.2013-0287OC, accessed 29 February 2024).
4. Huang D, Pachuda N, Sauer JM, Dobbins D, Steckbeck J. The engineered antibiotic peptide PLG0206 eliminates biofilms and is a potential treatment for periprosthetic joint infections. Antibiotics. 2021;11(1):41 (https://doi.org/10.3390/antibiotics11010041, accessed 29 February 2024).
5. Huang D, Dobbins D, Ghahramani P, Friedland I, Steckbeck J. A phase 1 study of the safety, tolerability, and pharmacokinetics of single ascending doses of a first-in-human engineered cationic peptide, PLG0206, intravenously administered in healthy subjects. Antimicrob Agents Chemother. 2022;66(1):e0144121 (https://doi.org/10.1128/AAC.01441-21, accessed 29 February 2024).
6. Azeredo da Silveira S, Shorr A. Critical parameters for the development of novel therapies for severe and resistant infections – a case study on CAL02, a non-traditional broad-spectrum anti-virulence drug. Antibiotics. 2020;9(2):94 (https://doi.org/10.3390/antibiotics9020094, accessed 29 February 2024).
7. Henry BD, Neill DR, Becker KA, Gore S, Bricio-Moreno L, Ziobro R et al. Engineered liposomes sequester bacterial exotoxins and protect from severe invasive infections in mice. Nat Biotechnol. 2015;33(1):81–8 (https://doi.org/10.1038/nbt.3037, accessed 29 February 2024).
8. Pletz MW, Bauer M, Brakhage AA. One step closer to precision medicine for infectious diseases. Lancet Infect Dis. 2019;19(6):564–5 (https://doi.org/10.1016/S1473-3099(19)30070-2, accessed 29 February 2024).
9. Laterre PF, Colin G, Dequin PF, Dugernier T, Boulain T, Azeredo da Silveira S et al. CAL02, a novel antitoxin liposomal agent, in severe pneumococcal pneumonia: a first-in-human, double-blind, placebo-controlled, randomised trial. Lancet Infect Dis. 2019;19(6):620–30 (https://doi.org/10.1016/S1473-3099(18)30805-3, accessed 18 January 2024).
10. Rzhepishevska O, Ekstrand-Hammarström B, Popp M, Björn E, Bucht A, Sjöstedt A et al. The antibacterial activity of Ga3+ is influenced by ligand complexation as well as the bacterial carbon source. Antimicrob Agents Chemother. 2011;55(12):5568–80 (https://doi.org/10.1128/AAC.00386-11, accessed 29 February 2024).
11. AR-501 (Panaecin™). In: Aridis Pharmaceuticals/Pipeline [website]. Los Gatos (CA): Aridis Pharmaceuticals; 2022 (https://www.aridispharma.com/ar-501/, accessed 29 February 2024).

Annex 22. Traditionals – CDI and *H. pylori*

Product name (INN or company code): ridinilazole

Pharmacology: chemical class and MoA: Ridinilazole is a non-absorbable bis-benzimidazole compound. It acts as an antibiotic by binding to DNA, leading to dysregulation of transcription and cell death in *C. difficile (1)*.

Spectrum of activity and potential resistance: Early evidence indicates bactericidal activities and a decrease in toxin A and toxin B concentrations of *C. difficile* strains exposed to ridinilazole *(2)*. It is hypothesized to lower risk for CDI recurrence while preserving the gut microbiome *(3)*. No cross-resistance is reported.

Sought therapeutic indication: Ridinilazole is being developed as a treatment option in non-fulminant CDI.

Pharmaceutical form, route of administration: Oral 200 mg, bid, every q12h for 10 days.

Phase of clinical development: 3

Clinical trial(s):

Phase 3: Two identical Phase 3 studies, Ri-CoDIFy 1 (NCT03595553) and Ri-CoDIFy 2 (NCT03595566), combined in the Ri-CoDIFy Phase 3 trial, are complete. Ri-CoDIFy was an interventional, quadruple-blind, parallel assignment, randomized, active-controlled non-inferiority study to compare the efficacy and safety of ridinilazole with vancomycin for treatment of CDI (NCT04802837).

- **Study population:** Adult patients with signs and symptoms of CDI, including diarrhoea, such that in the investigator's opinion CDI antimicrobial therapy was required, and with presence of either toxin A and/or B of *C. difficile* in a stool sample determined by a positive free toxin test produced within 72 h prior to randomization. Excluded were all participants receiving effective antibacterial drug therapy (> 24 h prior to randomization), or participants with moderate or severe liver disease, severe neutropenia, a baseline QTc (corrected QT interval) of > 500 ms, known history of congenital long QT syndrome, uncompensated heart failure, uncorrected abnormal K+ or Mg++ blood levels or severe left ventricular hypertrophy. Patients were randomly parallelly assigned to receive either oral ridinilazole (200 mg every 12 h) or oral vancomycin (125 mg every 6 h) for 10 days.
- **Time period:** January 2019 to November 2021.
- **Sites:** The study took place in over 180 sites in 28 countries.
- **Primary efficacy end-point** was achievement of a sustained clinical response, defined as clinical cure at the TOC visit and no recurrence within 30 days post-EOT.
- **Primary efficacy evaluation** was done on the micro-MITT population (all individuals with CDI confirmed by the presence of free toxin in stool who were randomly assigned to receive one or more doses of the study drug). A non-inferiority margin of 15% was selected.

Results: From a poster presentation by Okhuysen et al. (2022) *(4)*. The study did not meet its primary end-point. Ridinilazole achieved sustained clinical response (SCR) in 73% of patients vs 70.7% of the vancomycin group ($P = 0.4672$). Ridinilazole resulted in a significant reduction in recurrent CDI (rCDI) rate (8.1% vs 17.3%, $P = 0.0002$). This was most notable in the pre-specified population of in-patients not receiving other antibiotics (rCDI 6.7% in ridinilazole vs 16.5% in vancomycin, $P = 0.0005$). Patients in the ridinilazole group presented with increased microbiome diversity compared with those in the vancomycin group at both 10 ($P < .0001$) and 30 ($P \leq .0007$) days following treatment completion. *Note: Upon consultation, the FDA requested additional evidence of efficacy from at least one additional clinical trial.*

Product name (INN or company code): ridinilazole (continued)

- **Ri-CoDIFy 3** (NCT04802837), a study evaluating the safety, tolerability and PK of ridinilazole in adolescents, was terminated in alignment with a corporate decision to pursue further development of the drug candidate with a partner (as of an August 2023 update).
- **Phase 2 studies** have been conducted to evaluate the safety and efficacy of ridinilazole compared with two conventional antibiotics, fidaxomicin and vancomycin. The first of these two Phase 2 studies compared ridinilazole with vancomycin for the treatment of *C. difficile*-associated diarrhoea (CDAD) (NCT02092935).
  - **Time period:** 26 June 2014 to October 2015.
  - **Study design:** Randomized, double-blind, active-controlled, non-inferiority clinical study to investigate the efficacy and safety of ridinilazole 200 mg PO bid for 10 days (with alternating 200 mg placebo bid), compared with vancomycin 25 mg capsule qid for 10 days for treatment of CDAD.
  - **Study population:** Participants with signs and symptoms of *C. difficile* infection and a positive diagnostic test result were recruited from 33 centres in the USA and Canada and randomly assigned (1:1) to receive oral ridinilazole (200 mg every 12 h) or oral vancomycin (125 mg every 6 h) for 10 days.
  - **The primary end-point** was sustained clinical response, defined as clinical cure at EOT and no recurrence within 30 days, which was used to establish non-inferiority (15% margin).

