26 March 2015
EMA/CHMP/186699/2015
Committee for Medicinal Products for Human Use (CHMP)

Tamiflu

International non-proprietary name: OSELTAMIVIR

Procedure No. EMEA/H/C/000402/II/0110/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ε	epsilon, NONMEM residual error
η	eta, NONMEM inter-individual error
θ	theta, NONMEM fixed effect parameter
ω^2	omega^2, inter-individual variance
σ^2	sigma^2, residual variance
σ_{add}	Standard deviation (additive)
σ_{prop}	Standard deviation (proportional)
Σ	SIGMA, residual covariance matrix
Ω	OMEGA, inter-individual covariance matrix
AE	Adverse Event
ADR	Adverse Reaction
AUC	Area under the curve
BID	Twice daily (bis in die)
BLQ	Below the limit of quantification
CASG	Collaborative Antiviral Study Group
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL	Clearance (of oseltamivir phosphate)
CL/F	Apparent oral clearance (of oseltamivir phosphate)
CLM	Clearance of oseltamivir carboxylate
CLM/F	Apparent oral clearance (of oseltamivir carboxylate)
Cmax	Maximum concentration
Cmean	Mean concentration
Cmedian	Median concentration
Cmin	Minimum concentration
CNS	Central nervous system
CSR	Clinical Study Report
CV	Coefficient of variation
CV%	Percent coefficient of variation
DSR	Drug Safety Report
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HA	Haemagglutinin
HCE1	Human carboxylesterase 1
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IIV	Inter-individual variability
IPRED	Individual predicted value
ITT	Intent-to-treat
ITTI	Intent-to-treat-infected (with influenza)
i.v.	intravenous
IWRES	Individual weighted residuals
K	Elimination rate constant
KA	Absorption rate constant
Kij	Inter-compartment (from i to j) rate constant
LEG	Legally binding measure
MA	Marketing authorisation
MAH	Marketing Authorisation Holder
MoA	Mechanism of action
N.A.	Not applicable
NA	Neuraminidase
NAI	Neuraminidase Inhibitor
NCA	Non compartmental analysis

NICU	Neonatal intensive care unit
NIH	National Institute of Health
NPDE	Normalized prediction distribution error(s)
OC	Oseltamivir carboxylate
OD	Omne in die (once a day)
OFV	Objective function value
OP	Oseltamivir (phosphate)
PBPK	Physiologically based pharmacokinetics
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PD	Pharmacodynamic
PDCO	Paediatric Committee
%RSE	Percent relative standard error
%SE	Percent standard error
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PK	Pharmacokinetic
PRED	Population predicted value
PStc	Permeability–Surface Area product of tissue cellular membrane
PT	Preferred Term
RNA	Ribonucleic acid
RSE	Relative standard error
SAB	Safety Advisory Board
SAE	Serious Adverse Event
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
SPC	Summary of Product Characteristics
SVPC	Standardized visual predictive check
TCID50	50% tissue culture infective dose
V2/F	Oseltamivir apparent central volume
V3/F	Oseltamivir apparent peripheral volume
VM/F	Oseltamivir carboxylate apparent volume
VPC	Visual (posterior) predictive check

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd submitted to the European Medicines Agency on 9 July 2014 an application for a group of variations.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name**
Tamiflu	oseltamivir

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
B.IV.1.a.1	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IAin	I, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of the indication to include the treatment of influenza in infants below one year of age. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC. The Package Leaflet was proposed to be updated in accordance.

In addition, the MAH applied for a variation type IAIN to add a 3 ml plastic oral dispenser (for the Tamiflu 6mg/ml strength).

The group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) PIP/0062/2014 on the agreement of a paediatric investigation plan (PIP)

At the time of submission of the application, the PIP PIP/0062/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Bruno Sepodes

Timetable	Actual dates
Rapporteur's preliminary assessment report circulated on	15 September 2014
CoRapporteur's preliminary assessment report circulated on	25 September 2014
PRAC Rapporteur Assessment Report	25 September 2014
PRAC Rapporteur Updated Assessment Report	1 October 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	9 October 2014
Rapporteur Revised Assessment Report	16 October 2014
Request for supplementary information (RSI)	23 October 2014
PRAC and CHMP Rapporteurs Joint Assessment Report on MAH responses	3 March 2015
CHMP Opinion	26 March 2015

2. Scientific discussion

2.1. Introduction

Oseltamivir phosphate (OP) is an ethyl ester prodrug rapidly absorbed from the gastrointestinal tract after oral administration and metabolised to oseltamivir carboxylate (OC), a potent, stable and selective inhibitor of influenza A and B neuraminidase enzymes. Oseltamivir was granted marketing approval in Switzerland and the United States in 1999 and in the European Union in 2002. It is currently approved and marketed as Tamiflu in many countries worldwide for the treatment and prophylaxis of influenza in healthy adults and children aged 1 year and older. In the US, oseltamivir is indicated for the treatment of influenza in patients 2 weeks of age and older, and for influenza prevention in patients 1 year and older.

The first approved formulations in the EU were Tamiflu capsule (hard, 75 mg) and powder for oral suspension (12 mg/ml). Subsequently other formulations have been approved in 2007: capsule, hard, 30 mg and 45 mg, and powder for oral suspension, 6 mg/ml.

The currently approved indications for oseltamivir in the EU are:

Treatment of influenza

- *In patients one year of age and older who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms. This indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A (see section 5.1).*
- *Tamiflu is indicated for the treatment of infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).*
- *The treating physician should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure there is a potential benefit to the child.*

Prevention of influenza

- *Post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.*
- *The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.*
- *Tamiflu is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).*

(…) The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. (…)

In the initial EU MA granted to oseltamivir in May 2002, the indication for prevention of influenza was limited to adults and adolescents 13 years of age or older. In January 2006, the indication for prevention of influenza was extended to cover also children of 1–12 years of age (based on study WV16193). In response to the A/H1N1 pandemic in 2009, several Health Authorities, including the CHMP, the US Food and Drug Administration (FDA) and Centres for Disease Control (CDC), issued emergency dosing guidelines for infants aged less than 1 year based on provisional analyses of PK and safety data from the Collaborative Antiviral Study Group clinical trial CASG114 (Roche Study n. WP20749: Open-label, non-randomised, PK/PD and safety trial to evaluate oseltamivir in children less than 24 months of age with confirmed influenza infection).

In the EU, in September and October 2009 respectively, the Tamiflu indication was extended to include treatment of children between 6 and 12 months of age (Variation II/0068), and treatment of children between 0 and 6 months of age and prophylaxis of children less than 1 year of age (Variation II/0070) in case of an influenza pandemic. The recommended dosage for treatment was at that time estimated between 2 to 3 mg per kg of body weight twice daily, and the recommended dosage for prophylaxis was estimated between 2 to 3 mg per kg of body weight once daily and drug administration should not exceed 10 days. Of note, the dosing recommendation adopted in 2009 for children less than 1 year of age was based on limited data, i.e. interim analysis of CASG114. The protocol of the European study WP22849 was approved by CHMP and PDCO in August 2009 to investigate further the optimal dosage especially in the youngest age group (0-2 months). Within the renewal of the Tamiflu MA in 2012, interim results of CASG114 indicated that the doses recommended in the SmPC for infants and small children may be lower than those demonstrated adequate in the study.

As a post-authorisation measure (MEA 091.1), the MAH was requested to finalize and analyse studies CASG114 and WP22849 in order to refine the posology for infants and small children. The current variation is the result of this post-authorisation measure. As outcome of MEA 091.1, based on the discussions with the

PDCO, the CHMP requested the MAH to submit a type II variation application not later than September 30 2013 to include in the indication treatment of influenza in infants <1 year of age in a non-pandemic situation and to consider the update of the dosage regimen for infants, which is what the current application is covering. The proposed indication should include the use of Tamiflu for the treatment of influenza in infants below 1 year of age, with dosing regimen 3 mg/kg twice daily for 5 days. The indication regarding prophylaxis use of Tamiflu was not proposed to be modified, due to lack of data.

In line with the Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004), the approach taken to support this application is to extrapolate efficacy between adults and paediatric age groups and between different paediatric age groups based on PK data, relying on the consideration that similar levels of exposure can be assumed to induce similar levels of efficacy in different age groups.

The application is thus supported by two studies in infants <1 year of age, CASG114 and WP22849, and by subsequent population PK modelling and simulation analyses, with the aim of determining the PK, PD, and safety of oseltamivir. The current authorised formulation 6 mg/ml powder for oral suspension is the preferred strength for dosing the entire paediatric population, including infants below 1 year of age.

The type II extension of indication has been grouped with a variation IA_{IN} that covers the addition of a 3 ml dispenser in the outer carton of Tamiflu 6 mg/ml, since it is considered a consequential change of the requested extension of indication in infants below 1 year of age to enable adequate dosing in this paediatric subgroup.

2.2. Non-clinical aspects

2.2.1. Introduction

The non-clinical data presented by the MAH in support of this variation aimed at investigating the toxicology of oseltamivir in juvenile rats and the pharmacokinetics in juvenile rats and marmosets.

2.2.2. Pharmacology

This variation application concerns an age group that is highly vulnerable to influenza morbidity and mortality. OC is a specific inhibitor of the influenza A and B neuraminidase with a high degree of selectivity and antiviral potency (in vitro IC50 ~0.3–9 nM) and with little or no activity against other viral, bacterial, or mammalian neuraminidases. Administered orally as a prodrug, OP, OC has already been shown to be efficacious in a number of animal models (mice, ferrets and chickens). In addition, there is no scientific evidence in humans suggesting that the pharmacology or mode of action of oseltamivir would be any different in individuals <1 year of age compared to older age groups.

2.2.3. Pharmacokinetics

A cross-species comparison of the absorption and disposition of OP and OC was performed for previous applications in mice, rats, rabbits, dogs, ferrets and marmosets to provide a good basis for the safety assessment of the compounds. Single and repeat dose pharmacokinetic data have been obtained for the mouse, rat, rabbit, dog, ferret, and marmoset, the species used for the evaluation of the drug's safety and efficacy profiles, either as part of the main studies or in separate experiments run under similar conditions. The kinetic and metabolic profiles obtained from these studies indicate that human exposure to both the parent drug and its metabolite is suitably covered by the animal toxicity studies.

In addition to the existing pharmacokinetic data following IV and oral administration, a pharmacokinetic study in juvenile and adult marmoset monkeys has been performed to further expand the non-clinical safety package in support of the proposed indication. PBPK modelling using these data has been performed and verified to bridge nonclinical to clinical data and adult data to infant data, and further supports the safety margin calculations.

Studies in rats

High plasma and brain exposures of oseltamivir have been observed in 7-day old juvenile rats following oral administration of single doses of 300 to 1000 mg/kg of oseltamivir. A 4-fold higher plasma OP Cmax has been seen in juvenile rats as compared to adults. To follow-up on the unscheduled deaths observed after oral treatment with oseltamivir in 7-day old rats at doses higher than 500 mg/kg, a subsequent s.c. dosing study up to 50 mg/kg of OC was performed in rats of the same age. This resulted in maximum plasma and brain OC levels that exceeded levels observed in the previous study but no induction of adverse effects, toxicity, or mortality was observed.

The results of these studies confirmed the association between high exposures of the prodrug OP to major toxicity including mortality identified thus far in juvenile rats, but this association is not evident for the active neuraminidase inhibitor OC. The higher OP levels in juvenile rats were considered as a consequence of the lower metabolic turn-over due to age-dependent enzyme activity, which has been described in different species including humans to affect the hydrolysis of OP to OC, and of a lower renal clearance. In addition, an immature blood-brain barrier may have resulted in higher brain/plasma exposures.

Studies in marmosets

The marmoset is a better pharmacokinetic model for humans than the rat, as it converts OP to OC in the liver, rather than in plasma, and does not form any additional metabolites of the prodrug. In very young marmosets (2 to 4 days old) at the 10 mg/kg oseltamivir oral dose, 8 to 12 folds higher plasma OP Cmax and 6 to 22 folds higher plasma OC Cmax were seen in juveniles compared with adults. Also, a lower renal clearance was found in juveniles compared to adults.

A reduced rate of conversion of OP to OC observed in neonatal rats and marmosets is related to the expression of developmentally regulated carboxylesterases. However, even in very young marmosets, the active metabolite OC was generated in therapeutically relevant concentrations in plasma. The ratios of OP:OC have been lower in neonates than in adults, even though the in vitro data have suggested reduced carboxylesterase activity in the new-borns.

Across all species tested, high concentrations of radioactivity have been detected in the gastrointestinal tract, kidney and liver after oral administration of radioactive oseltamivir. Following an oral dose, both the prodrug and active metabolite crosses the blood-brain barrier, the former to a greater extent. The distribution of the drug-related material to the brain is generally limited. Higher brain/plasma ratios of OP observed in the 7 day old rats as compared to the adult rats are thought to be due to immature physiological processes. A concern of high CNS exposure to oseltamivir in relation to toxicity, including mortality, has been raised before. Markedly increased concentrations of the OP in brain were seen in new-born rats in earlier studies; later a calculation error was identified in this study that had resulted in an overestimation of the concentrations of both OP and OC in brain and plasma samples. The studies with 7-day old juvenile rats (which are roughly equivalent in maturity to the human newborn) have shown ~8-fold higher brain OP Cmax exposures as compared with the adult rats, and ~4-fold higher plasma Cmax.

Similarly, the higher prodrug and drug brain/plasma AUC ratios in juvenile rats vs. adult rats was detected as being still <1 for OP and <0.1 for OC. It is not known if the porosity of the blood-brain barrier to OP and OC in 7 day old rats is similar to that of human infants. There is a body of evidence indicating that the blood-brain barrier is structurally intact in the developing brain, although some differences in expression of

transporters may be evident, relative to adults. Thus far, the clinical studies in <1 year old children treated with Tamiflu, albeit small in size, have revealed no new safety concerns, including no CNS-related issues.

PBPK modelling and safety margins for clinical data in infants in comparison to juvenile preclinical data

A physiologically based pharmacokinetic (PBPK) model was generated to bridge preclinical to clinical data and adult data to infant data, and to further support the safety margin calculations. The individual PK parameters of the 122 subjects of infants less than 1 year (analysis data set pooled from the studies CASG 114 and WP22849) were analysed. From across the age strata sub-groups (0-1 month, 1-3 months, 3-6 months, 6-9 months and 9-12 months), the highest simulated exposures for OP and OC were identified, and used to calculate the safety margins in comparison to juvenile data from preclinical studies (Table 1). The safety margins in infants (for oral dosing) for OP Cmax were 55x as compared to juvenile marmosets data and 83x as compared to juvenile rats data (at NOAEL dose).

In addition, after i.v. delivery of oseltamivir the projected safety margins for OP Cmax in infants was 83x compared with data in juvenile marmosets. These seem adequate to support a low safety concern profile in infants aged less than 1 year. The safety margins for OC were 25x compared with Cmax in juvenile marmosets after oral delivery and 8x after i.v. delivery of oseltamivir, and 14x compared with juvenile rats. These seem acceptable, especially considering that toxicity in juvenile animals have been related to OP and not to OC. The projected safety margins in infants for AUC were > 40,000x (and 22,000x after i.v. dosing) when compared to data in juvenile marmosets, and 120x in comparison to juvenile rats. For OC, the margins for AUC were > 14,000x compared to juvenile marmosets and 11x compared to juvenile rats.

Table 1. Safety margins calculated by the MAH from nonclinical data compared to the simulated steady state exposures following 3mg/kg BID in infants <1 year of age1

Species [Ref. no.]	Route; duration	Age in Days	NOAEL (mg/kg)	Plasma C_{max} (ng/mL)		Plasma AUC_{0-24h} (µg.h/mL)		Safety Margin C_{max}		Safety Margin AUC	
Juveniles				**OP**	**OC**	**OP**	**OC**	**OP**	**OC**	**OP**	**OC**
Rat [116]	Oral; 2 weeks	20	500	16,600	10,100	59	71.2	200	15	187	11
Rat [117]	Oral; 4 weeks	48	500	6880	15,400	37.9	103	83	23	120	16
Rat [46]	Oral; single dose	7	1000	55,870	26,200	676	336	673	39	2139	53
		14	1000	66,900	142,000	352	752	806	214	1114	118
		24	1000	15,200	31,000	156	430	183	47	494	68
		42	1000	8630	45,200	79.6	507	104	68	252	80
Rat [45]	Oral; single dose	7	394	42,400	9380	410	139	511	14	1297	22
		42	1314	11,500	38,400	82.7	467	139	58	262	73
Rat [85]	SC; single dose	7	50		88,900		152		134		24
Marmoset [54] (all single dose)	Oral (Males)	–	10	7130	19000	17800	89900	86	29	56329	14129
	Oral (Females)	–	10	4590	16900	12900	83600	55	25	40823	13138
	IV (Males)	–	5	6890	5280	7100	25600	83	8	22468	4023
	IV (Females)	–	5	8780	5020	7480	22500	106	8	23671	3536
Infants <1 yr				**83**	**664**	**0.316**	**6.363**				

[1] Simulated median exposure data in infants less than 1 year of age dosed 3 mg/kg BID extracted from the Oseltamivir Simulation Report. Table reports margins derived from median model-predicted (Individual Simulation Method) values for oseltamivir (OP) and OC steady-state AUC_{0-tau} and C_{max} from the most conservative under 1 sub-group (oseltamivir C_{max} = 83 ng/mL, AUC = 0.316 µg*h/mL from infants 9-12 months; OC C_{max} = 664 ng/mL, AUC = 6.363 µg*h/mL from infants 0-1month).

OC, oseltamivir carboxylate; OP, oseltamivir phosphate/oseltamivir; BID, twice daily; SC, subcutaneous; IV, intravenous.

2.2.4. Toxicology

Single dose and repeat toxicity

The pre-clinical safety of OP and OC has been tested extensively in *in vitro* and *in vivo* pre-clinical toxicity studies. The main *in vivo* studies include single-dose and repeat-dose toxicity studies in rats for up to 27 weeks and marmosets for up to 39 weeks via the oral route of administration. Toxicity and pharmacokinetic

studies in juvenile rats include oral and s.c. administrations, and single and (oral) repeat-dose studies of up to 28 days duration. Toxicity studies are conducted in 7-day old juvenile rats, which could be considered comparable to human preterm new-borns in terms of metabolic and pharmacokinetic factors, and of CNS and immune system development. Pharmacokinetics has been studied in very young (2–4 days old) marmosets. In addition, pre- and postnatal development studies have been conducted in rats and rabbits.

The toxicology program demonstrated only few significant adverse findings in adult animals, which were observed mainly in rats, mice, and marmosets at systemic concentrations and exposures above those measured in human adults for both OP and OC. The target organs identified for toxicity were gastrointestinal system, kidneys, and bones. In addition, juvenile rats were shown to be more sensitive to OP toxicity (the toxicity profiles are similar in adult and juvenile rats). There has been no evidence that oseltamivir would have mutagenic or oncogenic potential.

Single, oral administration of > 657 mg/kg oseltamivir resulted in toxicity, including mortality, in juvenile 7 day old rats, but had no effect on adult rats. Mortality was considered as an indicator of general toxicity. The toxicity in the juvenile rats was seen at Cmax plasma concentrations of OP exceeding the concentrations measured in young infants (CASG 114). No toxicity was observed after repeated administration of up to 500 mg/kg oseltamivir to developing juvenile rats 7 to 21 days old or daily administration of 2500 mg/kg OP for 2 weeks to adult rats.

The data indicate that toxicity, including mortality, is associated with high levels of the prodrug OP, but not to OC. Subcutaneous administration of OC alone to 7-day old juvenile rats led to the highest maximum plasma and brain levels of OC thus far observed in 7-day old rats, but did not induce any adverse effects, toxicity, or lethality.

The underlying reasons for the much higher exposures to the prodrug in juvenile animals are considered to be the lower metabolic turn-over due to age-dependent enzyme activity, which has been described in different species and humans to affect the hydrolysis of OP to OC, and the lower renal clearance. In addition, OP crossed the blood-brain barrier more readily in 7 day old rats which resulted in higher exposures to OP in the brain, albeit brain/plasma exposure ratio are <1.

The toxicokinetics of OP and OC were studied in adult and new-born marmosets (after oral delivery of 2 and 10 mg/kg of oseltamivir), a species whose pharmacokinetic profile more closely resembles that of human compared to rats. The results showed that following administration of OP to neonatal marmosets, significant plasma concentrations of OC can be achieved. The resulting ratios OP:OC are lower in neonates than in adults, even though the in vitro data would suggest reduced carboxylesterase activity in the new-borns.

Pre- and postnatal development studies (in rats)

The no observed adverse effect level (NOAEL) for dams and offspring is 500 mg/kg/day when administered orally to the female F0 generation from day 6 of pregnancy to day 20 postpartum. At 1500 mg/kg/day, there were reductions in the number of pups surviving to day 4 postpartum when compared with controls. This adverse effect may be interpreted as a result of the general maternal toxicity seen at this dose.

2.2.5. Ecotoxicity / environmental risk assessment

The estimated theoretical increase of oseltamivir usage followed by the addition of the new indication for Tamiflu in children <1 year of age with the dosing regimen 3 mg/kg twice daily (BID) for 5 days would be <0.5% of the population of Europe. The environmental risk arising from widespread Tamiflu administration during an influenza pandemic in Europe have been previously assessed and resulted in no significant environmental risk. The addition of a new indication for Tamiflu as treatment of influenza in infants below 1 year of age is not expected to lead to a significant increase in environmental exposure even following widespread use of oseltamivir in the newly indicated population.

2.2.6. Discussion on non-clinical aspects

The data indicate that oseltamivir related toxicities including mortalities identified thus far in juvenile rats are associated with high levels of the prodrug OP, but not with OC and is determined chiefly by Cmax after an i.v. bolus, as opposed to overall AUC exposure. The underlying reasons for higher OP levels in juvenile rats and marmosets are related to the lower metabolic turn-over due to age-dependent enzyme activity, which has been described in different species and humans to affect the hydrolysis of OP to OC, and to the lower renal clearance.

The non-clinical studies have generally shown low CNS penetration of OP and OC and no pharmacodynamic CNS effects in vivo. In addition, investigations into the in vitro receptor binding properties of oseltamivir and OC reconfirmed that OC is a highly selective inhibitor of influenza neuraminidase (NA). The 7-day old juvenile rats have showed higher OP/OC brain/plasma ratios than adult rats (~8-fold) related to the immature blood-brain barrier.

In addition, in its responses to the first round of questions the MAH has summarised the blood brain barrier (BBB) data on the developing brain, which indicate that it is structurally intact and regardless of some differences in expression of transporters and junction-associated proteins, these are expressed and active. Despite any differences in functioning of the BBB in neonates, in the newborn marmoset and the 7-day rat, the brain:plasma concentration ratio has remained low for both oseltamivir and OC. In these juvenile animals, ~4-times higher plasma concentrations of oseltamivir were detected than in the adult. In young rats, the brain exposure levels were only quantifiable after the high doses corresponding to the 300-fold higher plasma exposures than in human. Nonclinical (toxicity, pharmacokinetic and metabolism) data available from newborn, juvenile and adult marmosets and rats do not suggest an increased risk in newborns when administered 3 mg/kg of Tamiflu despite the higher plasma concentrations and incomplete maturation of the BBB in the newborn. Thus far no safety data from Roche studies is available in infants under two weeks of age, but there have been no new safety signals in the data from a total of 135 patients aged < 1 year of age.

The response and the nonclinical data thus far, do not bring in new information for the safety of the Tamiflu for children especially in the youngest population (< 2 weeks of age), but the high safety margin suggests low safety concern for infants less than 1 year of age in general. The safety profile in infants <2 weeks of age is not likely to be significantly different to that in infants > 2 weeks of age.

Neonatal rats and marmosets have reduced rate of conversion of OP to OC due to developmentally regulated carboxylesterase activity. In very young marmosets plasma concentrations of OP higher by a factor of 6 to 8 compared with adults have been found. Therapeutically relevant plasma concentrations of OC have been detected in new-born marmosets, demonstrating that efficient conversion of pro-drug is retained in new-born animals and the ratios of OP:OC have been lower in neonates than in adults. The data from animal studies, in which the clearance of OP was less in juveniles than in adults, seems less relevant to the treatment of children aged 1 year or less; the simulated Cmax of OP in infants including 0–1 months old children (following 3 mg/kg BID) was less than the observed exposure of OP in adults following administration of 150 mg of Tamiflu.

A physiologically based pharmacokinetic model for marmosets and humans has been developed to bridge preclinical to clinical and adult to infant data, and to support the safety margin calculations. The model is able to simulate the pharmacokinetics of OP and OC in these two species, including age dependencies. This modelling supports the finding that metabolic turnover in infants is sufficient at therapeutic doses to produce therapeutic levels of active metabolite. Simulations in infants demonstrate that the pharmacokinetic profiles after oral seen in adults translates reliably to infants with a lower generation of the active OC by carboxylesterase enzyme activity on the one hand and a lower renal clearance of this active moiety on the other hand being the main factors to be expected. The projected safety margins in infants seem adequate to

confer low safety concern to the less than 1 year of age children. In conclusion, the age-related metabolic factors that may affect exposure have been shown to be not a major source of concern in humans, with no indication of increased risk to children below 1 year of age. Furthermore, based on the clinical safety data available so far, no new safety signal emerged for children less than 1 year of age and the safety events reported so far are consistent with either the established safety profile in older children or consistent with events expected to occur in this young age group.

2.2.7. Conclusion on the non-clinical aspects

Overall, oseltamivir has been shown to have a wide safety margin, with very high doses being needed before toxicity becomes evident in adult and juvenile animals. These margins are considered to be sufficiently wide to offset concerns relating to inter species differences. Toxicity including mortality in juvenile rats (7-day-old) has been associated with high levels of the prodrug, OP, but not with the active form OC. Age-dependant factors such as reduced hydrolysis of OP to OC and renal clearance have resulted in an increased plasma concentration of OP in juvenile animals. Age-related metabolic factors affecting exposure have been shown not to be a major source of concern in humans, with no indication of increased risk to children below 1 year of age thus far. The predicted Cmax of OP in infants including 0–1 months old children (following 3 mg/kg BID regimen) have been lower than the observed exposure of OP in adults on 150 mg BID regimen.

The available toxicity data in adult rodents, adult marmosets and juvenile rats, together with a solid understanding of the pharmacokinetics and metabolism of oseltamivir in humans and animals, including the most predictive species, juvenile marmosets, is adequate to ensure an appropriate risk/benefit ratio in children below 1 year of age when administered 3 mg/kg of Tamiflu. The safety profile in infants <2 weeks of age is unlikely to be significantly different than in infants > 2 weeks of age.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Tamiflu. Considering the above data, Tamiflu is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

PK/PD studies and analyses	
1. CASG 114 Clinical Study Report (CSR)*	87 patients enrolled, of whom 72 patients were < 1 year of age) including associated PK, PK-PD, and safety analyses for this study population
2. Interim WP22849 CSR*	54 patients [of the target 65] enrolled up to the end of the 2010-2011 influenza season), including associated PK, PK-PD, and safety analyses for this study population
3. Population PK Model*	Report based on pooled PK data from study CASG114 and interim WP22849
4. Integrated PD and PK-PD Analysis Report	An integrated analysis of these data from study CASG114 and interim WP22849

5. Modelling and Simulation Report supporting the proposed 3 mg/kg BID regimen for all patients aged < 1 year*	Report supporting the proposed 3 mg/kg BID regimen for all patients aged < 1 year
6. Addendum CSR for WP22849*	Addendum based on the planned 65 patients (54 from influenza season 2010/2011 and 11 from influenza season 2011/2012)
7. Updated Population PK Model Report*	Report including the additional 11 patients from influenza season 2011/2012 in study WP22849
8. Updated Simulation Report **	Report including the additional 11 patients from influenza season 2011/2012 in study WP22849
Clinical efficacy	The current variation to extend the indication of oseltamivir to infants aged 0–1 year is based on pooled PK and modelling and simulation data from studies CASG114 and WP22849. However, also descriptive PD results were submitted for these studies. Additionally, the MAH resubmitted CSRs or publications of some previous paediatric studies. The MAH had included also some studies in adult population which were not assessed or reviewed as irrelevant for the variation.
9. CASG114 CSR*	Descriptive and resistance data
10. Initial WP22849 CSR*	Descriptive and resistance data
11. Addendum WP22849 CSR*	Descriptive and resistance data
12. WV15758 CSR*	Pivotal efficacy study in children aged 1–12 years
13. WV16193 CSR*	A randomized, open-label, parallel group study of oseltamivir used for the management of influenza in households (adults, adolescents, children aged 1–12 years)
14. JV16284 CSR	JV16284: Phase II clinical study of oseltamivir phosphate for the treatment of influenza in Japanese children (aged 1–12 years)
15. PP16351 CSR*	An open label study of the pharmacokinetics of oseltamivir in children after a single dose. (Children aged 0–5 years)
16. NP15826 CSR*	An open label study of the pharmacokinetics of Ro 64-0796/GS4104 in children (Children aged 5–18 years)
Clinical safety	The submitted data and reports are partially overlapping.
17. Addendum to Clinical Overview	Includes pooled safety population from the pivotal studies CASG114 and WP22849, 124 patients <1year of age.
18. Addendum to Summary of Clinical Safety	Includes • Pooled safety population from the pivotal studies CASG114 and WP22849, 124 patients <1year of age. • Safety data from earlier prospective and retrospective studies • Post-marketing surveillance adverse events (AEs)
19. Pooled safety population	Pooled data from CASG114 and WP22849 (N=124) and 11 additional patients from WP22849
20. Drug Safety Report No. 1060267	Adverse events entered with Tamiflu onto the Roche safety database in children less than 1 year of age (report excludes data from the two studies CASG 114 and WP 22849) for EU filing
21. NV25182 CSR	Prospective observational safety study in children < 2 years of age (N=1065) with specific reference to infants < 1 year (exposed to oseltamivir N=161, no antivirals N=360).
22. Comprehensive report on neuropsychiatric adverse events in relation to Tamiflu Research Report 1027907, Nov 2007*	This report was not assessed within this procedure. It has been previously assessed, resulting in update of the SmPC in year 2008 (variation II/0060) with the information on CNS AEs, even though contribution of oseltamivir to these effects is unknown.
23. Publications of previous independent observational studies	Japan (4 studies referred to, two publications included) Germany (1 study) (total subjects <1 year of age: N=2362)

Two additional paediatric studies are ongoing:

- NV25719: Open label, randomized, two-arm multi-centre trial to evaluate PK/PD of two doses of oseltamivir in the treatment of influenza in immunocompromised patients aged 0-13 years. To be completed by October 2015.
- Open label, prospective, multicentre, observational study to evaluate safety, anti-viral activity and clinical outcomes of oseltamivir for treatment of immunocompromised children from at least 37 weeks of gestational age to less than 18 years. To be completed by October 2015.

2.3.2. Pharmacokinetics

Pharmacokinetic (PK) properties of pro-drug oseltamivir and the active metabolite oseltamivir carboxylate (OC) are established. The only new PK data submitted were the observed exposures to oseltamivir and OC in studies CASG114 and WP22849 and subsequent population PK modelling and simulations.

Absorption and Distribution

In summary, the active moiety of all Tamiflu formulations is the pro-drug oseltamivir (as oseltamivir phosphate). Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration and is extensively converted by hepatic carboxyl-esterase 1 to the active metabolite oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as active metabolite. Exposure to oseltamivir (AUC) is less than 5% of the exposure to OC. Plasma concentrations of both oseltamivir and OC are proportional to dose and are unaffected by co-administration with food.

The volume of distribution of intravenously dosed OC is approximately 23 to 26 litres (~0.3 l/kg) in healthy adults, a volume equivalent to extracellular body fluid. The binding of OC to human plasma proteins is negligible (approximately 3%).

Elimination

Absorbed oseltamivir is primarily (>90%) eliminated by conversion to OC, which is not further metabolised and is eliminated by glomerular filtration and tubular secretion in the urine. Clearance of intravenously dosed OC is approximately 20 l/h in healthy adults. Elimination half-life (t½) of OC after oral dosing of oseltamivir is approximately 6 to 10 hours in adults with normal renal function. This is significantly longer than the t½ of intravenously administered OC (approximately 1 to 2 hours), which indicates that release of OC from the liver is the rate-limiting step in the elimination of OC after oral administration of oseltamivir. Less than 20% of an oral radiolabelled dose is eliminated in faeces; this probably represents unabsorbed drug.

Results of studies CASG114 and WP22849 (see section 2.3.5 for study details)

The primary objective of studies CASG114 and WP22849 was to define the PK of oseltamivir and oseltamivir carboxylate. PK parameters obtained using non-compartmental analyses in these studies are summarised below. Some parameters were not estimated in all subjects because the elimination T½ could not always be calculated; in addition, the parameter estimates obtained using NCA may not accurately reflect true exposure because only four post-dose blood samples were drawn. Note that the PK parameter values are not standardized for oseltamivir dose.

Table 2. Study WP22849

	3 mg/kg Age 91– <365 days	2.5 mg/kg Age 31–90 days	2 mg/kg Age 0–30 days
N	40	20	5
Oseltamivir			
C_{max} (ng/ml)	78.6 (28.4, 195)	56.9 (21.7, 197)	30.3 (3, 95.3)
AUC_{0-12} (h*ng/ml)	281 (114, 605)	189 (103, 497)	133 (90.3, 263)
T½ (h)	2.03 (0.928, 5.3)	1.9 (0.972, 5.54)	1.55 (1.13, 2.82)
Oseltamivir carboxylate			
C_{max} (ng/ml)	506 (187, 856)	518 (262, 1010)	477 (380, 691)
AUC_{0-12} (h*ng/ml)	4620 (3050, 8690)	4490 (3080, 11200)	NC
T½ (h)	8.46 (4.48, 37)	8.21 (5.29, 62.3)	NC

Data are median (min, max). NC: Not calculated. Source: WP22849 CSR - Addendum, Appendix 3

Table 3. Study CASG114

	Cohort IIA 3 mg/kg 9–11 months	Cohort IIB 3.5 mg/kg 9–11 months	Cohort III 3 mg/kg 6–8 months	Cohort IV 3 mg/kg 3–5 months	Cohort V 3 mg/kg 0–2 months
N	7	8	24	10	23
Oseltamivir					
C_{max} (ng/ml)	83.35 (38.6, 138)	115.0 (37.1, 279)	114.5 (33.6, 536)	63.0 (23.3, 104)	84.2 (26.8, 131)
AUC_{0-12} (h*ng/ml)	296.4 (125.5, 357.3)	393.2 (198.3, 1110.7)	412.5 (165.8, 1060.3)	246.5 (121.0, 443.1)	265.5 (49.7, 415.0)
T½ (h)	2.84 (0.98, 4.12)	2.13 (1.85, 5.99)	2.84 (1, 21.54)	4.40 (2.23, 16.96)	2.53 (1.44, 7.66)
Oseltamivir carboxylate					
C_{max} (ng/ml)	347.5 (200, 705)	497 (338, 747)	440.5 (169, 864)	427 (361, 807)	535 (103, 1120)
AUC_{0-12} (h*ng/ml)	3401 (2277, 6487)	4068 (3146, 7171)	3949 (1759, 7958)	4292 (3497, 7028)	4688 (873, 10242)
T½ (h)	11.13 (5.40, 51.9)	14.56 (7.22, 25.7)	10.29 (1.02, 78.3)	9.09 (6.25, 19.0)	6.64 (4.65, 28.7)

Data are median (min, max). Source: CASG 114 CSR, Table 12A and Table 12B

2.3.3. Pharmacodynamics

Mechanism of action

The pharmacodynamic properties of oseltamivir are established. Oseltamivir is a pro-drug of the active metabolite, oseltamivir carboxylate (OC). OC is a selective and highly specific inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virus surface. Viral neuraminidase activity is essential for the release of recently formed virus particles from infected cells and is also important for viral entry into uninfected cells. Inhibition of this viral enzyme hinders the release of virions from infected cells, thus reducing further spread of infectious virus in the body. The result is a reduction in viral replication, infection and pathogenicity (in *in vitro* and *in vivo* animal models).

Primary and secondary pharmacology

The dose-response relationship and time course of effect have been previously assessed for adults, adolescents, and for children older than one year of age.

No new studies on primary or secondary pharmacology were submitted for this variation, which is acceptable based on the current requirements.

2.3.4. PK/PD modelling

The strategy of the MAH for determining a dose recommendation for infants <1 year of age was first of all to analyse the data for evidence of a PK/PD relationship and to propose a suitable dose in infants based on that evidence. Secondly, if no PK/PD relationship could be established, the OC and oseltamivir exposures associated with safe and effective use of oseltamivir in older children and in adults would be targeted. The population PK model and simulations would be used to determine the optimal dose for infants <1 year of age.

Population PK modelling

Oseltamivir and OC concentrations and relevant subject characteristic data from infants less than 1 year of age with confirmed influenza that participated in clinical studies CASG114 (N=68) and WP22849 (N=65, i.e. 54 patients in the 2010/11 influenza season and 11 patients in the 2011/12 influenza season) were pooled, and a population PK analysis was performed by the MAH. The population PK analysis was conducted via nonlinear mixed-effects modelling with the NONMEM software, Version 7.2.0. After several runs for base model and covariate model development, a final model was obtained with the consideration that oseltamivir PK was described by a two-compartment model with first-order absorption, and oseltamivir prodrug was assumed to be completely converted to OC, which was described by a one-compartment model with estimated apparent clearance and volume parameters. All clearance and volume parameters were scaled allometrically with the fixed power coefficients of 0.75 and 1 for clearance and volume parameters, respectively.

In addition, apparent clearance and volume of oseltamivir carboxylate linearly increased with age. Use of post-conceptual age instead of age did not improve the model. Model parameters were shown to be independent of gender. The final population PK model was evaluated using bootstrap, visual predictive check (VPC), standardised VPC (SVPC), predictive check simulations (PCS), and normalised prediction distribution errors (NPDE) plots. There was a good agreement that the final model was able to estimate the OC concentrations with good accuracy and OP concentrations with reasonable accuracy. For a typical patient (8 kg, 24 weeks of age), oseltamivir apparent clearance, central volume, inter-compartment clearance and peripheral volume were estimated at CL/F = 80.4 l/h, V2/F = 166 l, Q/F = 19.6 l/h, and V3/F = 348 l, respectively, while oseltamivir carboxylate apparent clearance and volume were estimated at CLM/F = 4.75 l/h, and VM/F = 40.2 l.

The increase of the clearance parameter with age is probably explained by maturation of the kidneys (i.e. the major elimination pathway). The reason for increasing volume parameter with age is intuitively less certain. Alterations in hepatic volume and effectiveness of intra-hepatic trapping could contribute to the impact of age on apparent volume of distribution. Extracellular water content (as % of body weight) is largest at birth, thus, one would expect the allometrically scaled volume parameter to decrease rather than increase with age. The observation might also reflect altered bioavailability (F) or redistribution of body fluids in the patient population.

PK/PD modelling

In the first step, the MAH explored associations of PK parameters of OC (Cmin, Cmax, AUC) and exploratory PD markers (e.g. time to resolution of clinical symptoms and to cessation of viral shedding, and slope of viral decline). Both data from the individual studies (CASG114 and WP22849) and from pooled dataset using population PK model derived OC exposures were used. No convincing PK-PD relationship was observed, however, and the PK/PD modelling analysis did not provide information that would clearly direct selection of a recommended dose for infants <1 year of age. This is not surprising because dosage in the aforementioned studies was designed to provide an effective exposure to all patients and the number of enrolled patients was relatively small.

PK simulations

Because the PK/PD analyses did not provide definite associations between PK exposures and PD endpoints, the MAH has based the dosing recommendations for infants <1 year of age on the PK exposure target values that have been associated with safe and effective use of oseltamivir in older children and in adults. The most relevant population for bridging purposes was considered to be 1-2 year old children. Given the limited available data in this population, consideration of bridging information from the extensive Phase III and clinical pharmacology investigations in adults and adolescents was also used to support dosing recommendations for infants <1 year of age.