Study results and conclusions: Ridinilazole demonstrated an overall response rate (ORR) at TOC visit of 66.7% (n = 24/36) in the ridinilazole arm compared with 42.4% (14/33) of those in the vancomycin arm, for a percentage difference of 21.1% (90% CI: 3.1–39.1, P = 0.0004) *(5)*. The safety profile of ridinilazole was similar to that of vancomycin. Nausea (20%) and abdominal pain (12%) were the most commonly reported adverse reactions associated with ridinilazole *(5)*.

- The second of the two Phase 2 studies compared ridinilazole with fidaxomicin for the treatment of CDI (NCT02784002).
  - **Time period:** December 2014 to August 2016.
  - **Study design:** Randomized, open-label, active-controlled clinical study to investigate the safety and efficacy of ridinilazole (200 mg bid) for 10 days compared with fidaxomicin (200 mg bid) for 10 days for the treatment of CDI.
  - **Study population:** 27 participants with clinical diagnosis of CDI plus laboratory diagnostic test. The study was conducted in three countries (Czechia, United Kingdom, USA). Included in the study were adults (≥ 18 years of age) with clinical diagnosis of CDI confirmed by laboratory diagnostic test who had not received > 30 h antimicrobial treatment for their current CDI. Excluded were patients with life-threatening or fulminant CDI and those ≥ 2 episodes of CDI in the previous year and pregnant or breastfeeding women.
  - **The primary end-point** was safety. Sustained clinical response at day 30 and clinical cure rates at day 12 were among secondary end-points.
  - **Study results and conclusions:** The study reported comparable sustained clinical response rates on day 30 post-EOT: 50% for ridinilazole compared with 46.2% for fidaxomicin; treatment difference, 2.9% (95% CI: −30.8 to 36.7). The study also reported that ridinilazole preserved gut microbiome diversity to a greater extent than fidaxomicin during CDI treatment. The study concluded that this finding is consistent with low CDI recurrence rates.

Adverse events from Phase 2 studies: According to a Phase 2 study that assessed the safety and efficacy of ridinilazole vs vancomycin for treatment of CDI in 100 patients, 82% of those treated with ridinilazole had adverse events (n = 41/50), mostly mild (40% GI tract related). One serious adverse event (hypokalaemia) was reported *(5)*.

Product name (INN or company code): CRS3123 (REP 3123)

Pharmacology: chemical class and MoA: CRS3123 is a diaryldiamine derivative that selectively inhibits Gram-positive bacterial methionyl-tRNA synthetase *(6)*.

Spectrum of activity and potential resistance: CRS3123 is active against aerobic Gram-positive bacteria, including *C. difficile*, and inhibits toxin production in vitro *(6)*. It shows little activity against Gram-negative bacteria, including anaerobes, and no effect on human methionyl-tRNA synthetase enzyme *(7)*. In vivo evidence of efficacy for CDI treatment was obtained from the hamster model *(8)*.

Sought therapeutic indication: Under development for the treatment of CDI.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial (s):

- **Phase 2:** A randomized, double-blind, comparator-controlled, multicentre study to evaluate the safety and efficacy of crs3123 compared with oral vancomycin in 108 adults with *C. difficile* infection (NCT04781387, currently recruiting).
  - **Study population:** Two dosages of CRS3123 (200 mg and 400 mg) administered twice-daily compared with vancomycin 125 mg administered four times daily in approximately 100 adults 18 years or older diagnosed with a primary episode or first recurrence of CDI. The duration of treatment for all study treatment arms is 10 days. Patients with clinically documented CDI will be enrolled at up to 30 sites in Canada and the USA.
  - **Primary end-point:** Rate of clinical cure at TOC in the ITT population.
  - **Results:** None as yet.
- **Phase 1:** Randomized, double-blind, placebo-controlled, single ascending dose trial to determine the safety and PK of CRS3123 administered orally to healthy adults (NCT01551004, completed April 2014).

Adverse events / preclinical PK and safety: From the Phase 1 study (NCT01551004), CRS3123 was generally safe and well tolerated, with no serious adverse events or severe TEAEs reported *(7)*. Faecal concentrations were above the MIC90 value of 1 µg/mL at all dosages tested *(7)*. Subjects receiving either of the two lower doses of CRS3123 exhibited minimal disruption of normal gut microbiota after 10 days of twice-daily dosing *(7)*. CRS3123 was inactive against important commensal anaerobes, including *Bacteroides*, bifidobacteria and commensal clostridia. Beneficial microbiome effects were also observed *(7)*.

Product name (INN or company code): oxaquin (DNV3837, MCB-3837; prodrug of MCB3681) (*C. difficile*)

Pharmacology: chemical class and MoA: Oxaquin (DNV3837/MCB-3837) is an oxazolidinone-quinolone hybrid and prodrug of MCB-3681 that is administered intravenously *(9)*.

Spectrum of activity and potential resistance: Oxaquin has been reported to be active against Gram-positive gut microflora bacteria but to be sparing of Gram-negative organisms in human volunteer studies with iv administration over 5 days *(10,11)*. In in vitro studies, MICs of oxaquin for *C. difficile* ranged from 0.008 mg/L to 0.5 mg/L *(10,11)*. There was no evidence of oxaquin resistance from limited data *(10,11)*.

Sought therapeutic indication: Under development for the treatment of CDI.

Pharmaceutical form, route of administration: Intravenous.

Phase of clinical development: 2

Clinical trial(s):

Phase 2: An exploratory, open-label, oligo-centre study to evaluate the safety, efficacy and PK of iv DNV3837 in 40 subjects with *C. difficile* infection (NCT03988855, recruiting).

Product name (INN or company code): oxaquin (DNV3837, MCB-3837; prodrug of MCB3681) (*C. difficile*) (continued)

- **Study population:** Subjects with severe or non-severe CDI. DNV3837 is administered at a dose of 1.5 mg/kg actual body weight/day via iv infusion, for a total maximum daily dose of 120 mg in subjects with CDI. Infusions will be administered once a day for 10 consecutive days. The study will be conducted in two subsequent parts. In part 1 of the study, 10 subjects of either sex with severe or non-severe CDI will be enrolled to receive DNV3837. In part 2 of the study, up to 30 subjects with severe or non-severe CDI will be enrolled to receive DNV3837.
- Primary end-points:
- to evaluate the safety of iv DNV3837;
- to evaluate the efficacy of iv DNV3837;
- to assess the PK of DNV3837 and DNV3681 in plasma and of DNV3681 in urine and faeces;
- to assess *C. difficile* using microbiological assessments;
- to assess the proportion of subjects colonized with VRE, ESBL organisms or CRE in faeces; and
- to assess changes in the faecal microbiome using 16S RNA analysis.

- **Results:** By day 5 of the study, all 12 volunteers exhibited faecal concentrations of MCB3681 ranging from 98.9 to 226.3 mg/kg *(12)* caused no ecological changes in the skin, nasal or oropharyngeal microbiota; no new colonizing aerobic or anaerobic Gram-positive bacteria were found with MCB3681 MICs of ≥ 4 mg/L *(12)*. Faecal microbiota was normalized on day 19 *(12)*.

Product name (INN or company code): ibezapolstat (ACX-362E)

Pharmacology: chemical class and MoA: Ibezapolstat (ACX-362E) is a first-in-class dichlorobenzyl purine analogue that binds to and inhibits bacterial DNA polymerase IIIC. DNA pol IIIC is essential for replicative DNA synthesis in Gram-positive bacteria with a low G+C content such as Clostridioides (new target and new MoA) *(13,14,15)*.