Oseltamivir carboxylate exposure target values were based on observed AUC values in 12 infants aged 1 and 2 years old from study PP16351 receiving a single dose (approximately 30 mg) of oseltamivir. The observed OC AUCs achieved in children 1-2 years old were between exposures obtained from the approved 75 mg BID regimen and 150 mg BID in adults, which were the doses that were shown to be safe and effective in the pivotal Phase 3 studies WV15670 and WV15671 in adults. To define an acceptable dosage regimen, it was required to provide at least the OC exposures as observed in other populations with approved dosage, and that that adequate clinical and preclinical safety margins remained for projected Cmax and AUC values for both oseltamivir and OC.

In brief, the population PK model was used to simulate the typical oseltamivir and OC concentration-time courses, compute metrics of exposure (Cmax, Cmin, AUC), and to evaluate the distribution of the exposures in infants. Simulations were performed separately for the subgroups of patients that differ by age: 0-1 month, 1-3 months, 3-6 months, 6-9 months, and 9-12 months. Simulations were carried out with dosages 2, 2.5, 3, and 3.5 mg/kg BID.

The first set of simulations (Simulations 1) utilised 133 subjects of the analysis data set. The second set (Simulations 2) utilized 66,500 subjects with individual PK parameters sampled from the model-predicted distributions. Demographic characteristics (age and weight) of these subjects were obtained by replicating 133 subjects of the analysis data set 500 times. Then, expected oseltamivir and OC steady-state exposure metrics of each of these simulated subjects were simulated for the dosing regimens.

The predicted OP and OC exposure with the 3 mg/kg BID dosage for 133 patients from the analysis dataset (Simulations 1) and for the simulated 66,500 subjects (Simulations 2) are summarised in Table 4 and Figure 1, and in Table 5 and Figure 2, respectively. The overall results of the two simulations were in good agreement. The median values differed by less than 5%, except for OC exposure in the age group 9-12 months where Simulations 1 predicted 15-20% higher exposure. The 3 mg/kg BID regimen is predicted to provide higher OC exposure in the youngest infants than in older infants (Table 4 and Table 5). Median AUC was predicted to be higher by 19 to 45%, median Cmax by 32 to 53%, and median Cmin by 20 to 30%. Variability of the predicted OC exposure is markedly higher in the age group 0-1 months than in older infants. In contrast, exposure to oseltamivir was predicted not to increase with decreasing age in infants less than 1 year old.

The predicted OC and oseltamivir exposure for 133 patients from the analysis dataset using the 3 mg/kg BID dosage are compared with the observed historical data from paediatric and adult patients in Figure 3 and Figure 4. The exposure to OC and oseltamivir in infants less than 1 year of age exceeds those observed in adults on 75 mg BID and in children 1-5 years of age after a single 30 mg to 45 mg dose. Nevertheless, they are lower than the exposure after 150 mg BID in adults, which was used as the alternative dosage in Phase 3 clinical trials WV15670 and WV15671. The predicted OC exposure using the 2.5 mg/kg BID dosage is summarized in Figure 5.

Table 4. Simulated steady-state AUC, Cmax and Cmin following 3 mg/kg BID dose: Simulations 1.

Age	N	Oseltamivir			Oseltamivir carboxylate		
		AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}
0 to 1 months	13	234 (125 - 383)	55 (19 - 109)	4 (2 - 8)	5651 (1724 - 9799)	619 (200 - 959)	334 (79 - 640)
1 to 3 months	33	240 (135 - 445)	58 (29 - 117)	4 (1 - 11)	5535 (3971 - 8350)	571 (426 - 839)	297 (170- 519)
3 to 6 months	23	247 (166 - 399)	72 (33 - 118)	4 (2 - 8)	4851 (2973 - 7109)	536 (337 - 710)	284 (140 - 475)
6 to 9 months	35	312 (210 - 596)	69 (40 - 128)	7 (2 - 17)	4556 (3014 - 7164)	463 (288 - 685)	275 (165 - 481)
9 to 12 months	29	294 (189 - 565)	75 (34 - 147)	5 (2 - 15)	4762 (2717 - 6771)	470 (275 - 663)	280 (154 - 446)

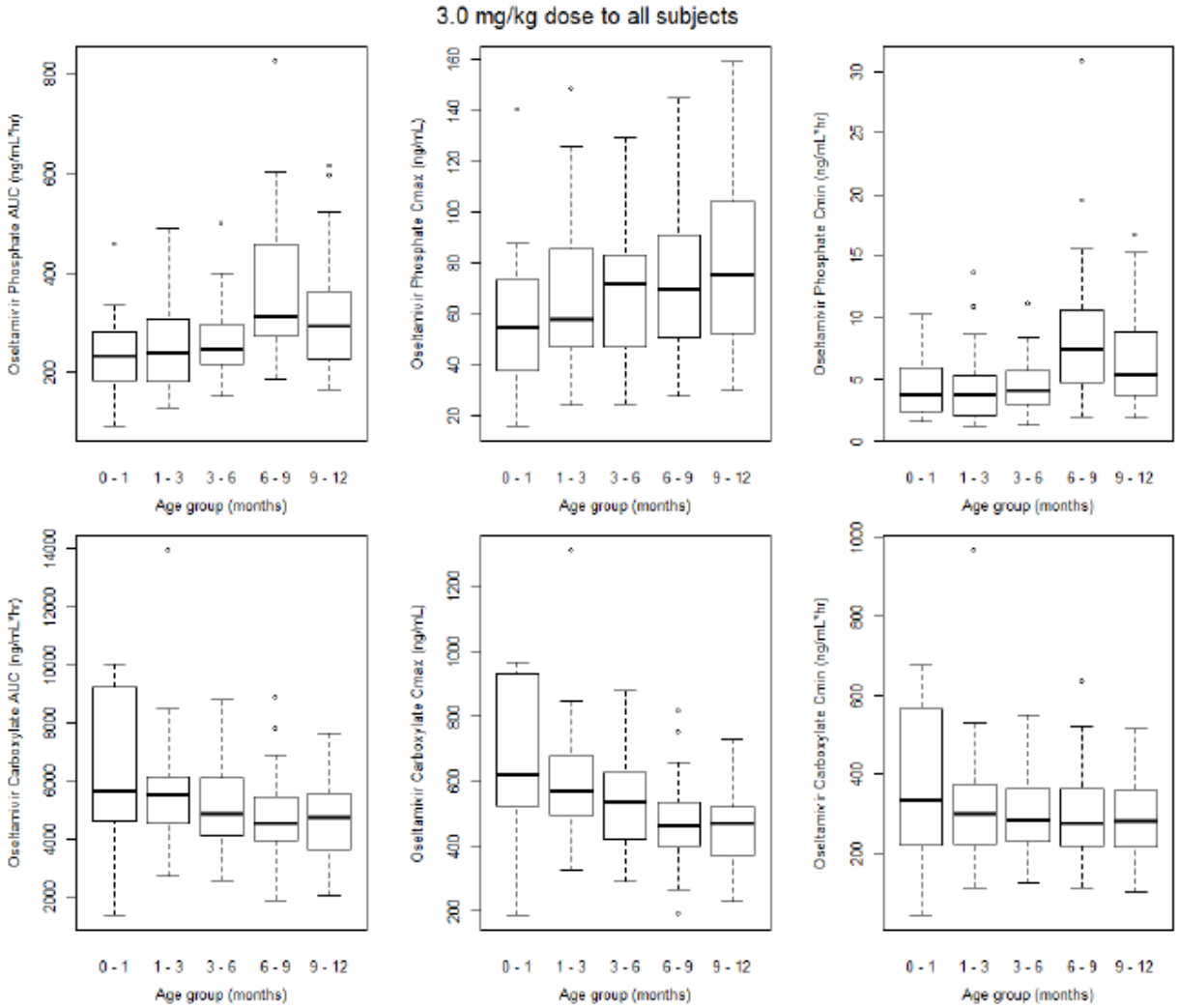
Data are median (90% coverage interval) of model-predicted values for 133 subjects of the analysis dataset.

Table 5. Simulated steady-state AUC, Cmax and Cmin following 3 mg/kg BID dose: Simulations 2.

Age	Oseltamivir			Oseltamivir carboxylate		
	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}
0 to 1 months	249 (130 - 472)	62 (26 - 135)	4 (1 - 13)	5798 (3247 - 10365)	622 (369- 1027)	319 (137 - 678)
1 to 3 months	261 (137 - 499)	64 (27 - 140)	5 (1 - 14)	5652 (3110 - 10242)	600 (349 - 998)	321 (137 - 679)
3 to 6 months	278 (145 - 529)	66 (28 - 144)	5 (1 - 15)	5020 (2793 - 9035)	521 (303 - 870)	293 (130 - 612)
6 to 9 months	294 (153 - 562)	68 (29 - 150)	6 (2 - 17)	4535 (2497 - 8193)	464 (269 - 785)	273 (121 - 562)
9 to 12 months	302 (158 - 580)	69 (29 - 154)	6 (2 - 17)	4003 (2228 - 7234)	406 (235 - 685)	246 (111 - 500)

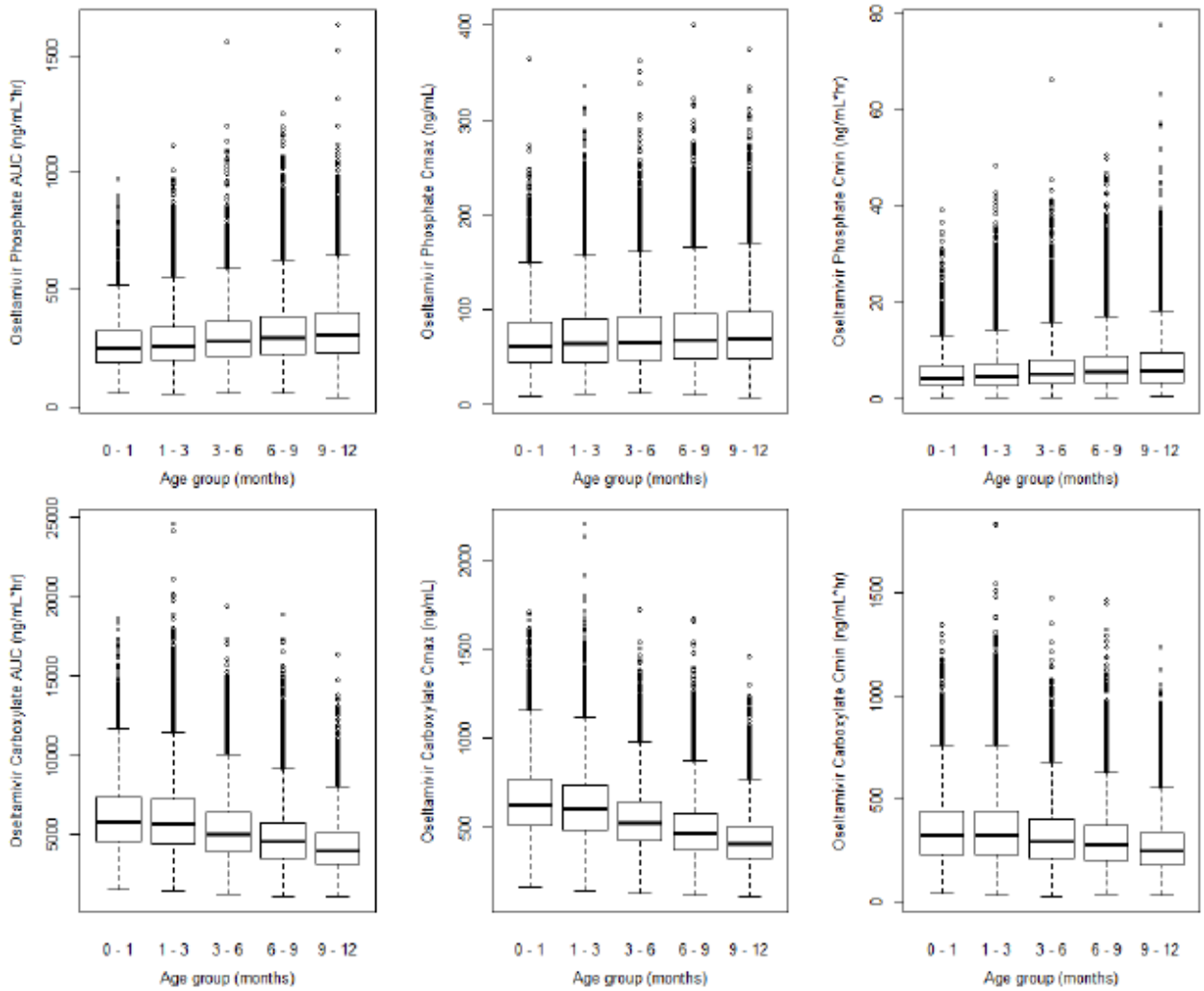
Data are median (90% coverage interval) of model-predicted values for 66,500 simulated subjects.

Figure 1. Distributions of oseltamivir (top) and OC (bottom) steady-state AUC, Cmax, and Cmin values by age: Simulations 1



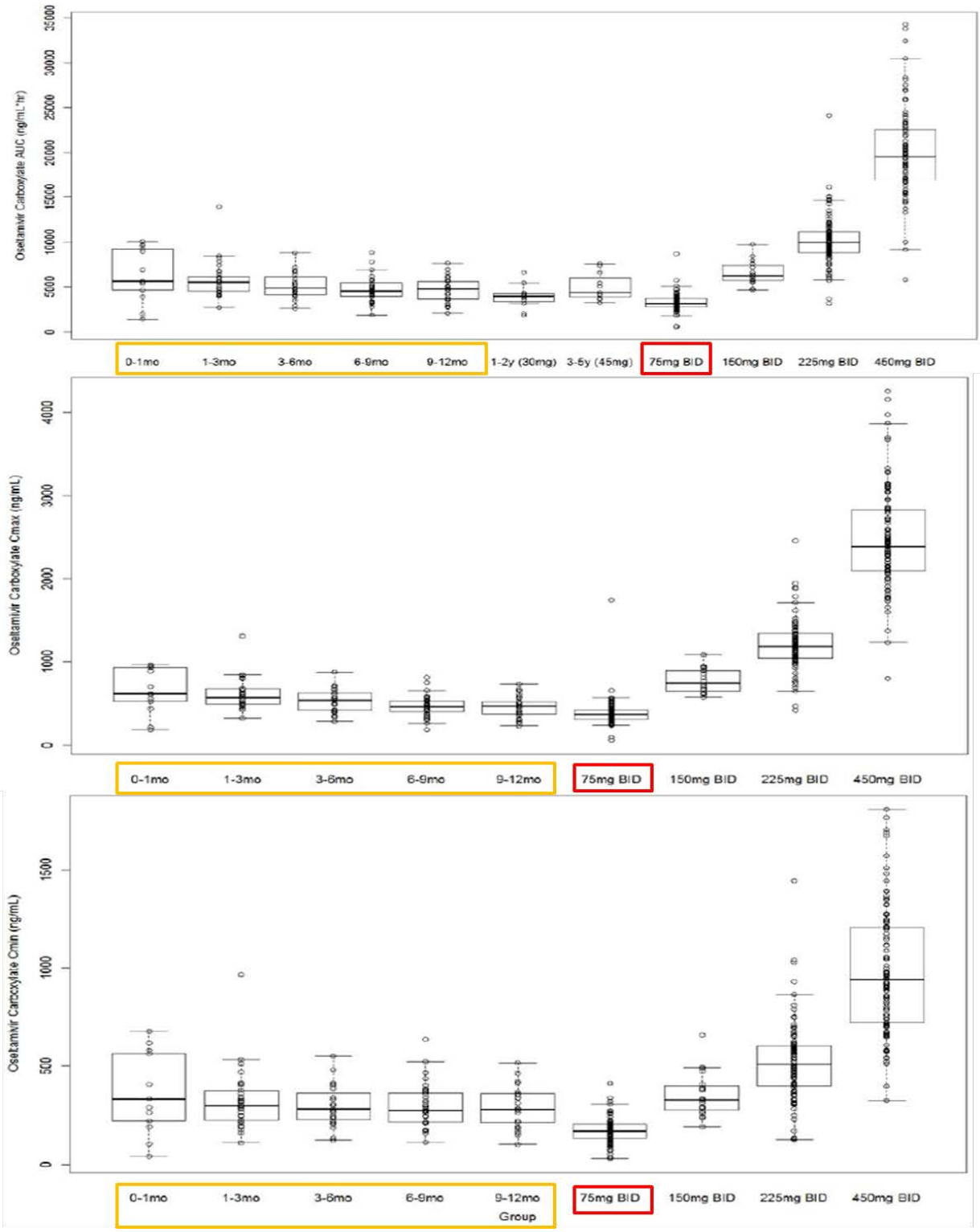
Model-predicted values for 133 subjects from the analysis data set administered 3 mg/kg BID doses. Median values of the exposure metrics are designated by a black line in the centre of the box. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles.

Figure 2. Distributions of oseltamivir (top) and OC (bottom) steady-state AUC, Cmax, and Cmin values by age: Simulations 2



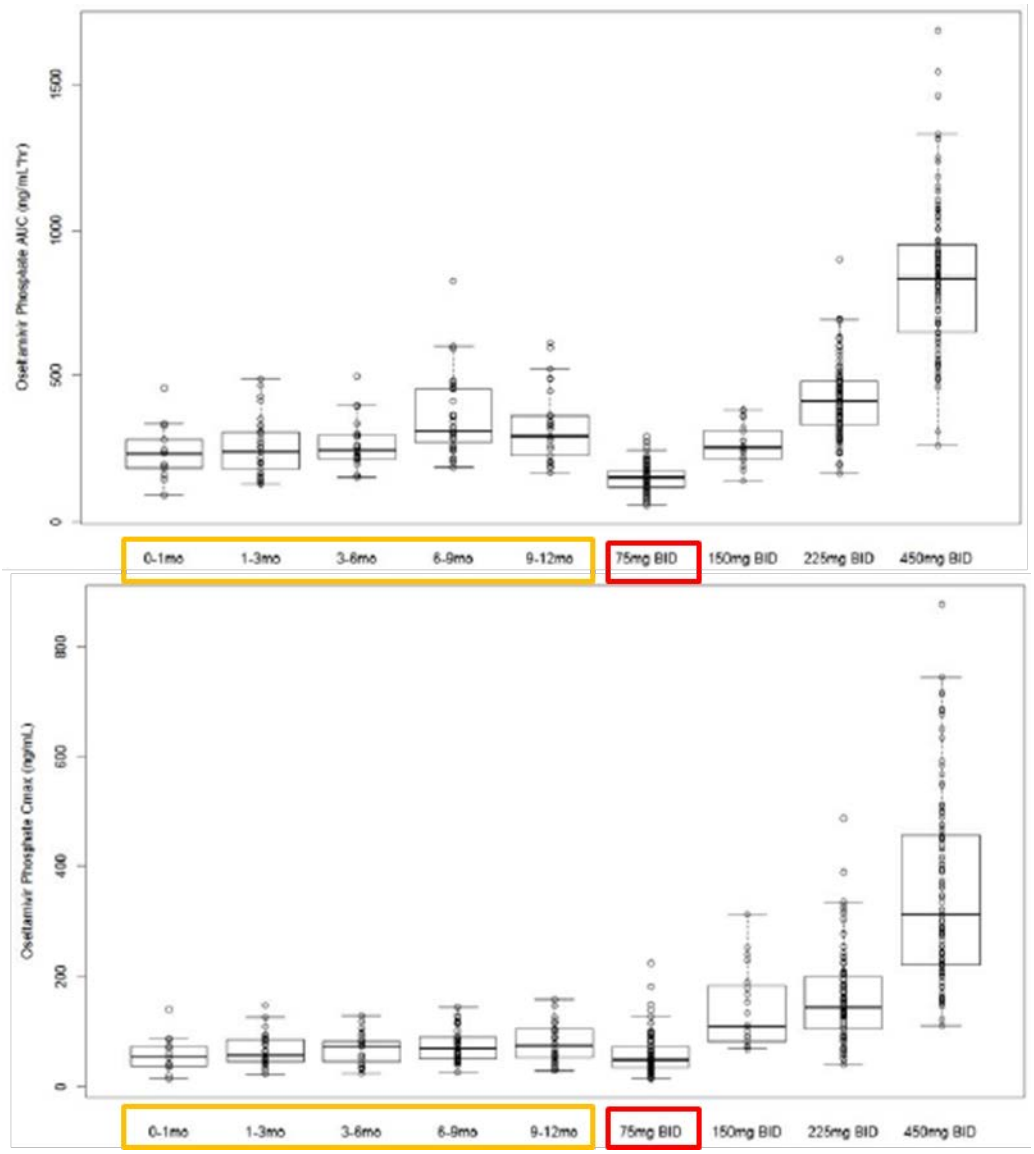
Model-predicted values for 66,500 simulated subjects administered 3 mg/kg BID doses. Median values of the exposure metrics are designated by a black line in the centre of the box. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles.

Figure 3. Predicted OC steady-state AUC, Cmax, and Cmin with oseltamivir 3 mg/kg BID in infants and the exposure observed in paediatric and adult subjects.



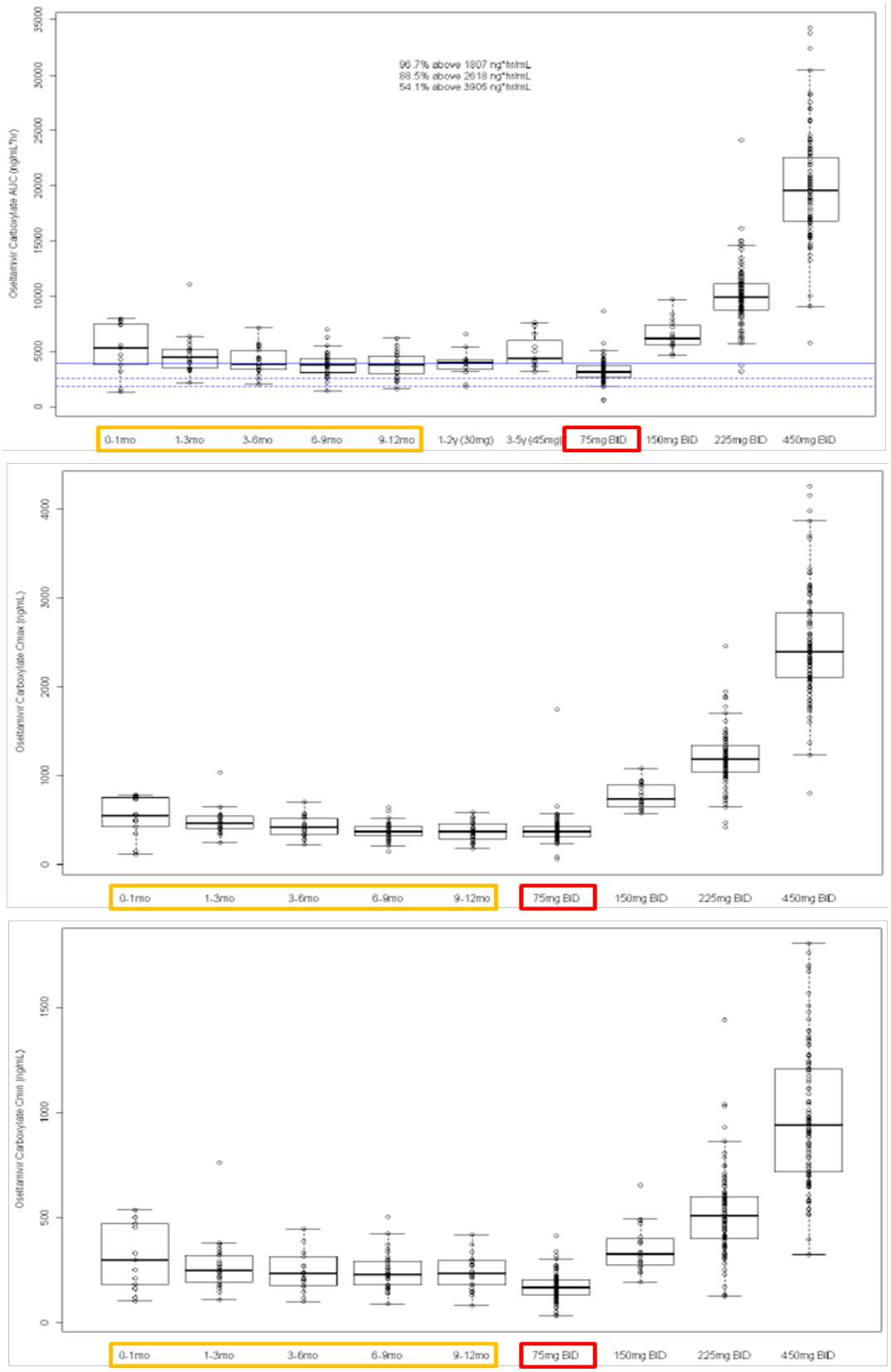
Median values of the exposure metrics are designated by a black line in the centre of the box. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR.

Figure 4. Predicted oseltamivir steady-state AUC and Cmax with oseltamivir 3 mg/kg BID in infants and the exposure observed in paediatric and adult subjects.



Median values of the exposure metrics are designated by a black line in the centre of the box. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR.

Figure 5. Predicted OC steady-state AUC, Cmax, and Cmin with oseltamivir 2.5 mg/kg BID in infants and the exposure observed in paediatric and adult subjects.



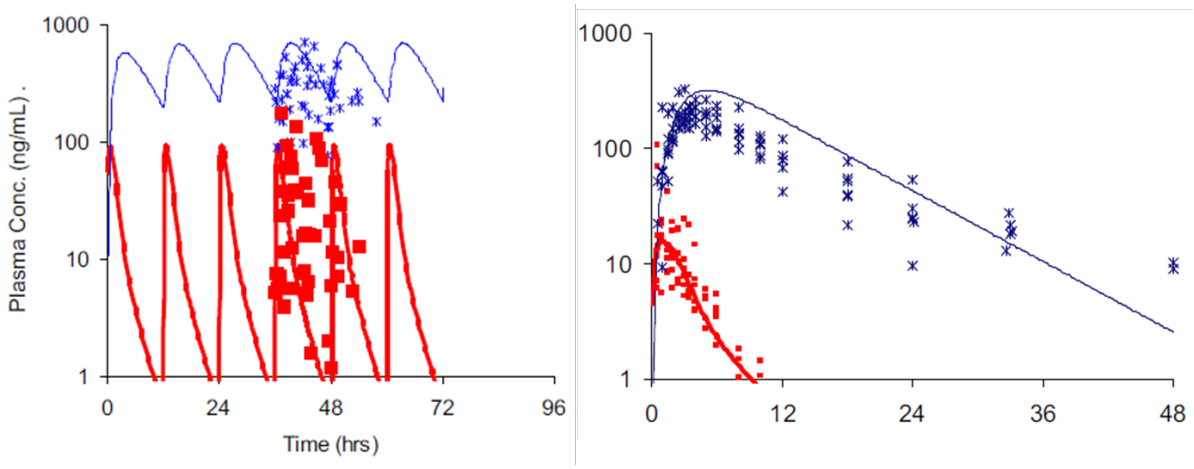
Median values of the exposure metrics are designated by a black line in the centre of the box. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR.

PBPK model in support of use of oseltamivir in neonates

The physiologically based disposition and absorption models for marmoset monkeys and human were implemented in GastroPlus™ version 6.1. The marmoset model was generated based on the standard GastroPlus™ ACAT monkey model and the human disposition model using the Population Estimates for Age-Related Physiology (PEAR) module. In summary, modelling strategy was to first construct a physiological model for adult marmosets based on data taken from literature and in-house sources and subsequently scale the model to newborn marmoset. Simulated plasma concentrations were verified against measured concentrations after oral and IV doses and model parameters were adjusted to match observed data. One of the key parameters of the model was PStc. It represents a permeability limited flux of OC which is the product of the drug specific cellular membrane permeability and the surface area available for transfer between the systemic circulation and the hepatocytes. It is obvious that the value of PStc is not measured *in vivo* and it is not easily predicted. Therefore, the value of PStc was optimized to fit the plasma profile of OC in adult marmosets and scaled across ages and between species based on an allometric relationship with liver weight.

The processes driving pharmacokinetics of oseltamivir and OC are known and the structure and chosen parameters of the PBPK model were chosen adequately. The PBPK model was able to predict oseltamivir and OC exposure after oral oseltamivir dose in adults and in 1-year-old infants with moderate accuracy (Figure 6). For adults the model overestimates OC concentrations in the early elimination phase and underestimates the terminal concentrations. Predicted OC Cmax is appropriate but tmax may occur too late. Parameter sensitivity analysis indicated that OC concentrations, particularly Cmax, were sensitive to changes in the cell membrane permeability parameter PStc but not to changes (±3-fold) in the metabolic clearance parameter CLint (representing conversion of oseltamivir to OC in hepatocytes; mediated by CES1). This is in agreement with physicochemical characteristics of OC, which is a hydrophilic acid, mostly ionized at physiological pH and has poor penetration across lipid membranes in vitro. Plasma OC concentrations were also sensitive to variability in renal function which is expected as OC is eliminated by the kidneys. Plasma oseltamivir concentrations were sensitive to changes in hepatic metabolism (CLint parameter). This is in agreement with the study showing that carriers of CES1 c.428G>A polymorphism causing decreased CES1 activity have increased oseltamivir exposure but similar OC exposure compared with noncarriers (Tarkiainen 2012).

Figure 6. Simulated and observed oseltamivir and OC concentration-time profiles in 1-year-old infants (left) and in adults (right)



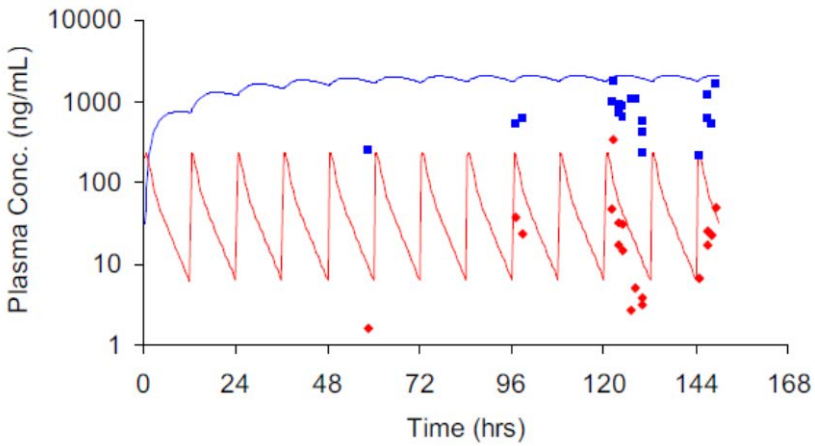
Lines represent simulated values; dots represent concentrations observed in studies CASG114 and 15517.
Red = Oseltamivir; Blue = Oseltamivir carboxylate.

The model for a newborn infant was adapted from the adult model as follows:

- The physiological model parameters (organ sizes, blood flows) were scaled down to be appropriate for a 1 day old of body weight 4 kg.
- Liver PSTc for OC in was scaled from the value in adult using allometric scaling and the liver weight ratio between a 1 day old and an adult.
- For OC Vss was increased to 1.1 L/kg due to the larger extracellular space in newborns.
- Metabolic conversion in liver was scaled down based on the reduced liver size and accounting for in vitro data showing a 10-fold lower intrinsic clearance in newborns versus adults.
- The renal clearance was reduced to 10% of adult value.

Simulations with the newborn model of a dose of 2 mg/kg given twice daily separated by 12 hours were compared to the observed data from 20 infants in study CASG119 (Figure 7). The median gestational age, median chronological postnatal age, and median weight at time of PK sampling of infants in CASG119 were 27.5 weeks, 2.5 weeks, and 1684 grams, respectively, and the mean dose was 1.75 mg/kg oseltamivir phosphate twice daily. One blood sample was drawn from each subject at presumed steady state; sample collection was scheduled to fully encompass the 12-h dosing interval. The simulated average concentration at steady state (C_{avg}) was more than twice the observed value (1700 ng/ml vs. 780 ng/ml, respectively). Even though the dose used in modelling was slightly higher than that used in CASG119 (2.0 mg/kg vs. 1.75 mg/kg) and the observed data are very limited it is obvious that the PBPK model overestimates the OC exposure. Importantly, the infants in study CASG119 were premature, and it is expected that their renal and hepatic functions at the time of treatment were less developed than those in full-term newborn infants.

Figure 7. Simulated and observed oseltamivir and OC concentration-time profiles in newborn infants



Lines represent simulated values; dots represent concentrations observed in study CASG119.
Red = Oseltamivir; Blue = Oseltamivir carboxylate.

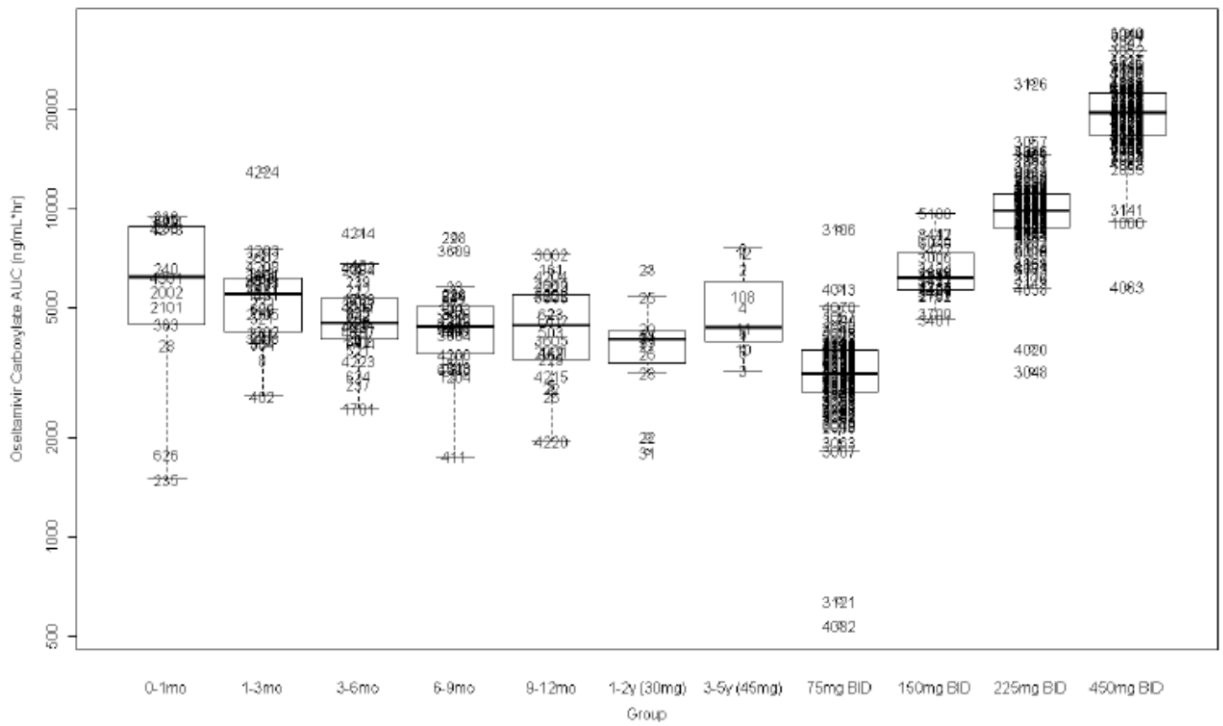
To conclude, the PBPK model cannot be used to directly predict, with acceptable precision, the specific dose for newborn infants (0-2 weeks of age). Further development of the model is not expected to sufficiently improve the predictive properties of the model in newborn infants because there are not sufficiently robust data on key parameters of the model for this age group.

Development of renal function in relation to oseltamivir PK and available data in infants aged 2-8 weeks olds

OC is eliminated by renal excretion; both glomerular filtration and tubular secretion are quantitatively important mechanisms in adults. In contrast, the prodrug oseltamivir is almost exclusively eliminated by metabolism to OC; renal function is not expected to affect oseltamivir concentrations. The MAH has reviewed

appropriate literature addressing maturation of kidney function in infants. In summary, nephrogenesis is complete by 36 weeks of gestation. At birth the GFR is very low; however, it increases rapidly and in full-term infants its value doubles during the first 1-2 weeks of life due to increased cardiac output and decreased renal vascular resistance. The maturation of renal tubular functions (secretion and reabsorption) is known in less detail but it is likely that these processes reach adult values more slowly than GFR. Furthermore, even the healthy newborn infants are a very heterogeneous population and renal function in infants is sensitive to e.g. vasoactive factors and dehydration. These aspects are reflected in both simulated and observed exposure data from studies CASG114 and WP22849, as shown in this figure:

Simulated Oseltamivir carboxylate AUC values for a 3 mg/kg dose:



Numbers represent individual study subjects.

One fundamental pharmacokinetic aspect not discussed by the MAH is that the extracellular water (ECW) content in neonates is approximately two times higher than in adults: ~40-45% vs. 20% of bodyweight, respectively (Oh, 2012). For drugs that distribute primarily into ECW, such as OC, the volume of distribution per kg of bodyweight is highest in neonates and it decreases with increasing age. This means that to achieve similar OC concentration in ECW infants need higher oseltamivir dose per kg body weight than adults.

As the elimination rate of OC is decreased in infants (compared with older children and adults) a higher degree of accumulation is likely to take place. Importantly, the PK data from studies CASG114 and WP22849 was collected on day 3 of the treatment, i.e. at the time close to steady state.

It cannot be avoided that plasma concentrations of OC (as well as most of the other drugs) will be more variable in newborn infants than in older populations. The interindividual variability in absorption and metabolism of oseltamivir is probably higher in neonates than in older populations and renal excretion capacity increases rapidly during the first weeks of life. Factors such as water balance and concomitant disease will further increase the interindividual variability. The MAH proposes the dosage 3 mg/kg BID for 5 days for all infants to ensure that those infants with lower exposures do not fall far outside the range associated with efficacy as this could lead not only to potential treatment failure but also to encourage the development of resistance. The CHMP endorses the reasoning of the MAH. It is inherent in this approach that

some infants will experience higher exposures which, however, are expected to be safe and well tolerated based on the overall knowledge on safety profile of Tamiflu, including data from clinical studies using higher dosage than 75 mg BID.

Published data on use of oseltamivir in neonates

Oseltamivir and OC concentrations were reported in 3 of the 9 articles submitted by the MAH.