Spectrum of activity and potential resistance: Ibezapolstat exhibits low MIC values against MDR *C. difficile* isolates. The overall MIC50/90 (mg/L) for ibezapolstat against *C. difficile* was 2/4, compared with 0.5/4 for metronidazole, 1/4 for vancomycin and 0.5/2 for fidaxomicin *(16)*. In vivo studies of ibezapolstat demonstrate minimal systemic absorption, and the drug was able to prevent recurrence when administered for 14 days. Its unique MoA is claimed to bypass cross-resistance with other frequently used antibiotics *(17)*.

Sought therapeutic indication: Treatment of CDI.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2b

Clinical trial (s):

Phase 1: A three-part, randomized, placebo-controlled study of the tolerability and safety of ibezapolstat in healthy male and female subjects of normal range body mass index (BMI) (Midlands IRB# 220170383) *(18)*.

- **Adverse events (from the Phase 1 trial):** Multiple dose levels of ACX-362E were well tolerated with no reported adverse events *(18)*. Blood levels indicated poor oral absorption. Faecal concentrations at higher doses exceeded the inhibitory concentrations for *C. difficile* and were sustained throughout the treatment course *(18)*. Beneficial microbiome effects were also observed.

Phase 2: ACX-362E (ibezapolstat) for oral treatment of *C. difficile* infection: a Phase 2A open-label segment followed by a Phase 2B double-blind vancomycin-controlled segment (NCT04247542, 2B not recruiting).

- **Phase 2a:** An open-label study of up to 20 patients at six study centres and was terminated early at 10 patients based on the protocol-specified trial oversight committee's assessment of the compelling efficacy and safety data. Patients were treated with 450 mg of oral ibezapolstat bid for 10 days.

Product name (INN or company code): ibezapolstat (ACX-362E) (continued)

  - **Results (webpage data):** All (10 of 10) patients were cured of CDI at end of treatment, and all (10 of 10) were sustained clinical cures 30 days after EOT. Ibezapolstat was well tolerated, with no reported serious adverse events *(19)*.

- **Phase 2b:** The Phase 2b clinical trial is designed to enroll 64 patients and is a randomized (1:1), non-inferiority, double-blind trial of oral ibezapolstat compared to oral vancomycin, an SOC to treat CDI. Subjects will receive either ibezapolstat 450 mg every 12 hours or vancomycin 125 mg orally every 6 h, in each case, for 10 days and followed for 28 ± 2 days following the end of treatment for recurrence of CDI.

Product name (INN or company code): MGB-BP-3

Pharmacology: chemical class and MoA: MGB-BP-3 is a first-in-class, non-absorbable antibiotic with a novel chemical structure (distamycin derivative), a new target and antibacterial MoA (DNA minor groove binder). It acts on multiple binding sites and interferes with transcription.i *(20,21)*.

Spectrum of activity and potential resistance: MGB-BP-3 is active against Gram-positive bacteria; resistance is found in Gram-negative bacteria through efflux pumps *(22)*.

Sought therapeutic indication: Developed for the treatment of CDI.

Pharmaceutical form, route of administration: Oral (not absorbed).

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2a:** An exploratory, open-label study assessing the safety, tolerability and efficacy of incremental doses of MGB-BP-3 (NCT03824795, completed April 2020).
  - **Study population:** In three sequential groups of 10 patients with CDAD. Patients will be administered an oral dose of MGB-BP-3 for 10 days (day 1 to day 10). At the end of the treatment period, patients will be followed for up to 8 weeks to assess the incidence of disease recurrence.
  - **Primary outcomes:** Number of participants with treatment-related adverse events assessed by the investigator, as per CTCAE (Common Terminology Criteria for Adverse Advents) v.5.0. Initial cure rate at 12 days post initiation of therapy.
  - **Topline results** published on the company's website *(23)*: Three dose levels were evaluated in the study with the maximum efficacy observed at 250 mg of MGB-BP-3, given twice daily for 10 days, achieving an initial cure and sustained cure of 100% *(23)*. This dosage regimen has now been confirmed for the next phase of clinical trials.
- **Phase 1:** A single-centre, double-blind, placebo-controlled study in 40 healthy men to assess the safety and tolerability of single and repeated ascending doses of MGB-BP-3 (NCT02518607, completed).

Adverse events: In (press release) data from Phase 1 and 2 studies, MGB-BP-3 showed a good safety and tolerability profile with no serious adverse events reported *(23)*.

Product name (INN or company code): rifasutenizol (TNP-2198)

Pharmacology: chemical class and MoA: Rifasutenizol (TNP-2198) is a stable conjugate of a rifamycin pharmacophore and a nitroimidazole pharmacophore *(24)*.

Spectrum of activity and potential resistance: It is reported to show unique antibacterial activity against anaerobic and microaerophilic bacteria and against strains resistant to both rifamycins and nitroimidazoles *(24)*.

Sought therapeutic indication: Under development for the treatment of *H. pylori* infection, CDI and bacterial vaginosis *(24)*.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 3

Clinical trial(s):

- **Phase 3:** To evaluate the efficacy and safety of rifasutenizol (TNP 2198) in combination with rabeprazole and amoxicillin in the primary treatment of 700 participants with *H. pylori* infection (NCT05857163, recruiting).

Study population: 700 (estimated) adult patients with *H. pylori* infection with positive 13C-UBT results (≥ 4 delta over baseline), and confirmation of infection of *H. pylori* by gastroscopic biopsy histology, will be randomized 1:1 to be assigned to test group or control group stratified by study site, and will receive 400 mg, bid rifasutenizol, 2 mg bid rabeprazole sodium enteric-coated tablets, 1 g bid amoxicillin capsules combined with clarithromycin placebo tablets and bismuth potassium citrate placebo capsules (test group), or bismuth-containing a quadruple regimen of amoxicillin capsules, 250 mg bid clarithromycin, rabeprazole sodium enteric-coated tablets and 400 mg bid bismuth potassium citrate capsules combined with rifasutenizol placebo capsules (control group) for 14 consecutive days.

  - **Time period:** May 2023 to October 2024.
  - **Sites:** China, no further details.
  - **Primary end-point:** Eradication rate of *H. pylori* strain 13C urea breath test will be performed 4–6 weeks after the last dose to evaluate the eradication effect of *H. pylori*.

- **Phase 1, Phase 1/2:** Three trials to evaluate the PK, efficacy and safety of rifasutenizol have been completed in China.

Adverse events / preclinical PK and safety: Not yet publicly available.

References

1. Mason CS, Avis T, Hu C, Nagalingam N, Mudaliar M, Coward C et al. The novel DNA binding mechanism of ridinilazole, a precision Clostridiodes difficile antibiotic. Antimicrob Agents Chemother. 2023;67(5):e0156322 (https://doi.org/10.1128/aac.01563-22, accessed 29 February 2024).
2. Bassères E, Endres BT, Khaleduzzaman M, Miraftabi F, Alam MJ, Vickers RJ et al. Impact on toxin production and cell morphology in *Clostridium difficile* by ridinilazole (SMT19969), a novel treatment for *C. difficile* infection. J Antimicrob Chemother. 2016;71(5):1245–51 (https://doi.org/10.1093/jac/dkv498, accessed 29 February 2024).
3. Cho JC, Crotty MP, Pardo J. Ridinilazole: a novel antimicrobial for *Clostridium difficile* infection. Ann Gastroenterol. 2019;32(2):134–40 (https://doi.org/10.20524/aog.2018.0336, accessed 29 February 2024).
4. Okhuysen PC, Ramesh M, Garey KW, Louie TJ, Cisneros JT, Stychneuskaya A et al. 730. A Phase 3, randomized, double-blind, study to evaluate the efficacy and safety of ridinilazole compared with vancomycin for the treatment of *Clostridioides difficile* infection. Open Forum Infect Dis. 2022;9(Suppl 2) (http://dx.doi.org/10.1093/ofid/ofac492.021, accessed 19 January 2024).
5. Vickers RJ, Tillotson GS, Nathan R, Hazan S, Pullman J, Lucasti C et al. Efficacy and safety of ridinilazole compared with vancomycin for the treatment of *Clostridium difficile* infection: a Phase 2, randomised, double-blind, active-controlled, non-inferiority study. *Lancet* Infect Dis. 2017;17(7):735–44 (https://doi.org/10.1016/S1473-3099(17)30235-9, accessed 29 February 2024).
6. Green LS, Bullard JM, Ribble W, Dean F, Ayers DF, Ochsner UA et al. Inhibition of methionyl-tRNA synthetase by REP8839 and effects of resistance mutations on enzyme activity. Antimicrob Agents Chemother. 2009;53(1):86–94 (https://doi.org/10.1128/AAC.00275-08, accessed 29 February 2024).
7. Nayak SU, Griffiss JML, Blumer J, O'Riordan MA, Gray W, McKenzie R et al. Safety, tolerability, systemic exposure, and metabolism of CRS3123, a methionyl-tRNA synthetase inhibitor developed for treatment of *Clostridium difficile*, in a Phase 1 study. Antimicrob Agents Chemother. 2017;61(8): e02760-16 (https://doi.org/10.1128/AAC.02760-16, accessed 29 February 2024).
8. Ochsner UA, Bell SJ, O'Leary AL, Hoang T, Stone KC, Young CL et al. Inhibitory effect of REP3123 on toxin and spore formation in *Clostridium difficile*, and in vivo efficacy in a hamster gastrointestinal infection model. J Antimicrob Chemother. 2009;63(5):964–71 (https://doi.org/10.1093/jac/dkp042, accessed 29 February 2024).
9. Dalhoff A, Rashid MU, Kapsner T, Panagiotidis G, Weintraub A, Nord CE. Analysis of effects of MCB3681, the antibacterially active substance of prodrug MCB3837, on human resident microflora as proof of principle. Clin Microbiol Infect. 2015;21(8):767.e1–767.e4 (https://doi.org/10.1016/j.cmi.2015.05.025, accessed 29 February 2024).
10. Freeman J, Pilling S, Vernon J, Wilcox MH. In vitro activities of MCB3681 and eight comparators against *Clostridium difficile* isolates with known ribotypes and diverse geographical spread. Antimicrob Agents Chemother. 2017;61(3):e02077-16 (https://doi.org/10.1128/AAC.02077-16, accessed 29 February 2024).
11. Rashid MU, Dalhoff A, Weintraub A, Nord CE. In vitro activity of MCB3681 against *Clostridium difficile* strains. Anaerobe. 2014;28:216–9 (https://doi.org/10.1016/j.anaerobe.2014.07.001, accessed 29 February 2024).
12. Rashid MU, Dalhoff A, Bäckström T, Björkhem-Bergman L, Panagiotidis G, Weintraub A et al. Ecological impact of MCB3837 on the normal human microbiota. Int J Antimicrob Agents. 2014;44(2):125–30 (https://doi.org/10.1016/j.ijantimicag.2014.03.016, accessed 29 February 2024).
13. Xu WC, Silverman MH, Yu XY, Wright G, Brown N. Discovery and development of DNA polymerase IIIC inhibitors to treat Gram-positive infections. Bioorg Med Chem. 2019;27(15):3209–17 (https://doi.org/10.1016/j.bmc.2019.06.017, accessed 29 February 2024).

14. van Eijk E, Boekhoud IM, Kuijper EJ, Bos-Sanders IMJG, Wright G, Smits WK. Genome location dictates the transcriptional response to PolC inhibition in *Clostridium difficile*. Antimicrob Agents Chemother. 2019;63(2):e01363-18 (https://doi.org/10.1128%2FAAC.01363-18, accessed 29 February 2024).

15. Torti A, Lossani A, Savi L, Focher F, Wright GE, Brown NC et al. *Clostridium difficile* DNA polymerase IIIC: basis for activity of antibacterial compounds. Curr Enzym Inhib. 2011;7(3):147–53 (10.2174/157340811798807597, accessed 29 February 2024).

16. Murray B, Wolfe C, Marra A, Pillar C, Shinabarger D. In vitro activity of the novel antibacterial agent ibezapolstat (ACX-362E) against *Clostridioides difficile*. J Antimicrob Chemother. 2020;75(8):2149–55 (https://doi.org/10.1093/jac/dkaa134, accessed 29 February 2024).

17. Saxena D, Kaul G, Dasgupta A, Chopra S. Bacterial DNA polymerase IIIC inhibitor, treatment of *C. difficile* infection. Drugs Future. 2021;46(8):613.

18. Garey KW, Begum K, Lancaster C, Gonzales-Luna A, Bui D, Mercier J et al. A randomized, double-blind, placebo-controlled, single and multiple ascending dose Phase 1 study to determine the safety, pharmacokinetics and food and faecal microbiome effects of ibezapolstat administered orally to healthy subjects. J Antimicrob Chemother. 2020;75(12):3635–43 (https://doi.org/10.1093/jac/dkaa364, accessed 29 February 2024).

19. FDA accepts interim analysis plan for ongoing Phase 2b ibezapolstat clinical trial and Acurx announces presentations at ECCMID 2023 scientific conference. In: PR Newswire/News [website]. Chicago (IL): Cision; 2023 (https://www.prnewswire.com/news-releases/fda-accepts-interim-analysis-plan-for-ongoing-phase-2b-ibezapolstat-clinical-trial-and-acurx-announces-presentations-at-eccmid-2023-scientific-conference-301793186.html, accessed 12 January 2024).

20. Khalaf AI, Waigh RD, Drummond AJ, Pringle B, McGroarty I, Skellern GG et al. Distamycin analogues with enhanced lipophilicity: synthesis and antimicrobial activity. J Med Chem. 2004;47(8):2133–56 (https://doi.org/10.1021/jm031089x, accessed 29 February 2024).

21. Nieminen L, Lemonidis K, Browning D, Hunter I, Suckling C, Tucker N. Transcriptomic analysis indicates the mode of action of the novel antibiotic MGB-BP-3 against *Staphylococcus aureus*. Access Microbiol. 2019;1(1A) (https://doi.org/10.1099/acmi.ac2019.po0424, accessed 29 February 2024).

22. Hind C, Clifford M, Woolley C, Harmer J, McGee LMC, Tyson-Hirst I et al. Insights into the spectrum of activity and mechanism of action of MGB-BP-3. ACS Infect Dis. 2022;8(12):2552–63 (https://doi.org/10.1021/acsinfecdis.2c00445, accessed 29 February 2024).

23. MGB biopharma announces successful outcome from phase II clinical study with MGB-BP-3 – a potential new gold standard, first-line treatment for *Clostridium difficile* infection (CDI). In: MGB Biopharma/News [website]. Bellshill: MGB Biopharma; 2020 (https://www.mgb-biopharma.com/mgb-biopharma-announces-successful-outcome-from-phase-ii-clinical-study-with-mgb-bp-3-a-potential-new-gold-standard-first-line-treatment-for-clostridium-difficile-infection-cdi/, accessed 19 January 2024).