- *Acosta EP et al, 2010*. The results of study CASG119 are reported. 32 babies in a neonatal intensive care unit (NICU) were exposed to influenza. Following the NICU exposure, the treating neonatologist elected to administer oseltamivir prophylactically to these neonates. Twenty of the 32 babies were enrolled on PK sampling study. The median gestational age, median chronological postnatal age, and median weight at time of PK sampling were 27.5 weeks, 2.5 weeks, and 1684 grams, respectively, and the mean administered dose was 1.73 mg/kg oseltamivir phosphate twice daily. One blood sample was drawn from each subject after the 5th dose; sample collection was scheduled to fully encompass the 12-h dosing interval. 17 oseltamivir and 18 OC concentrations were available for analyses. The data were modelled using the ADAPT 5.0 systems analysis software. The CASG114 dataset was used to establish a combined parent-metabolite model with 2 compartments for oseltamivir phosphate and 1 compartment for OC. The modelled steady state AUC_{0-12} was 9250 ng·h/ml and the mean of all raw OC concentrations was 728 ng/ml.
- *McPherson C et al, 2012*. Sixteen premature infants exposed to influenza in a NICU were enrolled. PK data was available for 8 infants <38 weeks postmenstrual age (PMA) at enrolment who received 1 mg/kg twice daily and for 4 infants >38 weeks PMA (gestational age 28-37 weeks at birth) who received 3 mg/kg once daily. For each infant, 1 sample was obtained during 0–3 h post dose and 1 sample after >3 h post dose on Day 3 to Day 5 of the treatment. The measured oseltamivir and OC concentrations are shown below:

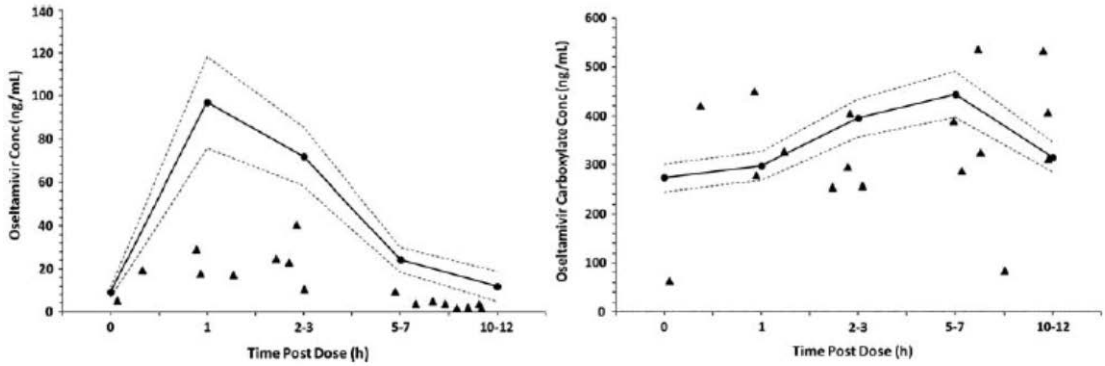


Figure 1. *Left panel*, Measured oseltamivir phosphate concentrations from pediatric patients in CASG 114 (circles; dashed lines 95% CI) and from premature infants <38 weeks PMA in the current study (triangles). *Right panel*, Measured oseltamivir carboxylate concentrations from pediatric patients in CASG 114 (circles, dashed lines 95% CI) and from premature infants <38 weeks PMA in the current study (triangles). The *x*-axis is represented in collection time windows, as this was the sample collection design in CASG 114. Abbreviations: CASG, Collaborative Antiviral Study Group; CI, confidence interval; PMA, postmenstrual age.

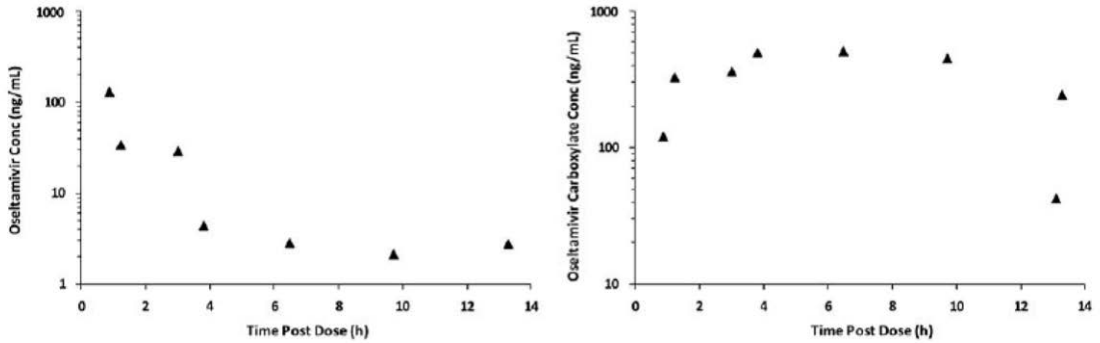


Figure 2. *Left panel*, Measured oseltamivir phosphate concentrations from premature infants >38 weeks PMA in the current study (triangles). *Right panel*, Measured oseltamivir carboxylate concentrations from premature infants >38 weeks PMA in the current study (triangles). Abbreviation: PMA, postmenstrual age.

- Maltezou HC et al, 2012. Oseltamivir was administered at 1.0 mg/kg BID to 13 neonates exposed to influenza H1N1. The infants were full-term (gestational age 36-41 weeks) and their median age at treatment was 15 days (range: 8-28 days). Eight blood samples were collected within the 24-h period after the fourth dose (before and at 1, 4, and 8 hours after each oseltamivir administration). A total of 72 concentration-time pairs were available for analysis. Population PK analysis was done with MONOLIX v 3.2 via MATLAB 2010. A single joint PK model was applied to describe the kinetics of oseltamivir and OC. A one-compartment disposition model was assumed and volume of distribution of OC was set at 0.45 l/kg. The mean (±SD) observed Cmax for OC and oseltamivir were 65.6 (±32.3) ng/ml and 9.4 (±4.5) ng/ml, respectively. The parameter estimates of the final model are summarised below:

Parameter	Estimate	RSE%	BSV%
K_a (h^{-1})	0.39	14	46.4
V_{OS}/F (L/kg)	1.05	6	22.6
V_{OSC}/F (L/kg)	0.44	10	21.2
CL_{OS}/F (L/h/kg)	24.8	9	13.9
CL_{OSC}/F (L/h/kg)	0.09	12	31.0
K_f (h^{-1})	1.21	13	31.1
Covariates			
For CL_{OS}			
Chronological age (d)	–0.53 ($P = 0.0028$)	33	—
Sex (male/female)	0.52 ($P = 0.0005$)	29	—
for K_f			
Sex (male/female)	0.41 ($P = 0.04$)	49	—

RSE% indicates % relative standard error of the estimate; BSV, % value of between-subjects variability; K_a, absorption rate constant of oseltamivir; K_f, formation rate constant of oseltamivir carboxylate; V_{OS}, volume of distribution of oseltamivir; V_{OSC}, volume of distribution of oseltamivir carboxylate; CL_{OS}, clearance of oseltamivir; CL_{OSC}, clearance of oseltamivir carboxylate; F, fraction of bioavailability.

The study populations of Acosta et al and McPherson et al were almost entirely premature newborns and the results of these studies cannot be directly extrapolated to term neonates. In contrast, Maltezou et al studied full-term infants aged 8-28 days. Furthermore, a relatively high number (8) of PK samples were collected for each subject. Even though the true Cmax was probably not captured in the study, the measured concentration data indicate that in term neonates the dose 1 mg/kg BID will produce markedly lower OC concentrations than the dosage approved for other populations for treatment of influenza. The population PK model was not described in sufficient detail to allow further analysis.

Conclusion

Influenza poses a clinically important risk to the very young infants e.g. in cases of influenza outbreak in neonatal intensive care units. Therapeutic alternatives to Tamiflu are currently limited. There is a clinical

need for recommended dosage of Tamiflu for newborn infants (0-2 weeks of age) as well as for older infants (<1 year of age). The CHMP acknowledges that the oseltamivir PBPK model cannot be used to directly predict, with acceptable precision, the specific dose for the newborn.

Clinical studies have shown that oseltamivir is efficiently metabolised to OC in both preterm and term newborns. The absolute level of renal function is the most important factor regulating elimination of OC. The glomerular filtration rate increases rapidly during the first days after birth due to increased cardiac output and decreased renovascular resistance. Newborn infants are inherently a variable population, thus, their OC plasma concentrations will be more variable than those in other populations. The MAH proposes the dosage 3 mg/kg BID for 5 days in therapeutic indication "Treatment of influenza" for all infants to ensure that those infants with lower exposures do not fall far outside the range associated with efficacy as this could lead not only to potential treatment failure but also to encourage the development of resistance. This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. The CHMP endorses this rational. It is inherent in this approach that some infants will experience higher exposures that, however, are expected to be safe and well tolerated based on the overall knowledge on safety profile of Tamiflu, including data from clinical studies using higher dosage than 75 mg BID.

2.3.5. Main studies

The current variation to extend the indication of oseltamivir to infants aged 0-1 years is based on pooled pharmacokinetic, modelling and simulation data from two open-label, controlled clinical studies, CASG114 and WP22849. Both were pharmacokinetic/pharmacodynamic studies which did not include efficacy parameters. The study reports of both studies have been assessed in previous procedures; nevertheless, the studies are described below.

Study CASG114

Study title

A Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Oseltamivir (Tamiflu) for the Treatment of Children Less than 24 Months of Age with Confirmed Influenza Infection.

CASG114 (MAH study n. WP20749), referred to as CASG114 in this report, is a National Institute of Health (NIH)-sponsored study supported by the MAH that was conducted from 2006 to 2010 in the United States by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG). The study was a pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir for the treatment of children less than 24 months of age with confirmed influenza infection.

Methods

The study was a prospective, age stratified, open label, pharmacokinetic, pharmacodynamic and safety evaluation of oseltamivir for the treatment of children less than 24 months of age with confirmed influenza infection. The primary purpose of the study was to define the pharmacokinetics of an oral dose of oseltamivir using a targeted area-under-curve (AUC) approach. The study is part of the PIP for Tamiflu. While the MAH could not exert any control on the direction or on the analyses of the study, they had full access to the raw data, which needed to be incorporated into the PK model and PK-PD analyses.

The study was closed before reaching recruitment target due to concerns on logistics and feasibility. A total of 87 subjects were enrolled into the study from 16 centres, and 81 subjects completed treatment.

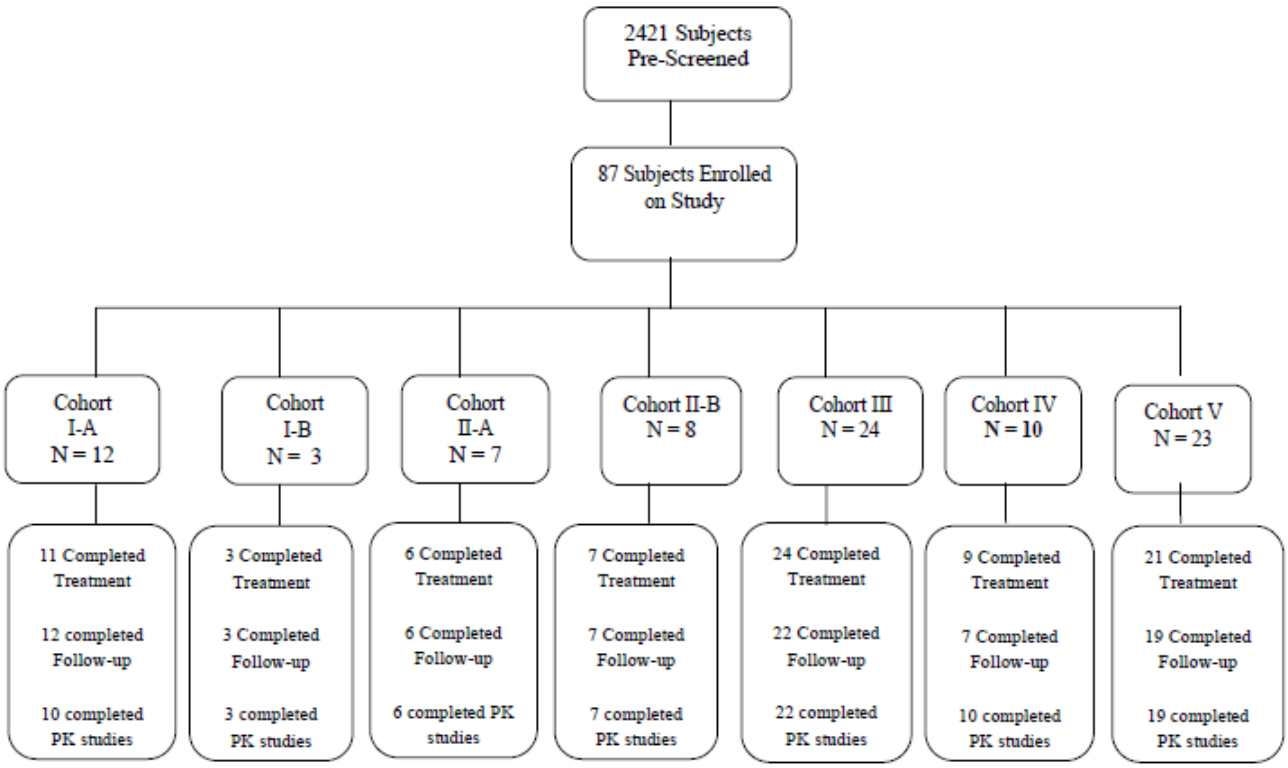
For children from birth through 8 months of age, the dose achieving the targeted OC concentrations was 3.0 mg/kg BID. For infants 9–11 months of age, a higher dose of 3.5 mg/kg BID was needed to achieve the targeted exposure.

Study title	A pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir (Tamiflu) for the treatment of children less than 24 months of age with confirmed influenza infection (CASG114)
Study centres	16 academic medical centres in the United States.
Period of trial	2006-2010. Clinical phase I/II
Objectives	Primary: • To define the pharmacokinetics (PK) of oseltamivir and oseltamivir carboxylate in children with confirmed influenza less than two years of age. These PK data will lead to a more precise dosing recommendation for this population. Secondary: • To describe the frequency of all adverse events (AEs), including neurologic AEs, among treated children • To assess the clearance of virus and viral ribonucleic acid (RNA) (quantitative) as a function of drug PK • To determine the potential for the development of resistance to oseltamivir as a function of pharmacokinetics and age (or cohort)
Design	Prospective, age-stratified, open-label
Study subjects	Children < 24 months of age
Inclusion criteria	• Signed informed consent from parent(s) or legal guardian(s) • Age: o Cohort I 12–23 months o Cohort II 9–11 months o Cohort III 6–8 months o Cohort IV 3–5 months o Cohort V 0–2 months • Confirmed laboratory diagnosis of influenza by viral culture or rapid influenza diagnostic test within 96 hours prior to study enrolment • Duration of influenza symptoms ≤ 96 hours
Study medication	Oseltamivir oral suspension 12 mg/mL
Dose/route/regimen/duration (please see text for explanation on Cohorts IA and IB; and IIA and IIB)	Cohort IA (12-23 month old): 30 mg BID Cohort IB (12-23 month old): 3.5 mg/kg BID Cohort IIA (9-11 month old): 3.0 mg/kg BID Cohort IIB (9-11 month old): 3.5 mg/kg BID Cohort III (6-8 month old): 3.0 mg/kg BID Cohort IV (3-5 month old): 3.0 mg/kg BID Cohort V (0-2 month old): 3.0 mg/kg BID Oral administration for 5 days (10 doses)
Criteria for evaluation	• Efficacy: N.A. (Phase I/II study) • Pharmacodynamics: o Correlation of clearance of viral RNA (by PCR) to PK and age of subject. o Correlation of clearance of virus (by culture) to PK and age of

	subject. o Correlation of development of oseltamivir resistance to PK and age of subject. • Pharmacokinetics: o OC AUC_{12} between 2,660 ng•hr/mL and 7,700 ng•hr/mL. • Safety: o Number and characteristic of AEs described as neurologic events. o Overall reported AEs thought to be associated with study therapy.
Statistical methods	The statistical methods are largely descriptive. Means, medians, maximums, and minimums are computed for continuous variables. Frequencies and proportions are computed for categorical variables. Spearman correlation coefficients are used to describe the association of PK parameters to various patient and disease parameters.

Results

Participant flow



Recruitment

A total of eighty-seven subjects were enrolled into the study from 16 centres (all in the US). Ten sites were activated but did not enrol any subjects into this study. The participant flow presents accrual activity into this study from the influenza season of 2006/2007 through 2010 when the study closed.

All subjects received at least two doses of study medication with the possible exception of one subject, who was included in the baseline demographic assessment only, and all but three subjects received at least seven doses. Sixty-eight (78%) had at least 10 doses administered on study (completed treatment). Eight subjects were lost to follow-up and three subjects withdrew consent.

Baseline data

Of the enrolled subjects, 59 % were male. The median enrolment ages were 16.5, 16, 10, 10, 6, 4, and 1 month, respectively for the seven cohorts. Fifty-five of the 87 subjects were Caucasian (58%, 33%, 57%, 50%, 67%, 60% and 74%, respectively for the seven cohorts).

Median duration of illness before enrolment was 3 days, 2 days, 2 days, 2.5 days, 3 days, 2.5 days and 2 days, respectively for the seven cohorts. Table 6 presents demographic information on the study population.

Table 6. Demographics of study population in study CASG114

DEMOGRAPHIC INFORMATION	COHORT I-A	COHORT I-B	COHORT II-A	COHORT II-B	COHORT III	COHORT IV	COHORT V
Sample Size							
Total	12	3	7	8	24	10	23
Gender							
Male	9 (75 %)	2 (66.7 %)	4 (57.1 %)	2 (25 %)	11 (45.8 %)	8 (80 %)	15 (65.2 %)
Female	3 (25 %)	1 (33.3 %)	3 (42.9 %)	6 (75 %)	13 (54.2 %)	2 (20 %)	8 (34.8 %)
Age (months)							
Median	16.50	16	10	10	6	4	1
Min-Max	(12 , 22)	(13 , 21)	(9 , 10)	(9 , 11)	(6 , 8)	(3 , 5)	(0.43 , 2)
N	12	3	7	8	24	10	23
Race							
Caucasian	7 (58.3 %)	1 (33.3 %)	4 (57.1 %)	4 (50 %)	16 (66.7 %)	6 (60 %)	17 (73.9 %)
African American	1 (8.3 %)	2 (66.7 %)	1 (14.3 %)	3 (37.5 %)	3 (12.5 %)	2 (20 %)	3 (13 %)
Amer. Indian/Alaska Native	--	--	--	--	--	1 (10 %)	--
Asian	--	--	--	--	1 (4.2 %)	1 (10 %)	--
Native Hawaiian	2 (16.7 %)	--	1 (14.3 %)	--	--	--	2 (8.7 %)
More than one race	1 (8.3 %)	--	1 (14.3 %)	1 (12.5 %)	2 (8.3 %)	--	1 (4.3 %)
Unknown/not reported	1 (8.3 %)	--	--	--	2 (8.3 %)	--	--
Ethnicity							
Hispanic/Latino	6 (50 %)	1 (33.3 %)	--	2 (25 %)	11 (45.8 %)	5 (50 %)	16 (69.6 %)
Not Hispanic/Latino	5 (41.7 %)	2 (66.7 %)	5 (71.4 %)	5 (62.5 %)	11 (45.8 %)	5 (50 %)	6 (26.1 %)
Unknown	1 (8.3 %)	--	2 (28.6 %)	1 (12.5 %)	2 (8.3 %)	--	1 (4.3 %)
Symptom Duration Prior to Enrollment (days)							
Median	3	2	2	2.50	3	2.50	2
Min-Max	(1 , 4)	(2 , 4)	(2 , 4)	(1 , 4)	(1 , 4)	(1 , 4)	(1 , 4)
N	12	3	7	8	24	10	23
Gestational Age							
Unknown	--	--	--	--	--	--	--
Pre-term (<= 37 wks.)	4 (33.3 %)	--	--	4 (50 %)	11 (45.8 %)	5 (50 %)	5 (21.7 %)
Full-term (38-42 wks.)	8 (66.7 %)	2 (66.7 %)	7 (100 %)	4 (50 %)	13 (54.2 %)	5 (50 %)	18 (78.3 %)
Post-term (> 42 wks.)	--	1 (33.3 %)	--	--	--	--	--
Current Weight (kgs.)							
Median	11.39	12.70	8.50	8.50	7.35	6.20	4.30
Min-Max	(8.12 , 20.60)	(12.20 , 13.50)	(7.30 , 10.70)	(5.10 , 10.40)	(4.62 , 11.30)	(3.50 , 8.86)	(3.27 , 5.60)
N	12	3	7	8	24	10	23
DEMOGRAPHIC INFORMATION	**COHORT I-A**	**COHORT I-B**	**COHORT II-A**	**COHORT II-B**	**COHORT III**	**COHORT IV**	**COHORT V**
Confirmed Influenza Diagnosis							
Viral culture	1 (8.3 %)	--	--	1 (12.5 %)	--	--	1 (4.3 %)
Rapid influenza diagnostic test	11 (91.7 %)	3 (100 %)	7 (100 %)	7 (87.5 %)	24 (100 %)	10 (100 %)	22 (95.7 %)
Location of subject							
Inpatient non-ICU	8 (66.7 %)	1 (33.3 %)	3 (42.9 %)	2 (25 %)	6 (25 %)	2 (20 %)	18 (78.3 %)
Inpatient ICU	1 (8.3 %)	1 (33.3 %)	--	2 (25 %)	--	--	5 (21.7 %)
Outpatient	3 (25 %)	1 (33.3 %)	4 (57.1 %)	4 (50 %)	18 (75 %)	8 (80 %)	--
Missing	--	--	--	--	--	--	--

In total, there were 8 patients lost to follow-up and 3 who withdrew consent. Ten subjects did not have PK results, due to early termination (2), failure to return for PK draw visit (2), parental refusal to allow completion of PK sampling (3) and insufficient blood draw (3). In Cohort V (aged 0-2 months), there were 23 patients, three of whom were lost to follow-up and one was terminated due to consent withdrawal by guardian.

Outcomes and estimation

Primary endpoint

The results on the primary endpoint, pharmacokinetics of oseltamivir and oseltamivir carboxylate in children, are discussed in section 2.3.6 of this assessment report.

Secondary endpoint

The results of the secondary safety endpoints ('To describe the frequency of all adverse events (AEs), including neurologic AEs, among treated children') are described in the section on Clinical Safety.

The results on the virological secondary endpoints 'To assess the clearance of virus and viral ribonucleic acid (RNA) (quantitative) as a function of drug PK; to determine the potential for the development of resistance to oseltamivir as a function of pharmacokinetics and age (or cohort)') are described below.

Virological results (pharmacodynamic)

Influenza-associated events were assessed by the subjects' parents at each visit and included cough, crying more than usual, diarrhoea, fever, poor appetite, not sleeping well, irritable/fussy, not playing/malaise, headache, sore throat, muscle aches/pain, cough, nasal congestion, vomiting, tachycardia, tachypnoea, otitis media, wheezing and oxygen use.

Cessation of influenza symptoms by cohort are presented in Table 7.

Table 7.

DAYS TO NO SYMPTOMS	COHORT I-A (N=12)	COHORT I-B (N=3)	COHORT II-A (N=7)	COHORT II-B (N=8)	COHORT III (N=24)	COHORT IV (N=10)	COHORT V (N=23)
Days to No Symptom							
Median	10	10	10	30 + *	10	7.50	10
Min-Max	(5 , 30 +)	(10 , 30 +)	(5 , 30 +)	(1 , 30 +)	(3 , 30 +)	(5 , 30 +)	(1 , 30 +)
N	12	3	7	8	24	10	23

*** Times were censored at 30 days**

Influenza viral load ($TCID_{50}$) was also measured by culture by cohort and day of study. Spearman correlation coefficients of the $TCID_{50}$ values from culture with the log viral load by PCR were calculated for each study day (Table 8).

Table 8. Spearman Correlations of TCID50 with Log10 (Viral Load)

Day	Correlation	p-value
1	0.83353	$p < 0.0001$
3	0.74543	$p < 0.0001$
5	0.82836	$p < 0.0001$
10	0.22631	$p = 0.0615$

The median days to viral loads less than 50 copies/ml by cohort were as follows: Cohort IA: 5 days (11 subjects); Cohort IB: 4.5 days (2 subjects); Cohort IIA: 4 days (5 subjects); Cohort IIB: 4 days (5 subjects); Cohort III: 4 days (18 subjects); Cohort IV: 3 days (8 subjects); and Cohort V: 5 days (21 subjects). For subjects terminated early for any reason, all available data were used.

The following analyses yielded no statistically significant correlations or interesting trends:

1. Baseline viral load versus age (dose cohort);
2. Baseline viral load versus number of influenza symptoms at presentation (with and without adjustment for dose cohort);
3. Baseline viral load versus duration in days of symptoms (with and without adjustment for dose cohort);

4. Viral strain (H1, H3, B) versus number of symptoms at presentation (with and without adjustment for dose cohort);
5. Viral strain (H1, H3, B) versus duration of symptoms (with and without adjustment for dose cohort); and
6. Baseline viral load versus viral strain (H1, H3, B) (with and without adjustment for dose cohort).

Resistance results

Haemagglutinin (HA) and neuraminidase (NA) are major influenza surface antigens. The HA protein is responsible for virus attachment to the sialic acid receptors on the host cell, whereas the enzymatic activity of the influenza NA plays a key role in releasing progeny virions from the host cell and also in facilitating viral spread throughout the upper airways. Both NA and HA influence virus susceptibility to NAIs. Influenza viruses with reduced sensitivity to NAI typically contain mutations in the NA which directly or indirectly alter the shape of the NA catalytic site, thus reducing the inhibitor binding ability. The most frequently reported change conferring oseltamivir resistance in that viral context is the H275Y neuraminidase mutation. Besides NA mutations, NAI resistance could also emerges in vitro due to mutations in or near the HA receptor binding site. Such HA changes are thought to reduce viral dependency on NA activity.

Over the four influenza seasons 2006-2010 in the Northern Hemisphere, a total of 87 subjects were enrolled at 16 academic medical centres across the United States. Specimens from 19 subjects were all culture-negative, thus no additional resistance investigation was performed on these as per protocol. The number of virus specimens isolated from each lineage and subtype was the following:

- Influenza A H1N1, 8 subjects;
- Influenza A H1N1 pandemic, 37 subjects;
- Influenza A H3N2, 18 subjects; and
- Influenza B, 5 subjects.

Seasonal influenza A/H1N1 resistance: The presence of the H275Y oseltamivir resistance mutation was observed in the virus-positive samples of 6 out of 8 subjects as determined by sequencing. All of the sequenced isolates obtained in 2009 carried this mutation. All the mutations were present in each of these specimens at baseline and likely reflect the genotype of the acquired infection.

Pandemic influenza A/H1N1 resistance: Isolates from 37 subjects were sequenced to provide genotypic information on the HA and NA. None of the sequences carried the H275Y oseltamivir resistance mutation by sequencing analysis at baseline. However, isolates from two individuals acquired H275Y mutations during the course of therapy. Additionally, one subject had a mixed virus population where a detectable minority carried the H275Y mutation.

Influenza A/H3N2 resistance: No mutations associated with oseltamivir resistance were identified in 18 influenza A/H3N2 infected subjects providing genotyping information for NA.

Influenza B resistance: Polymorphisms were observed at position 198 in B isolates, but it did not appear to correlate with susceptibility to OC.

The study was not designed to assess efficacy. As all subjects received the same antiviral therapeutic intervention and there was no control group, these results are descriptive. The virus type/subtype findings were consistent with the epidemiological data from the 2009-2010 influenza pandemic.

Study WP22849

Study title

An Open-Label, Prospective, Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Oseltamivir in the Treatment of Infants 0 to <12 Months of Age with Confirmed Influenza Infection in the 96 Hours Prior to the First Dose.

In response to the H1N1 flu pandemic in 2009, Health Authorities issued emergency dosing guidelines for infants aged less than 1 year based on provisional analyses of PK and safety data from the CASG114 clinical trial. Given the limited data available at that time, differing dosing recommendations for infants <1 year were suggested by the Health Authorities. The study WP22849 was conducted to further investigate and harmonise the appropriate dosing recommendations for oseltamivir in this patient population.

WP22849 was a fully MAH-sponsored study conducted in Europe. The study was an open-label, non-randomised, prospective, PK/PD and safety evaluation of oseltamivir in the treatment of infants up to 12 months of age with laboratory confirmed influenza infection. The study is part of the Paediatric Investigational Plan (PIP).

Methods

Study title	WP22849: An open label, prospective, pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir (Tamiflu®) in the treatment of infants 0 to <12 months of age with confirmed influenza infection.
Study centres	11 centres in Europe (Spain, Italy, Germany, France, Belgium, Poland).
Period of trial	2010 to 2012
Objectives	Primary: • To define the pharmacokinetics (PK) of oseltamivir and oseltamivir carboxylate in children with confirmed influenza less than two years of age. Secondary: • To describe the frequency of all adverse events (AEs), including neurologic AEs, among treated children • To assess the clearance of virus and viral ribonucleic acid (RNA) (quantitative) as a function of drug PK • To determine the potential for the development of resistance to oseltamivir as a function of pharmacokinetics and age (or cohort) • To explore other pharmacodynamic (PD) parameters (e.g., resolution of fever).
Design	Prospective, open-label study of the PK/PD and safety of oseltamivir therapy in three cohorts of infants with influenza infection, according to postnatal age.
Study subjects	Children < 24 months of age
Inclusion criteria	• Signed informed consent from parent(s) or legal guardian(s) • Postnatal age (defined as date of birth to date of enrolment) of <1 year • Confirmed laboratory diagnosis of influenza by PCR or rapid influenza diagnostic test within 96 hours prior to first dose • Duration of influenza symptoms ≤ 96 hours prior to first dose
Study medication	Oseltamivir capsules, 75 mg, for pharmacy compounding to a final

	concentration of 10 mg/mL.
Dose/route/regimen/duration (please see text for explanation on Cohort IA and IB)	Cohort I: infants 91 to < 365 days, oseltamivir 3 mg/kg BID Cohort II: infants 31 to 90 days, oseltamivir 2.5 mg/kg BID Cohort III: infants 0 to 30 days, oseltamivir 2 mg/kg BID
Criteria for evaluation	• Pharmacokinetics: The following PK parameters of oseltamivir and OC were estimated from plasma drug concentrations by non-compartmental methods: AUC_{0-12}, C_{max}, and C_{min} (at steady-state) (primary variables) C_{last}, t_{max}, $t_{1/2}$, t_{last}, lambda Z (ke), CL/F, V/F, and CLm/F (secondary variables) Where the parameters are defined as follows: C_{max} : The maximum observed plasma concentration t_{max} : The time to the maximum observed plasma concentration C_{min} : The minimum observed plasma concentration C_{last} : The last measurable plasma concentration t_{last} : The time of the last measurable plasma concentration AUC_{0-12} : The area under the concentration versus time curve from time zero to 12 hours. Computed using the linear trapezoidal rule. Lambda Z: The apparent first-order elimination rate constant determined by linear regression analysis of terminal data points $t_{1/2}$: The apparent elimination half-life, computed as ln(2)/lambda Z CL/F: The total plasma clearance expressed as a function of bioavailability V/F: The volume of distribution expressed as a function of bioavailability CLm/F: The apparent plasma clearance of the metabolite expressed as a function of bioavailability The exposure variables AUC_{0-12}, C_{min}, and C_{max} (at steady state) were used for further exposure and response relationship analyses. • Pharmacodynamics: Although the study was not powered to detect differences in PD markers, the objective of the PD assessments was to derive relationships between drug exposure and virologic and selected clinical responses to treatment and AEs. In addition, the relationship between oseltamivir trough concentrations (Cmin) and viral resistance to inhibition by oseltamivir were examined. For assessing viral resistance, phenotyping (neuraminidase sensitivity expressed as half maximal inhibitory concentration [IC50] to oseltamivir) and genotyping (sequence analysis of the neuraminidase gene) were also done. The proportion of patients who developed otitis media, bronchitis, pneumonia, or sinusitis (secondary illnesses) at least 48 hours after the first dose, between Day 3 and Day 30 were summarized by treatment group and analysed as a PD parameter.

	• Safety: Safety during the entire study period including the following: AEs, vital signs, physical examination, and laboratory tests.
Statistical methods	<u>Pharmacokinetics:</u> For non-compartmental analyses (NCA), results that were below the limit of quantification (BLQ) were treated as concentrations of 0 ng/mL if they occurred before any measurable concentration, but treated as missing data if they occurred after one or more measurable concentrations. Predose actual sampling times were set to time zero. Actual sampling times were used for the non-compartmental plasma PK analysis and for the individual plasma concentration versus time profiles. Scheduled sampling times were used for the creation of summary tables and mean plasma concentration versus time profiles. T_{last} was <12 hours for all patients. The following WinNonlin default calculation rules were applied to estimate the concentration at t=12 hours for use in estimation of AUC_{0-12}: • If a start or end time occurred after the last numeric observation (ie, not "missing" or "BLQ") and Lambda Z was estimable, Lambda Z was used to estimate the corresponding Y: Y = exp(alpha – Lambda-Z * t) = exp(alpha – Lambda-Z * t_{last}) * exp(–Lambda-Z * (t-t_{last})) = (predicted concentration at t_{last}) * exp(–Lambda-Z * (t-t_{last})) • If a start or end time failed after the last numeric observation and Lambda Z was not estimable, the partial area was not calculated. • If the start time for a partial area was before the last numeric observation and the end time was after the last numeric observation, then the linear trapezoidal rule was used for the area from the last observation time to the end time of the partial area. A minimum of 3 data points were used for lambda Z estimation. By reporting tool convention, if n<3, no summary statistics were calculated. The following formulas were used for dose calculation: • Oseltamivir dose calculated as: MTDOSE (mL) * 10 mg/mL = Dose oseltamivir (mg) • Oseltamivir carboxylate(OC) dose calculated as: Dose oseltamivir (mg) * (MW OC / MW oseltamivir) = Dose OC (mg) with molecular weight ratio OC / oseltamivir = 284/312 = 0.91 No patients/time-points were excluded from the PK data analysis. Model-based analyses were conducted separately to estimate population PK parameters and to identify covariates (such as age and weight) that may influence them and their variability. Pharmacodynamics: The viral titer was measured by culture and reported in log10 (50% tissue culture infective dose [TCID50]). The viral load was analysed by PCR and reported as both cycle threshold and log10 particles/mL. The rate at which the amount of virus declines was calculated for both methods. The rate of decline of the viral RNA, measured by reverse transcriptase PCR, was calculated as the slope of log10 (TCID50) for all patients with positive culture at baseline. The patients' data points included all values between the baseline log10 (TCID50) and the 1st negative culture

	(log10 [TCID50] ≤ 0.5). The rate of decline of the viral load was calculated as the slope of log10 (particles/mL) for all patients with positive PCR at baseline. The patient data points included all log10 (particles/mL) values obtained between baseline and Day 11 (no limit of detection was available for PCR). The time to cessation of viral shedding (by culture) was calculated for all patients with positive culture at baseline using all data points between the start of the treatment and the 1st timepoint of negative culture (log10 [TCID50] ≤ 0.5) without subsequent positive culture results. These time-to-event analyses were only performed for the viral titer. The effect of oseltamivir on body temperature in this population was assessed. Fever was defined as axillary temperature > 37°C. Rectal temperature measurements were converted to the axillary temperature by subtracting 1°C prior to the analyses. The analyses included the time to resolution of fever and the rate of decline of body temperature to the afebrile state. Both the analyses were performed for all patients with fever at baseline. The time to resolution of fever was defined as the time from the initiation of treatment to first time the afebrile state was reached and maintained for at least 21.5 hours. The rate of decline in body temperature was calculated as the slope of body temperatures between the baseline temperature and the 1st temperature below 37°C.
Safety analyses	AEs were listed by patient and summarized by age cohort, by body system, and by preferred term within each body system. Summary tables for AEs included AEs occurring both on-treatment and off-treatment, defined as: • On-treatment AE: started after the first study oseltamivir administration but not more than 3days after the last study oseltamivir administration. • Off-treatment AE: started more than 3 days after the last study oseltamivir administration until Day 30. Influenza symptoms by intensity were reported separately from AEs. Neurologic assessments (Glasgow Coma Scale and Infant Face Scale) were analysed separately. Laboratory assessments were not collected routinely, only at unscheduled visits. Normal ranges were provided by the investigators, and therefore could differ across sites. The flagging of out-of-range values was using the investigator ranges.

Treatment

All patients received Tamiflu capsules, 75 mg, for pharmacy compounding to a final concentration of 10 mg/ml, at 12 hour intervals for 5 days (a total of 10 doses):

- Cohort I: infants 91 to < 365 days received oseltamivir 3 mg/kg BID.
- Cohort II: infants 31 to 90 days received oseltamivir 2.5 mg/kg BID.
- Cohort III: infants 0 to 30 days received oseltamivir 2 mg/kg BID.

Dosing could continue for a further 5 days (an additional 10 doses) if the specimen collected on Day 6 was positive for influenza or the patient had symptoms consistent with ongoing viremia. Therefore, the maximum possible number of doses was 20.

Sample size

A minimum of 65 and up to a maximum of 85 male and female infants were to be enrolled according to age into three cohorts (Table 9). Once eligibility was confirmed, patients were enrolled into the age-appropriate cohort in parallel.

Table 9. Planned enrolment per cohort

Cohort	Age Range (Postnatal age)	Minimum No. Patients Enrolled	Maximum No. Patients Enrolled
I	91 to < 365 days	40	50
II	31 to 90 days	20	25
III	0 – 30 days	5	10

Analysis populations

All enrolled patients are patients who showed positive influenza identified either by rapid diagnostic test or by PCR at screening, enrolled by the clinical cut-off date, and signed the ICF. Patients are reported according to the age cohort based on the patient's age at baseline.

Intent-to-treat patients with confirmed influenza infection (ITTI) are the all enrolled patients with a positive influenza infection confirmed by culture or PCR at baseline or anytime during the study. The ITTI population is the primary PD analysis population unless specified otherwise.

Safety Analysis Population includes all treated patients with at least one post-baseline safety assessment (i.e., using the vital signs as the criterion to identify the safety assessments).

The *pharmacokinetic analysis population* includes all treated patients with at least one blood sample evaluable for drug concentration level.

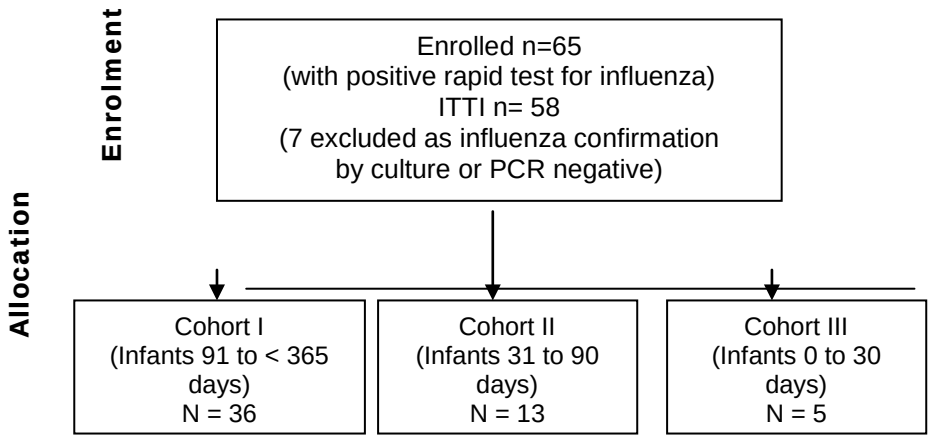
Patients could be excluded from the PK analysis population if they significantly violated the inclusion or exclusion criteria, deviated significantly from the protocol or if data were unavailable or incomplete, which could influence the PK analysis. Excluded cases were documented together with the reason for exclusion. All decisions on exclusions from the analysis were to be made prior to database closure. The population for the PK/PD analysis of the association of PD endpoints (temperature, viral kinetics, and resistance) with PK parameters (AUC, C_{min}, and C_{max}), includes patients in both the PK analysis population and the ITTI population.

No efficacy analysis was planned or performed.

Results

The results were reported in two separate CSRs; one for the first 54 patients recruited 2010-2011, and another including the 11 additional patients recruited 2011-2012.

Patient flow



Recruitment

The study was originally planned to start during the 2009/2010 pandemic; however the MAH had not been able to start recruitment of patients according to plan: by 19th January 2011 only 3 patients had been enrolled. WP22849 recruited 54 of the planned 65 infants in the 2010/11 influenza season and 11 patients in the 2011/12 influenza season. The originally planned minimum number of subjects was thus achieved.

Conduct of the study

A placebo arm was considered unethical for this population. As there are no drugs approved for the treatment of influenza in this population, there is no comparator arm. The study is therefore open label. The study has several inclusion and exclusion criteria. These criteria ensure that an infant enrolled in the study is protected and that the study population is homogenous enough to assess PK/PD and exclude co-morbidities that preclude the assessment of safety.