24. Ma Z, He S, Yuan Y, Zhuang Z, Liu Y, Wang H et al. Design, synthesis, and characterization of TNP-2198, a dual-targeted rifamycin-nitroimidazole conjugate with potent activity against microaerophilic and anaerobic bacterial pathogens. J Med Chem. 2022;65(6):4481–95 (10.1021/acs.jmedchem.1c02045, accessed 29 February 2024).

Annex 23. Non-traditional agents against CDI and *H. pylori*

Product name (INN or company code): IM-01

Pharmacology: chemical class and MoA: IM-01 is an egg-derived experimental polyclonal antibody targeting *C. difficile* toxin A, toxin B, spores and/or other virulent antigens responsible for the pathogenesis of CDI *(1)*.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)): A US patent filing for IM-01 states that its antibodies inhibited > 80% growth of three *C. difficile* isolates of hypervirulent NAP/B1/027 strains *(1)*. IM-01 is claimed to stimulate antibody production and cause toxin neutralization, reduction of spore burden, and inhibition of vegetative cell growth *(1)*.

Sought therapeutic indication: CDI in inflammatory bowel disease.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2:** To measure the clinical effectiveness of IM-01 for the treatment of mild-moderate CDI (NCT04121169, recruiting).

Study population: Consented adults 18–89-year-old, male or female, with CDI as per defined criteria (primary episode or relapse) in good general health (see full inclusion on clinicaltrials.gov).

  - **Primary outcome:** Clinical response to IM-01 treatment for CDI for 14 days, *C. difficile* pathogen count, spore count and *C. difficile* toxin titres in stool samples following IM-01 treatment.

Results: Of the 106 *C. difficile*-infected patients treated with IM-01, more than 94% showed improvement in clinical response, and negative stool test results were measured *(1)*. No relapse of the disease was reported during a 6-week follow-up period *(1)*.

Adverse effects / preclinical PK and safety: Results from a Phase 1 study (webpage data only).

Product name (INN or company code): SVT-1C469

Pharmacology: chemical class and MoA: SVT-1C469 is a live biotherapeutic product (LBP) *(2)*.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)): Servatus reports using a mix of bacterial strains claimed to inhibit pathogenic bacterial growth and modulate immune and inflammatory responses. No peer-reviewed data. Information only available on company website *(2)*.

Sought therapeutic Indication: *H. pylori* infection.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 1b

Clinical trial(s):

- **Phase 1:** A two-stage Phase 1 study to assess safety and efficacy of SVT-1C4610 as monotherapy for the treatment of *H. pylori* infection in otherwise healthy adults (ACTRN12620000923965, recruitment complete). Completed Stage 1 (n = 13) *(2)*: no results publicly available as yet.

Adverse events / preclinical PK and safety: Not yet publicly available.

Product name (INN or company code): VE303

Pharmacology: chemical class and MoA: VE303 is a first-in-class, live biotherapeutic product *(3)*.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)): VE303 comprises eight clonal human commensals belonging to *Clostridium* clusters IV, XIVa and XVII, associated with clinical response in faecal microbiota transplants (FMT) *(3,4)*. VE303 is reported to suppress *C. difficile* growth in vitro and improve survival in vivo *(4)*.

Sought therapeutic indication: Recurrent CDI.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2:** A randomized, placebo-controlled double-blind study to evaluate safety, tolerability, PK/PD and efficacy of VE303 in prevention of subsequent CDI-associated diarrhoea compared with placebo following completion of at least one successful course of SOC antibiotics (NCT03788434, completed September 2021).
  - **Study population:** 79 participants with a qualifying CDI episode who had a prior history of CDI diarrhoea (≥ 18 years of age) or first occurrence of CDI diarrhoea with a higher risk for recurrence (≥ 75 years of age, or ≥ 65 years of age with one or more prespecified conditions) starting within 30 days (see clinicaltrials.gov for full criteria). Participants were randomized into three arms in a 1:1:1 ratio of high-dose VE303, low-dose VE303 and placebo.
  - **Primary outcome:** CDI recurrence week 8.
  - **Results:** CDI recurrence rates through week 8 were 13.8% (4/29) for high-dose VE303, 37.0% (10/27) for low-dose VE303 and 45.5% (10/22) for placebo (P = 0.006, high-dose VE303 vs placebo) *(5)*.
- **Phase 1a/1b:** This Phase 1a/1b, first-in-human, open-label, single-centre, dose-escalation study aims to evaluate the safety and microbiota changes induced by ingestion of VE303 following administration of oral vancomycin and VE303 administered without vancomycin pre-treatment in healthy volunteers. Healthy volunteers (n = 23) received oral vancomycin 125 mg qid for 5 days followed by VE303 capsules at escalating single, then multiple doses (total dose range 1.6×10^9 to 1.1×10^{11} CFU) (NCT04236778, completed March 2019).
  - **Results:** VE303-related adverse events were mostly gastrointestinal, all grade 1 and transient in 35% of healthy volunteers. Colonization with VE303 strains was abundant, detected at 24 weeks and dose dependent *(4)*. VE303 expanded 10- to 100-fold, and each strain was detectable within 2 days after dosing. VE303 was found to enhance subjects' microbiota and metabolic recovery after vancomycin treatment *(4)*.

Product name (INN or company code): MET-2

Pharmacology: chemical class and MoA: MET-2 (microbial ecosystem therapeutic-2) is a stool-derived oral capsule with a consortium of 40 lyophilized commensal bacteria species *(6)*.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)): MET-2 represents several bacterial phyla cultured from the stool of an intensely screened, single healthy donor to eliminate any potential risks posed by changes in donor health via subsequent manufacturing, reportedly conferring safety benefits over traditional FMTs *(7)*. It is also being investigated in psychiatric indications, specifically depression and anxiety *(8)*. Non-clinical publicly available data are limited.

Sought therapeutic indication: Treatment of recurrent CDI.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 1

Clinical trial(s):

- **Phase 1:** An open-label, single-centre, multiple-dose pilot study of 19 patients, designed to measure the resolution of diarrhoea, and the feasibility of administration and safety of MET-2 for the treatment of recurrent CDI in patients who have experienced at least two prior episodes of CDI and have developed recurrence after having completed SOC oral antibiotic therapy to treat CDI (NCT02865616, completed March 2020).
- **Phase 1:** A Phase 1b, placebo-controlled, study of the safety and efficacy of MET-2 in 11 patients with ulcerative colitis (NCT03832400, completed March 2020).
- **Phase 1:** The safety, efficacy and tolerability of MET-2 in 60 people with major depression (NCT04602715, recruiting as of May 2021 update).
- **Phase 1:** The safety, efficacy and tolerability of MET-2 in 21 people with major depression and/or generalized anxiety disorder (NCT04052451, completed May 2020).

Adverse events: In its Phase 1 open-label trial (NCT02865616) at day 40, 79% of patients receiving MET-2 did not have recurrent CDI, which increased to 95% 40 days after receiving a second dose *(9)*. There were no serious adverse events or deaths *(9)*. At 130 days, 84% of patients did not have recurrent CDI. Stool analysis showed increased microbiota diversity and increased abundance of MET-2-containing bacteria during final analysis when compared with baseline *(6,9)*.