To ensure that infants may be able to benefit from treatment, only infants with confirmed influenza were allowed to enrol in the study. This was essential to differentiate influenza from other viral illnesses, including respiratory syncytial virus (RSV) or sepsis, which will not respond to oseltamivir therapy. In the pivotal trials in children and adults, efficacy was demonstrated when oseltamivir was given within 48 hours of flu symptom onset. However, given the greater morbidity in this population and the time taken for laboratory confirmation, in this trial, infants with flu symptoms up to 96 hours prior to administration of the first dose were enrolled.

Infants with concurrent gastrointestinal conditions that preclude absorption of the drug are unlikely to benefit from therapy with oseltamivir and were, therefore, excluded. Following absorption, the liver is one of the main sites for conversion of the prodrug oseltamivir to the active moiety oseltamivir carboxylate (OC), which is excreted by the kidneys. To ensure the safety of the infant, infants with hepatic decompensation or renal failure were disallowed from participating in the study.

The kidney is the primary route of excretion of oseltamivir. The kidney changes dramatically through gestation and the first year of life. These developmental changes will have an important effect on the PK of oseltamivir in this population. Although nephrogenesis is complete by 36 weeks gestation, glomerular filtration rate (GFR) is still much lower at birth compared with older children and while there is rapid improvement following birth, GFR only reaches values comparable to adults and older children by age 6–12 months. In addition, tubular function increases throughout foetal and infant maturation but is delayed compared with GFR. However, as with GFR, there is improving function across this study population which will impact oseltamivir PK. To minimise the potential degree of variability in these developmental factors within the study population, only infants with a post-conceptual age of at least 36 weeks were enrolled into the study.

There were no protocol violations relating to trial conduct that affected the analysis.

There was one major protocol violation of “inadequate consent”. One patient’s data were excluded from the database and the analysis, although 2 doses of oseltamivir (total of 26 mg) were received by this patient, because the original informed consent form was lost and therefore it was not possible for the study monitor to review/monitor the data. On Day 2 of the study, the infant was removed from the study and the data from this patient was deleted from the database and the original data remain with the investigator. In the one day the patient received study drug, no AEs were reported.

The non-inclusion of a placebo arm was considered acceptable by the CHMP in a PK/PD and safety study. It is important to note that the study recruited only infants with a post-conceptual age of at least 36 weeks. Therefore, information on preterm infants remains missing.

The current and proposed SmPC reflect this matter in section 4.1 as follows: 'Tamiflu is indicated in adults and children including full term neonates' and in Section 4.8 as follows: 'Insufficient data are available for infants who have a post-conceptual age of less than 36 weeks.'

Baseline data

Overall, 55% of patients were male and 94% white. The number of subjects enrolled was 40, 20, and 5 in cohorts I, II, and III, respectively. The median gestational age was 39 weeks (range 25-41).

Influenza type was A was found in 42 of 65 patients (65%); 16 patients (25%) had influenza type B and 7 (11%) had unconfirmed influenza. These 7 patients were excluded from the ITTI population. Of the 42 type A patients reported in the ITTI population, 32 (76.2%) were A(HIN1)pdm09 and 10 were A(H3). A majority (68%) of the patients had influenza symptoms for ≤ 48 hours: 68%, 70%, and 3/5 in Cohorts I, II, and III, respectively.

Only 60% of subjects were febrile at baseline. However, based on location, the study population seems to represent a sample of patients with rather severe influenza, as 70 % of subjects were hospitalised, including 8 % treated in an intensive care unit.

Only 5 subjects were below 1 month of age, and the youngest study subject was 18 days old.

Numbers analysed

All available data from enrolled patients were included in the safety analyses. Influenza was confirmed in 58/65 patients by culture (50% tissue culture infective dose $TCID_{50}$ test) or by viral load (PCR test). These 58 patients comprised the intent-to-treat infected (ITTI) population. The 7 patients excluded (6 from the original study report of 54 patients) from the ITTI population were patients enrolled with a positive rapid test for influenza although the presence of influenza was not confirmed by culture or PCR.

Outcomes and estimation

There were altogether 42 subjects with Influenza A, 16 with Influenza B and 7 with influenza of unknown type. 5 patients were treated in an intensive care unit, 40 hospitalized but not in an intensive-care unit, and 20 outpatients. The PK data are assessed in section 2.3.6 of this report. The secondary endpoints are descriptive, therefore no estimation was performed.

No exposure-response relationships (efficacy, resistance or safety) were evident following exploratory analysis.

Influenza-associated events

Fever, rhinitis/nasal congestion/coryza, cough, and pharyngitis were the most frequently reported influenza symptoms at baseline in the 65 patients. At baseline, 60% of the ITTI patients had fever. At Day 3, 90% of the patients had already become afebrile with all patients becoming afebrile by Day 10. Three patients reported secondary illnesses (otitis media and pneumonia), all subsequently resolved without sequelae.

Virological results and resistance

All ITTI patients had positive viral culture (or PCR) at baseline or during the study. All patients, except one, had negative viral culture at Day 11. At Day 6, after 10 treatment doses, 60% of patients had stopped shedding (by culture). The overall median time to cessation of viral shedding by culture was close to 5 days, and the distribution of time to cessation of viral shedding was similar across the 3 age cohorts. By Day 18, all patients had stopped shedding viruses.

Seven patients (10,8%) developed treatment-emergent viral resistance due to mutations in the neuraminidase gene, all type A. The narratives for each patient with post-baseline resistance are provided. None of these patients had a longer duration of treatment and their disease course was not unusual from a clinical point of view.

Four patients were treated for a total of 10 days (20 doses) due to patient remaining symptomatic and/or influenza PCR positive at Day 6. One had influenza B. In one of these patients, a local assessment of resistance showed the presence of NA 275Y mutation that could not be confirmed centrally as the only post-baseline sample could not be cultured. The other 3 had no evidence of oseltamivir resistance.

The study was not planned to demonstrate efficacy. Consequently, as there was no control group, it is not possible to determine the effect of oseltamivir treatment in the course of influenza in the study population.

The emergence of resistance to oseltamivir during this study is in line with other data on development of resistance during oseltamivir treatment.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10. Summary of trial CASG114

Study title	A pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir (Tamiflu®) for the treatment of children less than 24 months of age with confirmed influenza infection (CASG114)
Study centres	16 academic medical centres in the United States.
Period of trial	2006–2010. Clinical phase I/II
Objectives	Primary: • To define the pharmacokinetics (PK) of oseltamivir and oseltamivir carboxylate in children with confirmed influenza less than two years of age. These PK data will lead to a more precise dosing recommendation for this population. Secondary: • To describe the frequency of all adverse events (AEs), including neurologic AEs, among treated children • To assess the clearance of virus and viral ribonucleic acid (RNA) (quantitative) as a function of drug PK • To determine the potential for the development of resistance to oseltamivir as a function of pharmacokinetics and age (or cohort)
Design	Prospective, age-stratified, open-label
Study subjects	Children < 24 months of age
Inclusion criteria	• Signed informed consent from parent(s) or legal guardian(s) • Age: o Cohort I 12–23 months o Cohort II 9–11 months o Cohort III 6–8 months o Cohort IV 3–5 months o Cohort V 0–2 months • Confirmed laboratory diagnosis of influenza by viral culture or rapid influenza diagnostic test within 96 hours prior to study enrolment • Duration of influenza symptoms ≤ 96 hours
Study medication	Oseltamivir oral suspension 12 mg/ml
Dose/route/regimen/duration (please see text for explanation on Cohorts IA and IB; and IIA and IIB)	Cohort IA (12–23 month old): 30 mg BID Cohort IB (12–23 month old): 3.5 mg/kg BID Cohort IIA (9–11 month old): 3.0 mg/kg BID Cohort IIB (9–11 month old): 3.5 mg/kg BID Cohort III (6–8 month old): 3.0 mg/kg BID Cohort IV (3–5 month old): 3.0 mg/kg BID Cohort V (0–2 month old): 3.0 mg/kg BID Oral administration for 5 days (10 doses)

Criteria for evaluation	• Efficacy: N.A. (Phase I/II study) • Pharmacodynamics: o Correlation of clearance of viral RNA (by PCR) to PK and age of subject. o Correlation of clearance of virus (by culture) to PK and age of subject. o Correlation of development of oseltamivir resistance to PK and age of subject. • Pharmacokinetics: o OC AUC_{12} between 2,660 ng•hr/ml and 7,700 ng•hr/ml. • Safety: o Number and characteristic of AEs described as neurologic events. o Overall reported AEs thought to be associated with study therapy.
Statistical methods	The statistical methods are largely descriptive. Means, medians, maximums, and minimums are computed for continuous variables. Frequencies and proportions are computed for categorical variables. Spearman correlation coefficients are used to describe the association of PK parameters to various patient and disease parameters.

Table 11. Summary of trial WP22849

Study title	WP22849: An open label, prospective, pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir (Tamiflu®) in the treatment of infants 0 to <12 months of age with confirmed influenza infection.
Study centres	11 centres in Europe (Spain, Italy, Germany, France, Belgium, Poland).
Period of trial	2010 to 2012
Objectives	Primary: • To define the pharmacokinetics (PK) of oseltamivir and oseltamivir carboxylate in children with confirmed influenza less than two years of age. Secondary: • To describe the frequency of all adverse events (AEs), including neurologic AEs, among treated children • To assess the clearance of virus and viral ribonucleic acid (RNA) (quantitative) as a function of drug PK • To determine the potential for the development of resistance to oseltamivir as a function of pharmacokinetics and age (or cohort) • To explore other pharmacodynamic (PD) parameters (e.g., resolution of fever).
Design	Prospective, open-label study of the PK/PD and safety of oseltamivir therapy in three cohorts of infants with influenza infection, according to postnatal age.
Study subjects	Children < 24 months of age
Inclusion criteria	• Signed informed consent from parent(s) or legal guardian(s) • Postnatal age (defined as date of birth to date of enrolment) of <1 year • Confirmed laboratory diagnosis of influenza by PCR or rapid influenza diagnostic test within 96 hours prior to first dose • Duration of influenza symptoms ≤ 96 hours prior to first dose
Study medication	Oseltamivir capsules, 75 mg, for pharmacy compounding to a final concentration of 10 mg/ml.
Dose/route/regimen/duration (please see text for explanation on Cohort IA and IB)	Cohort I: infants 91 to < 365 days, oseltamivir 3 mg/kg BID Cohort II: infants 31 to 90 days, oseltamivir 2.5 mg/kg BID Cohort III: infants 0 to 30 days, oseltamivir 2 mg/kg BID
Criteria for evaluation	• Pharmacokinetics: The following PK parameters of oseltamivir and OC were estimated from plasma drug concentrations by non-compartmental methods: AUC_{0-12}, C_{max}, and C_{min} (at steady-state) (primary variables) C_{last}, t_{max}, $t_{1/2}$, t_{last}, lambda Z (ke), CL/F, V/F, and CLm/F (secondary variables) Where the parameters are defined as follows: C_{max} : The maximum observed plasma concentration t_{max} : The time to the maximum observed plasma concentration C_{min} : The minimum observed plasma concentration C_{last} : The last measurable plasma concentration t_{last} : The time of the last measurable plasma concentration AUC_{0-12} : The area under the concentration versus time curve from time

	zero to 12 hours. Computed using the linear trapezoidal rule. Lambda Z: The apparent first-order elimination rate constant determined by linear regression analysis of terminal data points $t_{1/2}$: The apparent elimination half-life, computed as ln(2)/lambda Z CL/F: The total plasma clearance expressed as a function of bioavailability V/F: The volume of distribution expressed as a function of bioavailability CLm/F: The apparent plasma clearance of the metabolite expressed as a function of bioavailability The exposure variables AUC_{0-12}, C_{min}, and C_{max} (at steady state) were used for further exposure and response relationship analyses. • Pharmacodynamics: Although the study was not powered to detect differences in PD markers, the objective of the PD assessments was to derive relationships between drug exposure and virologic and selected clinical responses to treatment and AEs. In addition, the relationship between oseltamivir trough concentrations (Cmin) and viral resistance to inhibition by oseltamivir were examined. For assessing viral resistance, phenotyping (neuraminidase sensitivity expressed as half maximal inhibitory concentration [IC50] to oseltamivir) and genotyping (sequence analysis of the neuraminidase gene) were also done. The proportion of patients who developed otitis media, bronchitis, pneumonia, or sinusitis (secondary illnesses) at least 48 hours after the first dose, between Day 3 and Day 30 were summarized by treatment group and analysed as a PD parameter. • Safety: Safety during the entire study period including the following: AEs, vital signs, physical examination, and laboratory tests.
Statistical methods	<u>Pharmacokinetics</u>: For non-compartmental analyses (NCA), results that were below the limit of quantification (BLQ) were treated as concentrations of 0 ng/ml if they occurred before any measurable concentration, but treated as missing data if they occurred after one or more measurable concentrations. Pre dose actual sampling times were set to time zero. Actual sampling times were used for the non-compartmental plasma PK analysis and for the individual plasma concentration versus time profiles. Scheduled sampling times were used for the creation of summary tables and mean plasma concentration versus time profiles. Tlast was <12 hours for all patients. The following WinNonlin default calculation rules were applied to estimate the concentration at t=12 hours for use in estimation of AUC0-12: • If a start or end time occurred after the last numeric observation (i.e., not "missing" or "BLQ") and Lambda Z was estimable, Lambda Z was used to estimate the corresponding Y: Y = exp(Alpha – Lambda-Z * t) = exp(Alpha – Lambda-Z * tlast) * exp(–Lambda-Z * (t-tlast)) = (predicted concentration at tlast) * exp(–Lambda-Z * (t-tlast)) • If a start or end time failed after the last numeric observation and Lambda Z was not estimable, the partial area was not calculated. • If the start time for a partial area was before the last numeric observation and the end time was after the last numeric observation, then the linear trapezoidal rule was used for the area from the last observation time to the end time of the partial area. A minimum of 3 data points were used for lambda Z estimation. By reporting tool convention, if n<3, no summary statistics were calculated. The following formulas were used for dose calculation: • Oseltamivir dose calculated as: MTDOSE (ml) * 10 mg/ml = Dose oseltamivir (mg) • Oseltamivir carboxylate(OC) dose calculated as: Dose oseltamivir (mg) * (MW OC / MW oseltamivir) = Dose OC (mg) with molecular weight ratio OC / oseltamivir = 284/312 = 0.91 No patients/time-points were excluded from the PK data analysis. Model-based analyses were conducted separately to estimate population PK

	parameters and to identify covariates (such as age and weight) that may influence them and their variability. Pharmacodynamics: The viral titre was measured by culture and reported in log10 (50% tissue culture infective dose [TCID50]). The viral load was analysed by PCR and reported as both cycle threshold and log10 particles/ml. The rate at which the amount of virus declines was calculated for both methods. The rate of decline of the viral RNA, measured by reverse transcriptase PCR, was calculated as the slope of log10 (TCID50) for all patients with positive culture at baseline. The patients' data points included all values between the baseline log10 (TCID50) and the 1st negative culture (log10 [TCID50] ≤ 0.5). The rate of decline of the viral load was calculated as the slope of log10 (particles/ml) for all patients with positive PCR at baseline. The patient data points included all log10 (particles/ml) values obtained between baseline and Day 11 (no limit of detection was available for PCR). The time to cessation of viral shedding (by culture) was calculated for all patients with positive culture at baseline using all data points between the start of the treatment and the 1st time point of negative culture (log10 [TCID50] ≤ 0.5) without subsequent positive culture results. These time-to-event analyses were only performed for the viral titre. The effect of oseltamivir on body temperature in this population was assessed. Fever was defined as axillary temperature > 37°C. Rectal temperature measurements were converted to the axillary temperature by subtracting 1°C prior to the analyses. The analyses included the time to resolution of fever and the rate of decline of body temperature to the afebrile state. Both the analyses were performed for all patients with fever at baseline. The time to resolution of fever was defined as the time from the initiation of treatment to first time the afebrile state was reached and maintained for at least 21.5 hours. The rate of decline in body temperature was calculated as the slope of body temperatures between the baseline temperature and the 1st temperature below 37°C.
Safety analyses	AEs were listed by patient and summarized by age cohort, by body system, and by preferred term within each body system. Summary tables for AEs included AEs occurring both on-treatment and off-treatment, defined as: • On-treatment AE: started after the first study oseltamivir administration but not more than 3days after the last study oseltamivir administration. • Off-treatment AE: started more than 3 days after the last study oseltamivir administration until Day 30. Influenza symptoms by intensity were reported separately from AEs. Neurologic assessments (Glasgow Coma Scale and Infant Face Scale) were analysed separately. Laboratory assessments were not collected routinely, only at unscheduled visits. Normal ranges were provided by the investigators, and therefore could differ across sites. The flagging of out-of-range values was using the investigator ranges.

2.3.6. Discussion on clinical pharmacology

Exposure in neonates

Conversion of OP into the active metabolite OC is primarily mediated by the hepatic enzyme human carboxylesterase 1 (HCE-1). OC is almost exclusively excreted from the kidneys via both glomerular filtration and tubular secretion. Following birth, HCE-1 expression increases rapidly during the first year of life, and initial low levels of HCE-1 may result in reduced conversion to the active metabolite in neonates. Despite renal clearance increasing with age, exposure to the active metabolite increases gradually starting from the age of 3 years up to the age of 16 (Karadag-Oncel E, Ceyhan M. Oseltamivir in Neonates, Infants and Young Children: A Focus on Clinical Pharmacology. *Infectious Disorders - Drug Targets* 2013). Variability in HCE-1 expression in neonates may explain the larger variation in plasma concentrations of OC in that age group. Under dosing may reduce efficacy and hypothetically increase development of antiviral resistance.

On the other hand, renal maturation continues post-natally, thus in the smallest neonates excretion of OC may be reduced and exposure increased.

Dosage

The MAH has evaluated and successively explored the potential PK/PD relationship of the doses of oseltamivir used for the treatment of influenza confirmed cases in patients aged <1year. The main finding is that there was no significant correlation between exposure and clinical effect, as assessed by the duration of symptomatic disease and duration of viral shedding, which was not different from the duration profile already described for non-antiviral treated population in the literature. This lack of correlation does not seem to be adequately explained by the PK profile that has been reported for the younger population. In one of the studies, an inverse correlation between AUC and duration of symptomatic disease was observed.

Both the simulated data and the non-compartmental PK results of individual studies suggest similar trends by age group of OC and oseltamivir exposure in infants <1 year of age. The highest (and the most variable) exposure to OC on days 3-4 of treatment is observed in the youngest infants. This may be explained by slower renal elimination.

Considering the limits of the PK/PD data to support a dosing recommendation based on dose-response patterns, the MAH proposed a bridging strategy to define the dose for this age group, based on extrapolation from older age groups, i.e. groups closely age-related, and based on current recommendation made by regulatory agencies. The MAH proposed to use a weight-based uniform recommendation of 3 mg/kg BID dose for the paediatric population aged <1 year. Overall this strategy is endorsed as this is predicted to provide higher OC exposures than those observed with approved doses in adults and children aged 1–5 years, but the exposure is expected to be in the range well tolerated in adult patients. With the dosage 2.5 mg/kg BID most patients, but not all, would probably achieve the targeted OC exposure. Consequently, the proposed higher dosage yields more reliably an efficacious exposure in all infants. As the emergence of resistant mutations during treatment is hypothetically related to exposure, the proposed dosage of 3 mg/kg might be beneficial also from the viewpoint of resistance (see below for further details).

No data from new-born (younger than 2 weeks of age) infants were available from studies CASG114 and WP22849 to apply to the population PK model. Clinical data indicate that oseltamivir is efficiently metabolised to OC also in newborns. The absolute level of renal function is the most important factor regulating elimination of OC. The glomerular filtration rate increases rapidly during the first days after birth due to increased cardiac output and decreased renovascular resistance. OC is mainly distributed to extracellular water (ECW) and the ECW content in new-born is approximately two times higher than in adults: ~40-45% vs. 20% of bodyweight, respectively. Consequently, the volume of distribution per kg bodyweight is highest in infants. This means that to achieve similar OC concentration in ECW infants need higher oseltamivir dose per kg body weight than adults.