Product name (INN or company code): RBX7455

Pharmacology: chemical class and MoA: RBX7455 is a live biotherapeutic product manufactured from a microbiota-based suspension prepared from human stool.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)): RBX7455 is designed to rehabilitate the human microbiome by delivering a broad spectrum of live microbes into a patient's intestinal tract via a ready-to-use and easy-to-administer format *(10)*. RBX7455 and Rebyota (RBX2660, enema) baseline participant Microbiome Health Index values were similar among the trials *(10)*. It is also under study in paediatric Crohn's disease (NCT03378167) and hepatic encephalopathy (NCT04155099).

Sought therapeutic indication: Treatment of recurrent CDI.

Pharmaceutical form, route of administration: Oral capsules.

Phase of clinical development: 1

Clinical trial(s):

- **Phase 1:** To demonstrate the efficacy and safety of RBX7455 for the treatment of recurrent CDI in 30 subjects who have had at least one recurrence after a primary episode (i.e., at least two episodes) and have completed at least two rounds of SOC oral antibiotic therapy (NCT02981316, completed July 2020).

Adverse events and safety: 9 of 10 group 1 patients (90%), 8 of 10 group 2 patients (80%) and 10 of 10 group 3 patients (100%) were recurrence-free at the 8-week end-point with durability to 6 months *(11)*. There were no serious investigational product-related events. After treatment, responders' microbiomes showed increased Bacteroidia and Clostridia *(11)*.

Product name (INN or company code): SYN-004 (ribaxamase)

Pharmacology: chemical class and MoA: SYN-004 (ribaxamase) is a recombinant BLI enzyme orally administered with iv-administered β-lactams that degrades the excess of IV antibacterial agents in the proximal gastrointestinal tract, helping to preserve the gut microbiome *(12)*.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)): In in vitro studies, SYN-004 is reported to hydrolyse penicillins and cephalosporins *(12)*. In animal studies, SYN-004 was shown to degrade ceftriaxone in the gastrointestinal tract of dogs and protected the microbiome of pigs from ceftriaxone-induced changes *(12)*.

Sought therapeutic indication: SYN-004 is being investigated as therapy to mitigate predisposition to *C. difficile* in patients being treated with iv-administered β-lactams and in allogeneic haematopoietic cell transplantation (Allo-HCT) recipients.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 1/2:** Evaluation of the safety and tolerability of SYN-004 in 36 adult Allo-HCT recipients (NCT04692181, recruiting).
  - **Study population:** Consented male or female adults 18 years of age or older undergoing myeloablative allo-HCT for a haematologic malignancy or myeloproliferative disorder.
  - **Primary outcome:**
    - SYN-004 systemic absorption;
    - systemic antibiotic concentrations;
    - bacteraemia;
    - bacterial intestinal infections;
    - grade 3 or 4 adverse events; and
    - overall survival.
  - **Interim (poster) results:** No serious adverse events were attributable to SYN-004 *(13)*.
- **Phase 2:** A double-blind, placebo-controlled, multicentre study of SYN-004 compared to placebo for the prevention of *C. difficile* in 413 patients with a diagnosis of a lower respiratory tract infection (NCT02563106, completed November 2016).
  - **Study population:** Patients 50 years of age or older with clinical diagnosis of moderate-to-severe lower respiratory tract infection consisting of signs and symptoms of a lower respiratory tract infection and a pneumonia severity index (PORT) score for CAP of 90–130, inclusive (minimum hospital stay of 5 days and iv ceftriaxone > 5 days).
  - **Primary outcome:** Percentage of patients with CDI at 4 weeks of follow-up.
  - **Results:** For the period of study and 4 weeks after antibiotic treatment, two (1%) patients in the ribaxamase group and seven (3.4%) patients in the placebo group were diagnosed with an infection with *C. difficile* (risk reduction 2.4%,, 95% CI: −0.6 to 5.9; one-sided $P = 0{\cdot}045$) *(14)*. Researchers found that adverse events were similar between groups. More deaths were reported in the ribaxamase group (11 deaths vs five deaths in the placebo group) *(14)*.

Product Name (INN or company code): ADS024 (formerly ART24)

Pharmacology: chemical class and MoA: ADS024 (ART24) is an orally delivered single-strain live biotherapeutic product *(15)*.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.): The ADS024 cells were shown to kill *C. difficile* in vitro with limited impact on other commensal bacteria *(16)*. In addition to directly killing *C. difficile*, ADS024 also produces proteases capable of causing proteolytic cleavage of *C. difficile* toxins (TcdA, TcdB) *(15,16)*. In independent experiments, the lowest ratio of ADS024 : *C. difficile* CFU that resulted in *C. difficile* killing (> 3 log reduction in 24 h) was 275 : 1; lower ratios inhibited the growth rate of *C. difficile* without complete killing *(16)*. In a mouse model of CDI, oral gavage of ART24 cells demonstrated a protective effect with improved survival (90% in ART24-dosed groups vs 70% in the saline control group at day 10), and a reduction in disease-related clinical observations *(17)*.

Sought therapeutic indication: Being investigated for the prevention of recurrent CDI.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 1

Clinical trial(s):

- **Phase 1:** A randomized, placebo-controlled, double-blind study of ART24 in 36 subjects recently cured of CDI having completed an SOC course of CDI antibiotics (NCT04891965, completed October 2020).

Adverse events / preclinical PK and safety: Not yet publicly available.

Product name (INN or company code): MBK-01

Pharmacology: chemical class and MoA: MBK-01 is a heterologous lyophilized faecal microbiota from healthy donors (for FMT) acting through restoration of gut microbial diversity.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)): Modification of the microbiome to eliminate or prevent carriage of resistant or pathogenic bacteria. No data disclosed. Previous FMT studies with different products showed efficacy in preventing recurrent CDI *(18)*, and three FMT products were recently approved to prevent recurrence of CDI (see Table 1b of the report), whereas contrasting results were obtained for eradication of intestinal colonization by MDR pathogens *(19,20,21,22)*.

Sought therapeutic indications: Primary or recurrent CDI and eradication of intestinal colonization by CRE.

Pharmaceutical form, route of administration and proposed posology: A single dose of four capsules of MBK-01 orally.

Phase of clinical development: Phase 3 for the indication: primary or recurrent CDI; and Phase 2 (NCT04760665) for the indication: eradication of intestinal colonization by CREB.

Clinical trial(s):

- **Phase 3** (NCT05201079): A randomized, controlled, open-label clinical trial in patients with primary or recurrent CDI, to evaluate the efficacy and safety of capsules of lyophilized faecal microbiota vs fidaxomicin.
  - **Study population:** Adult patients who undergo an episode of CDI (either the first episode or subsequent recurrences), with an episode of diarrhoea defined as ≥ 3 stools/24 h, at the beginning of the episode and confirmation of the presence of *C. difficile* toxin A and/or B in faeces, by a direct toxin detection test or by the polymerase chain reaction (PCR) technique for detection of toxin-producing genes, at the start of the episode that is going to be treated in the clinical trial (the toxin test must be positive within 7 days prior to enrolment of the patient in the trial).

Product name (INN or company code): MBK-01 (continued)

- **Time period:** October 2021 to June 2023.
- **Sites:** 21 sites in Spain.
- **Primary end-point:** Absence of diarrhoea. Number of episodes of diarrhoea (three or more stools/24 h) observed with different time frames:
  - 8 weeks after the start of the treatment;
  - 72 h after the start of the treatment;
  - 3 weeks after the start of the treatment;
  - 3 months after the start of the treatment; and
  - 6 months after the start of the treatment.

Diarrhoea resolution: < 3 stools/24 h for at least two consecutive days after the end of the treatment.

- **Phase 2 clinical trial against CREB** (NCT04760665): The KAPEDIS trial is a single-centre, randomized, superiority, double-blind controlled with placebo clinical trial, to demonstrate the effectiveness of faecal microbiota transplantation for selective intestinal decolonization of patients colonized by KPC-producing *K. pneumoniae* (KPC-Kp) *(23)*.
  - **Study population:** 120 patients with a positive rectal swab for KPC-Kp within 1 week before randomization, with absence of active infection by KPC-Kp at the time of assessment as well as in the month prior to inclusion in the study, will be randomized 1:1 to receive encapsulated lyophilized FMT or placebo *(23)*.
  - **Time period:** October 2021 to September 2024.
  - **Sites:** Spain, number of sites not specified.
  - **Primary end-point:** Percentage of patients with intestinal decolonization at 30 days after FMT. Decolonization will be considered as the absence of isolation of KPC-Kp in culture from rectal swab together with the absence of detection of carbapenemase by means of PCR.
  - **Primary efficacy evaluation** will be performed in the ITT population (all randomized patients).

Product name (INN or company code): NTCM-M3 (VP20621)

Pharmacology: chemical class and MoA: NTCD-M3 is a naturally occurring non-toxigenic strain of *C. difficile* which lacks the genes that can express *C. difficile* toxins *(24)*.

Spectrum of activity: activity on pathogens)confirmed or potential (in vitro, in vivo, animal model, etc.)): Limited publicly available non-clinical data. Phase 2 trial topline results below.

Sought therapeutic indication: Prevention of recurrent CDI.

Pharmaceutical form, route of administration: Oral.

Phase of clinical development: 2

Clinical trial(s):

- **Phase 2:** Randomized, double-blind, placebo-controlled, dose-ranging study to assess the safety and efficacy of VP20621 for prevention of recurrence of CDI in 173 adults previously treated for CDI (NCT01259726, completed 2013).
  - **Study population:** Patients were randomly assigned to receive one of four treatments: oral liquid formulation of NTCD-M3, 10*(4)* spores/day for 7 days ($n = 43$), 10^7 spores/day for 7 days ($n = 44$), or 10^7 spores/day for 14 days ($n = 42$) or placebo for 14 days ($n = 44$).

Product name (INN or company code): NTCM-M3 (VP20621) (continued)

- **Primary outcome:** Safety and tolerability of NTCD-M3 within 7 days of treatment. Exploratory secondary outcomes included faecal colonization with NTCD-M3 from last dose of study drug through week 6 and CDI recurrence from day 1 through week 6.
- **Results:** Among 168 patients who started treatment, 157 completed treatment *(25)*. Serious treatment-emergent adverse events were reported in 7% of patients receiving placebo and 3% of all patients who received NTCD-M3. Faecal colonization occurred in 69% of NTCD-M3 patients. Furthermore, recurrence occurred in two (2%) of 86 patients who were colonized vs 12 (31%) of 39 patients who received NTCD-M3 and were not colonized (OR, 0.01; 95% CI: 0.00–0.05; $P < .001$) recurrent CDI rates were lower in the treatment group vs. the placebo group at all doses.
- **Adverse effects and safety:** Among patients who recovered from CDI with metronidazole or vancomycin treatment, oral administration of NTCD-M3 spores was well tolerated, safe and effectively reduced CDI recurrence by colonizing the gastrointestinal tract *(25)*.

- **Phase 3:** According to the company website *(24)*, a single, randomized, double-blind, placebo-controlled Phase 3 clinical study, with agreed end-points, target CDI patient population, NTCD-M3 oral dosing regimen and patient numbers is being planned.

Product name (INN or company code): LMN-201

Pharmacology: chemical class and MoA: LMN-201 is a combination of a *C. difficile* targeting phage-derived endolysin and three toxin-binding proteins (5D, E3 and 7F) that all bind to *C. difficile* virulence mediator TcdB2 by different mechanisms *(26)*.

Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)): LMN-201 is reported to be 300- to 3000-fold more potent than bezlotoxumab, enhanced by a phage-derived endolysin that destroys the bacterium *(26)*.

Sought therapeutic indication: LMN-201 is intended to be administered concomitantly with antibiotics and for 8 weeks thereafter to provide protection from *C. difficile* reinfection while commensal bacteria recolonize the gastrointestinal tract *(27)*.

Pharmaceutical form, route of administration: Oral capsules.

Phase of clinical development: 2/3

Clinical trial(s):

- **Phase 1:** Exploratory study to assess delivery of LMN-201 components via enteric capsules in the gut of 12 individuals with ostomies (NCT04893239, completed February 2022).
- **Phase 2/3:** Randomized, double-blind, placebo-controlled study of LMN-201 for prevention of *C. difficile* infection recurrence. A multisite study to evaluate the safety, tolerability and efficacy of LMN-201 in 375 participants recently diagnosed with CDI who are scheduled to receive or are receiving SOC antibiotic therapy against *C. difficile* (NCT05330182, not yet recruiting).
  - **Study population:** Consented adults 18 years old or older, male or female, with a diagnosis of CDI who are scheduled to receive or planning to receive a ≤ 28-day course of SOC antibiotic therapy for CDI (see clinicaltrials.gov for full criteria).
  - **Primary outcome measure:** Proportion of participants who achieve global cure.

Adverse events / preclinical PK and safety: Not yet publicly available.

References

1. Maiti PK. Use of polyclonal antibodies against *Clostridium difficile* for treatment of inflammatory bowel disease. US Patent 20180362618A1; 2017 (https://patents.google.com/patent/US10513552B2/en, accessed 19 January 2024).
2. Our research. In: Servatus Biopharmaceuticals/ Research [website]. Coolum Beach: Servatus Biopharmaceuticals; 2024 (https://servatus.com.au/our-research/, accessed 19 January 2024).
3. VE303. In: Vendata Biosciences/Pipeline [website]. Cambridge (MA): Vedanta Biosciences; 2024 (https://www.vedantabio.com/pipeline/ve303, accessed 19 January 2024).
4. Bobilev D, Bhattarai S, Menon R, Klein B, Reddy S, Olle B et al. 1953. VE303, a rationally designed bacterial consortium for prevention of recurrent *Clostridioides difficile* (*C. difficile*) infection (rCDI), stably restores the gut microbiota after vancomycin (vanco)-induced dysbiosis in adult healthy volunteers (HV). Open Forum Infect Dis. 2019;6(Suppl 2):S60 (https://doi.org/10.1093/ofid/ofz359.130, accessed 29 February 2024).
5. Louie T, Golan Y, Khanna S, Bobilev D, Erpelding N, Fratazzi C et al. VE303, a defined bacterial consortium, for prevention of recurrent *Clostridioides difficile* infection: a randomized clinical trial. JAMA. 329(16):1356–66 (https://doi.org/10.1001/jama.2023.4314, accessed 29 February 2024).
6. Gawey BJ, Khanna S. *Clostridioides difficile* infection: landscape and microbiome therapeutics. Gastroenterol Hepatol (N Y). 2023;19(6):319–28.
7. Carlucci C, Jones CS, Oliphant K, Yen S, Daigneault M, Carriero C et al. Effects of defined gut microbial ecosystem components on virulence determinants of *Clostridioides difficile*. Sci Rep. 2019;9(1):885 (https://doi.org/10.1038/s41598-018-37547-x, accessed 29 February 2024).
8. Chinna Meyyappan A, Milev R. The safety, efficacy, and tolerability of microbial ecosystem therapeutic-2 in people with major depression and/or generalized anxiety disorder: protocol for a Phase 1, open-label study. JMIR Res Protoc. 2020;9(6):e17223 (https://doi.org/10.2196/17223, accessed 29 February 2024).
9. Kao D, Wong K, Franz R, Cochrane K, Sherriff K, Chui L et al. The effect of a microbial ecosystem therapeutic (MET-2) on recurrent *Clostridioides difficile* infection: a Phase 1, open-label, single-group trial. Lancet Gastroenterol Hepatol. 2021;6(4):282–91 (https://doi.org/10.1016/S2468-1253(21)00007-8, accessed 29 February 2024).
10. Blount K, Jones C, Khanna S, Deych E, Shannon B. A prototype biomarker for microbiome rehabilitation in patients with *clostridium difficile* infections: application to a clinical trial of a lyophilized, non-frozen, oral, microbiota-based drug RBX7455. In: Rebiotix [website]. Roseville (MN): Rebiotix; n.d. (https://www.rebiotix.com/wp-content/uploads/prototype-biomarker-microbiome-rehabilitation-clostridium-difficile-infections-drug-rbx7455-poster.pdf, accessed 18 January 2024).
11. Khanna S, Khanna S, Pardi DS, Jones C, Shannon WD, Gonzalez C et al. RBX7455, a nonfrozen, orally administered investigational live biotherapeutic, is safe, effective, and shifts patients' microbiomes in a Phase 1 study for recurrent *Clostridioides difficile* infections. Clin Infect Dis. 2020;73(7):e1613–20 (https://doi.org/10.1093/cid/ciaa1430, accessed 29 February 2024).
12. Kaleko M, Bristol JA, Hubert S, Parsley T, Widmer G, Tzipori S et al. Development of SYN-004, an oral beta-lactamase treatment to protect the gut microbiome from antibiotic-mediated damage and prevent *Clostridium difficile* infection. Anaerobe. 2016;41:58–67 (10.1016/j.anaerobe.2016.05.015, accessed 29 February 2024).
13. Schroeder MA, Sappington H, Martin E, Reske KA, Teuscher V, Bristol A et al. Interim analysis of Syn-004 phase 1b/2a trial in hematopoietic cell transplant (HCT) recipients. Presented at the Tandem Meetings of the ASTCT and CIBMTR, Orlando, FL, USA, 15–19 February 2023; Poster LBA6 (https://tandem.confex.com/tandem/2023/meetingapp.cgi/Paper/22389, accessed 19 January 2024).
14. Kokai-Kun JF, Roberts T, Coughlin O, Le C, Whalen H, Stevenson R et al. Use of ribaxamase (SYN-004), a β-lactamase, to prevent *Clostridium difficile* infection in β-lactam-treated patients: a double-blind, Phase 2b, randomised placebo-controlled trial. Lancet Infect Dis. 2019;19(5):487–96 (10.1016/S1473-3099(18)30731-X, accessed 29 February 2024).

15. Adiso Therapeutics announces completion of enrollment in a Phase 1b study of ADS024 for the prevention of *C. difficile* recurrence, April 2022. In: PR Newswire/News [website]. Chicago (IL): Cision; 2022 (https://www.prnewswire.com/news-releases/adiso-therapeutics-announces-completion-of-enrollment-in-a-phase-1b-study-of-ads024-for-the-prevention-of-c-difficile-recurrence-301529450.html, accessed 12 January 2024).

16. O'Donnell MM, Hegarty JW, Healy B, Schulz S, Walsh CJ, Hill C. et al. Identification of ADS024, a newly characterized strain of Bacillus velezensis with direct Clostridiodes difficile killing and toxin degradation bio-activities. Sci Rep. 2022;12(1):9283 (https://doi.org/10.1038/s41598-022-13248-4, accessed 29 February 2024).

17. Murphy C, Murphy T, Farquhar R, Chesnel L, Artugen Therapeutics. ART24, a novel live biotherapeutic product in development for the prevention of CDI recurrence, is effective in a mouse model of CDI infection 2020. In: Artugen Therapeutics [website].

18. Allegretti JR, Mullish BH, Kelly C, Fischer M. The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. Lancet. 2019;394(10196):420–31 (https://doi.org/10.1016/S0140-6736(19)31266-8, accessed 29 February 2024).

19. Dinh A, Fessi H, Duran C, Batista R, Michelon H, Bouchand F et al. Clearance of carbapenem-resistant Enterobacteriaceae vs vancomycin-resistant enterococci carriage after faecal microbiota transplant: a prospective comparative study. J Hosp Infect. 2018;99(4):481–6 (https://doi.org/10.1016/j.jhin.2018.02.018, accessed 29 February 2024).

20. Saïdani N, Lagier JC, Cassir N, Million M, Baron S, Dubourg G et al. Faecal microbiota transplantation shortens the colonisation period and allows re-entry of patients carrying carbapenemase-producing bacteria into medical care facilities. Int J Antimicrob Agents. 2019;53(4):355–61 (https://doi.org/10.1016/j.ijantimicag.2018.11.014, accessed 29 February 2024).

21. Huttner BD, de Lastours V, Wassenberg M, Maharshak N, Mauris A, Galperine T et al. A 5-day course of oral antibiotics followed by faecal transplantation to eradicate carriage of multidrug-resistant Enterobacteriaceae: a randomized clinical trial. Clin Microbiol Infect. 2019;25(7):830–8 (https://doi.org/10.1016/j.cmi.2018.12.009, accessed 29 February 2024).

22. Seong H, Lee SK, Cheon JH, Yong DE, Koh H, Kang YK et al. Fecal microbiota Transplantation for multidrug-resistant organism: efficacy and Response prediction. J Infect. 2020;81(5):719–25 (https://doi.org/10.1016/j.jinf.2020.09.003, accessed 29 February 2024).

23. Pérez-Nadales E, Cano Á, Recio M, Artacho MJ, Guzmán-Puche J, Doblas A et al. Randomised, double-blind, placebo-controlled, Phase 2, superiority trial to demonstrate the effectiveness of faecal microbiota transplantation for selective intestinal decolonisation of patients colonised by carbapenemase-producing *Klebsiella pneumoniae* (KAPEDIS). BMJ Open. 2022;12(4):e058124 (https://doi.org/10.1136/bmjopen-2021-058124, accessed 29 February 2024).

24. NTCD-M3 – prevention of *C. difficile* infection recurrence. In: DestinyPharma/Pipeline [website]. Brighton: Destiny Pharma; 2024 (https://www.destinypharma.com/pipeline/ntcd-m3/#, accessed 12 January 2024).

25. Gerding DN, Meyer T, Lee C, Cohen SH, Murthy UK, Poirier A et al. Administration of spores of nontoxigenic *Clostridium difficile* strain M3 for prevention of recurrent *C. difficile* infection: a randomized clinical trial. JAMA. 2015;313(17):1719–27 (https://doi.org/10.1001/jama.2015.3725, accessed 29 February 2024).

26. Zhao H, Dodds M, Tasch M, Gewe M, Martinez A, Hutton M et al. Using synthetic activity to design ultra-potent antibody cocktails. bioRxiv. 2021.12.21.473715 (https://doi.org/10.1101/2021.12.21.473715, accessed 29 February 2024).

27. Lumen Bioscience receives fast track designation from U.S. FDA for LMN-201. In: Lumen Bioscience/News [website]. Seattle (WA): Lumen Bioscience; 2023 (https://www.lumen.bio/news/lumen-bioscience-receives-fast-track-designation-us-fda-lmn-201, accessed 19 January 2024).

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