Newborn infants are inherently a variable population; therefore their OC plasma concentrations will be more variable than those in other populations. The dosage 3 mg/kg BID for 5 days in therapeutic indication “Treatment of influenza” was proposed by the MAH to ensure that those infants with lower exposures do not fall far outside the range associated with efficacy as this could lead not only to potential treatment failure but also to encourage the development of resistance. This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. This is endorsed by the CHMP. It is inherent in this approach that some infants will experience higher exposures; however these are expected to be safe and well tolerated based on the overall knowledge on safety profile of Tamiflu, including data from studies CASG114 and WP22849 as well as from studies in adult subjects using higher dosage than 75 mg BID.

Viral resistance

Natural mutations associated with reduced susceptibility to oseltamivir in vitro have been detected in influenza A and B viruses isolated from patients without exposure to oseltamivir. Resistant strains selected during oseltamivir treatment have been also isolated from both immunocompetent and immunocompromised patients. Immunocompromised patients and young children regardless of their immune competence are at higher risk of developing oseltamivir-resistant virus during treatment.

Even though the duration of viral shedding has not been affected by the exposure to a specific dose and duration of treatment, resistance emerged quickly amongst virus isolated from this age group, particularly in younger patients (<3 months). This raises some concern but the issue is well known.

Although considering the limitations of the studies herewith assessed in terms of lack of correlation between exposure and clinical effects, the rationale for the choice of posology is endorsed (as mentioned above); however the data derived from dose simulations provide only some reassurance that the proposed dose regimen of 3 mg/kg BID will not be associated with a significant risk of emergence of resistance and subsequent resistant virus transmission.

The issue of resistance is being continuously monitored via the ongoing Influenza Resistance Information Study (IRIS, NV20237), whose interim report covering the period March 2012 to March 2013 was assessed in procedure MEA 075.10. The final CSR for IRIS is due in 2016. This report is outside the remit of the current procedure, however, in summary, these were the key findings:

- No naturally occurring NAI resistance mutations were detected in the study cohort;
- The occurrence of treatment-emergent development of resistance mutations post-baseline remained low in adults. Of the 19 (out of 968) patients with resistance mutations detected by mutation-specific RT-PCR, 15 were children, 13 of which aged 1–5 years, all of whom were treated with oseltamivir. In the age group of 1–5 years, treatment-emergent resistance was most pronounced: H1N1pdm09: 33.3% (6/18); H3N2: 9.2% (7/76), and all influenza type A: 13.8% (13/94). The denominator for this calculation was the number of influenza-positive patients (by RT-PCR) who received oseltamivir and had at least one later sample tested by RT-PCR. All but two of the patients with post-baseline resistance mutations had mixed populations of resistant and wild-type strains.

Of note, the results were very similar in the previous 4-year update: resistant strains emerging during treatment were detected in children but no background resistance was noted one year later. It is however noteworthy that the IRIS study only includes subjects aged 1 year onwards.

It is not known why very young children and immunocompromised patients are at higher risk of developing oseltamivir resistance during the course of treatment. It has been speculated that this may be due to drug exposure below the therapeutic range and to a longer time of viral shedding; however, studies comparing the emergence of resistance with different doses of oseltamivir have not been conducted.

Even though selection of resistant strains during oseltamivir treatment occurs, transmission of resistant viruses seems to be overall an uncommon event. In the IRIS study, baseline susceptibility of influenza viruses to neuraminidase inhibitors including oseltamivir has remained high. In line with this finding, it is important to note that the emergence of resistant strains has not been identified to consistently affect clinical response of individual patients to oseltamivir or to systematically cause localised or epidemic spreading of resistant influenza. The mechanisms behind this are not yet understood, although it could be speculated that resistant strains are less virulent, or that the total viral load of resistant viruses is too low to cause clinical symptoms. Non-clinical evidence seems to indicate that NAI resistant influenza viruses may differ substantially in fitness and transmissibility (Yen et al. *Antimicrob Agents Chemother*, 2005). At least

some of the resistant mutants are less fit, with reduced ability to replicate and transmit (Herlocher et al. *J Infect Dis*. 2004).

In conclusion, if resistant strains are more prone to develop in young children due to longer time of viral shedding, it is important that the dosage in infants be set as close as possible to the therapeutic level. Ensuring sufficient therapeutic levels of oseltamivir in infants is the scope of the current variation. Based on the PK analyses, the recommended dosage for infants is proposed to be higher than the currently approved posology for children in a pandemic context. The CHMP considers that increasing the dosage to a therapeutic level should not increase the emergence of resistant strains, but rather the opposite.

The risk of resistance is overall considered of no major impact on the approval of the current variation; however the CHMP considers that it should be addressed post-approval. The CHMP requests to discuss in future PSURs the epidemiological relevance of emergence of resistant mutations and any potential increased risk of transmission of resistant viral mutants within the environment that would be associated to the dosing regimen proposed for this age group, and to investigate and discuss if there is any information concerning different dosages and emergence of resistance in this age group.

2.3.7. Conclusions on clinical pharmacology

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate, OC). OC is a selective inhibitor of influenza virus neuraminidase enzymes, which are viral surface proteins important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity.

No new data on pharmacodynamics of oseltamivir were included in the submission.

In the current SmPC, oseltamivir is indicated for infants less than 1 year of age during an influenza pandemic for treatment and for post-exposure prevention. The current variation to extend the use in infants less than 1 year of age in the treatment of influenza is based on PK/PD modelling from studies CASG114 and WP22849 as described above. There is no proposal to modify the indication for prevention of influenza.

The recommended dosage for treatment of pandemic influenza in the currently approved SmPC is 2 mg/kg BID for infants aged 0 to 1 month; 2.5 mg/kg BID for infants aged >1 month to 3 months, and 3 mg/kg BID for infants aged >3 months to 12 months. The aforementioned dosage for infants <6 months of age was approved in variation II/70 by the CHMP. It was based on interim data from study CASG114, and no data were available for infants aged 0 to 1 month at the time. The dosage proposed in the current variation is 3 mg/kg for all infants aged 0 to 12 months, based on PK data and modelling from data obtained in studies CASG114 and WP22849.

The MAH has used pharmacokinetic data, modelling and simulation to support the dosage of oseltamivir in infants <1 year of age. More than 600 oseltamivir and OC concentrations in 133 infants were measured, which is an impressive amount of data in this population. The population PK model was developed and evaluated using acceptable methods. It adequately describes the concentration-time profile of OC after oseltamivir is administered orally in infants less than 1 year of age. The concentration-time profile of the prodrug oseltamivir is less accurately described.

The population PK model was used to simulate OC and oseltamivir exposure in infants less than 1 year of age. Target OC exposure was based on observed exposure data in infants 1-2 years of age; simulated exposures were also compared with observed exposure in older children and in adults.

The simulations indicate that a 3 mg/kg BID regimen in infants <1 year of age is predicted to provide OC exposures that exceed those observed with marketed doses in adults on 75 mg BID and children 1-5 years

of age. The highest and most variable exposure is predicted for infants < 1 month of age. OC exposures are, however, not anticipated in any infant group to exceed those observed with dosage 150 mg BID in adults, which was the alternative, well tolerated dosage in pivotal phase 3 studies. It is predicted that with a lower dosage (e.g. 2.5 mg/kg BID) the target OC levels will not be achieved in all patients. Predicted oseltamivir exposures are anticipated to be similar to some of the exposures that have been shown to be tolerated across the oseltamivir clinical pharmacology program. Both the simulated data and the NCA PK results of individual studies suggest similar trends by age group of OC and oseltamivir exposure in infants < 1 year of age.

2.4. Clinical efficacy

The efficacy and safety of oseltamivir used for treatment and prophylaxis during seasonal outbreaks of influenza has been previously demonstrated in children aged 1 year and above. The clinical trials were conducted in healthy children and in children with chronic asthma.

The extension of indication to children below 1 year of age is based on two PK/PD and safety studies, CASG114 and WP22849. No new studies designed to assess efficacy were performed to support this submission, and this was found acceptable.

The strategy for determining a dose recommendation for infants included i) that the data would be analysed for evidence of a PK/PD relationship, then that relationship would be used to propose a suitable dose in infants; ii) that if no PK/PD relationship could be established, bridging to drug exposures known to be associated with efficacy in children > 1 year of age would be done to propose a dosing recommendation for infants.

The data of the two pooled studies CASG114 and WP22849 were bridged to exposure in older children where clinical efficacy had already been established in a large phase III randomized controlled trial (WV15758).

This approach was deemed appropriate for this patient population as a formal randomised placebo controlled (no active comparator available for this age group) efficacy study would have required hundreds of infants to be enrolled. Given the extensive experience with oseltamivir in older children and adults together with the experience with infants during the pandemic, it seemed unnecessary to expose large number of infants to either the demands of clinical trial or a placebo treatment.

Independent evidence exists that even in new-born babies the conversion of the prodrug OP to the active OC by the hepatic carboxylase 1 occurs sufficiently for attaining therapeutic levels of OC (Standing et al. *Antimicrob Agents Chemother*, 2012).

Currently there are no robust efficacy and/or PK data available for oseltamivir treatment of pre-term infants.

For further details see the section on Clinical Pharmacology.

Supportive studies

The MAH included in the current submission Clinical Study Reports (CSR) for some of the efficacy and PK studies in adults and in children aged >1 year, which have been previously assessed at the time of MA or other subsequent regulatory procedures. The trial conduct and efficacy results of such studies, listed below, are not assessed within this procedure.

Double-blind, randomized, placebo controlled studies of oseltamivir in the treatment of influenza:

- In adults aged 18-65 years: WV15670, WV15671, and WV15730.
- in children aged 1-12 years: WV15758

Uncontrolled studies:

- WV16193: A randomized, open-label, parallel group study of oseltamivir used for the management of influenza in households.
- JV16284: Phase II clinical study of oseltamivir phosphate for the treatment of influenza in children.
- PP16351: An open label study of the pharmacokinetics of oseltamivir in children after a single dose. (Children aged 0-5 years).
- NP15826: An open label study of the pharmacokinetics of Ro 64-0796/GS4104 in children. (Children aged 5-18 years).

Of note, the included supportive studies do not contain efficacy data on oseltamivir treatment in children aged 0-1 years of age, and therefore they are considered supportive.

2.4.1. Conclusions on the clinical efficacy

The efficacy of oseltamivir in treatment of influenza in children aged 1 year and above has been previously demonstrated. The mode of action of oseltamivir is not age-dependent, thus similar exposure in adult and paediatric patients can be assumed to produce similar efficacy. Therefore pharmacokinetic data alone can be used to extrapolate efficacy, also between paediatric age groups, and no efficacy studies in infants below 1 year of age are required for the current extension of indication.

The pooled PK data from studies CASG114 and WP22849 and subsequent modelling and simulation are regarded as sufficient to establish a dose recommendation for infants. This approach is in line with the Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004).

The two studies included as secondary end-points descriptive data on pharmacodynamics (virological results), including viral resistance. There were no unexpected findings that would warrant further clinical investigation on efficacy or safety of oseltamivir treatment in infants.

2.5. Clinical safety

Introduction

Oseltamivir is well tolerated by most individuals both in short and in long-term administration. The most frequent adverse events, nausea and vomiting, are not uncommon but rarely lead to discontinuation of treatment.

A vast amount of observational and post-marketing surveillance data was already available on the safety of oseltamivir in children under one year of age. Safety information available from such prospective and retrospective observational sources was included in the current submission; the sources are listed as follows:

NV25182 CSR	Prospective observational safety study in children <2 years of age (N=1065) with specific reference to infants <1 year (exposed to oseltamivir N=161, no antivirals N=360).
Comprehensive report on neuropsychiatric adverse events in relation to Tamiflu Research Report 1027907, Nov 2007	This report was not assessed within this procedure. It has been previously assessed, resulting in update of the SmPC in year 2008 (variation II/0060) with the information on CNS AEs, even though contribution of oseltamivir to these effects is unknown.
Publications of previous	Japan (4 studies referred to, two publications included)

independent observational studies	Germany (1 study) (total subjects <1 year of age: N=2362)

In these studies and reports, oseltamivir was well tolerated and the safety profile was overall similar in infants below 1 year of age as in older children.

For the current submission, the MAH submitted new safety data from the pooled database of studies CASG114 and WP22849, as well as an updated report on AEs entered for Tamiflu into the Roche safety database for children less than 1 year of age (DSR 1060267). This is a summary of the safety data provided by the MAH for this application:

Addendum to Clinical Overview	Includes pooled safety population from the pivotal studies CASG114 and WP22849, 124 patients < 1year of age.
Addendum to Summary of Clinical Safety	Includes • Pooled safety population from the pivotal studies CASG114 and WP22849, 124 patients < 1year of age. • Safety data from earlier prospective and retrospective studies • Post-marketing surveillance adverse events (AEs)
Pooled safety population	Pooled data from CASG114 and WP22849 (N=124) and 11 additional patients from WP22849
Drug Safety Report No. 1060267	Adverse events entered with Tamiflu onto the Roche safety database in children less than 1 year of age (report excludes data from the two studies CASG 114 and WP 22849) for EU filing

Patient exposure

Oseltamivir is approved for the treatment and prophylaxis of children > 1 year of age in most countries globally.

Exposure according to the Addendum to Summary of Clinical Safety

To date, 9,955 human subjects aged 1-96 years have been exposed to oseltamivir in clinical studies (Tamiflu Investigator's Brochure, 2014 [10395]). A further 130.4 million patients of all ages are estimated to have received the marketed product up to September 2013 (based on prescription fill rates), of whom approximately half were under 12 years of age (Tamiflu IB, 2014 [10395]).

Exposure according to the DSR1060267

The estimated cumulative exposure to oseltamivir since 21 September 1999 via commercially obtained drug product until 20 September 2013 (IMS data until 30 June 2013) is 130,386,540 patients.

The estimated cumulative exposure to oseltamivir since 21 September 1999 via commercially obtained drug and through clinical trials until 20 September 2013 is 130.4 million patients.

According to historical IMS data, approximately 42% of prescriptions are for children (aged 0-16). Hence, it is assumed that of the 130.4 million subjects exposed, 54.7 million were children. It is unknown what percentage of the Tamiflu exposed population were children <1 year of age.

Discrepant estimations of the number of children exposed to oseltamivir were provided:

– About 65 million (i.e., half of 130,4 million) subjects aged below 12 years exposed to oseltamivir according to the Addendum to Summary of Clinical Safety; and

– About 55 million subjects aged below 16 years exposed to oseltamivir according to the DSR.

Obviously there cannot be more subjects exposed to oseltamivir aged below 12 years than subjects exposed to oseltamivir aged below 16 years. It is, however, acknowledged that the estimation of the age of subjects exposed to oseltamivir is difficult to perform reliably. Both estimated numbers are large and in the same order of magnitude.

2.5.1. Safety population from the pivotal studies CASG114 and WP22849

The core safety data for this application is based on two open-label, controlled clinical studies that were conducted in infants <1 year of age: CASG114 and WP22849. Both were PK/PD studies which did not include efficacy parameters, as discussed in previous sections of this report.

Table 12. Overview of Pivotal Studies Providing Main Safety Data of Oseltamivir in Infants<1 year of Age

Protocol	Population	Total Patients Enrolled	Total Patients Exposed	Safety Population	Duration (follow-up)	Region	Season	Recruitment Strata	Age (y)
WP20749	confirmed influenza#	72*	71	70‡	30 days	US	2006-2010	age	<1 (cohorts II-V)
WP22849	confirmed influenza#	65†	65	65	30 days	EU	2010-2012	age	<1

* 15 patients were enrolled in the oldest cohort ≥1 to < 2 years of age (Cohort 1). Data from these patients were not analyzed for this report. The 72 patients refer to those <1 year of age.

† In WP22849, 11 patients were recruited in the 2011-2012 influenza season and were not included in the pooled <1 year safety population discussed later in this report.

‡ One patient in cohort IIB (Patient No. 45) did not return for follow up visit, thus cannot confirm if study drug was administered--included in baseline demographic assessment, but not safety assessment. Thus 71 patients were exposed to oseltamivir treatment, but an additional patient (Patient No. 234) failed to return for follow up after withdrawal of consent and was removed from safety analysis, thus the safety population included only 70 patients.

Confirmed by rapid diagnostic test or polymerase chain reaction (PCR) in the local laboratory, but not confirmed in the central laboratory.

The study design of studies CASG114 and WP22849 is discussed in previous sections of this report. CSRs for both studies have been assessed in previous regulatory procedures, including safety findings. It is considered acceptable to pool the safety results of these two studies.

The initial analysis of the pooled safety population was conducted to support submission of the <1 year dataset to the FDA in 2012 and, at this time, safety analysis of the WP22849 study had only been conducted on the 54 patients who enrolled and completed the study during the 2010–2011 influenza season.

In both studies, a placebo arm was considered unethical for this population. As there are no drugs approved for the treatment of influenza in this population, there is no comparator arm. The number of patients included in both the CASG114 and WP22849 studies was agreed upon by FDA and EMA, respectively.

Pooling of safety data from both studies CASG114 and WP22849 (the initial 54 patients enrolled during the 2010-2011 influenza season) yielded a total study population of 124 patients (2 patients lost to follow-up were not included in the safety analyses population).

Exposure

Of the 124 patients treated with oseltamivir in the pooled safety population, 111 (90%) received 9 to 10 doses of oseltamivir across all age groups in the pooled safety dataset. Most patients (>95%) completed at least 5 days of BID oseltamivir treatment.

Overall, 111/124 (89.5%) patients received 9 to 10 doses of oseltamivir across all age groups, with 71.8% of patients <270 days of age and 43.5% <180 days of age in the pooled safety data set of 124 infants from studies CASG114 and WP22849. Table 13 lists the number of doses by age group:

Table 13. Extent of exposure to Study Treatment (safety population)

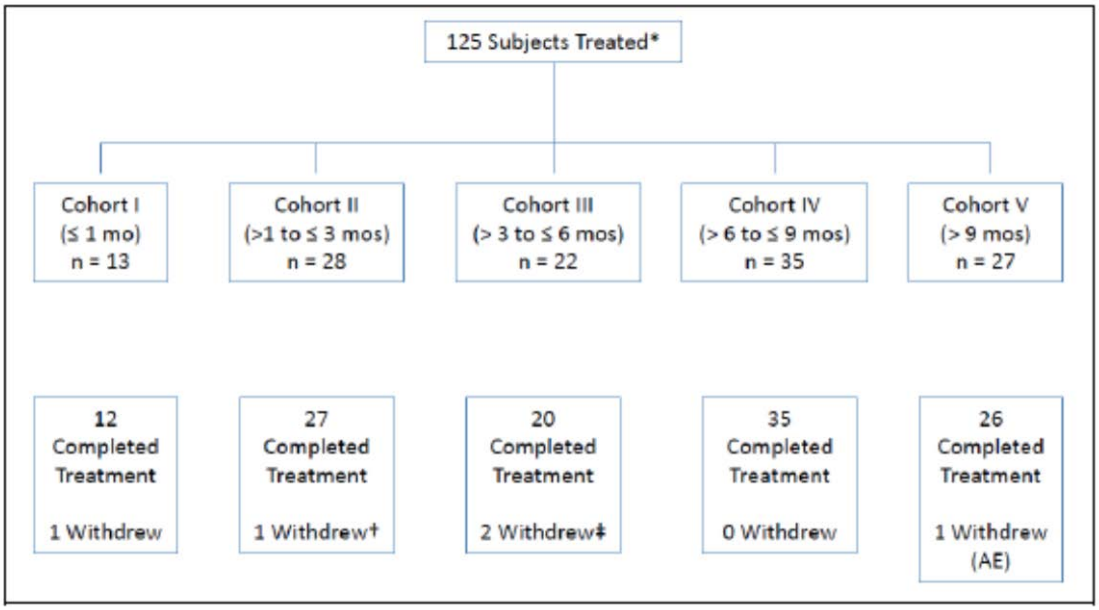
Total Number of Doses	≤30 days n = 13	31-90 days n = 27	91-180 days n = 22	181-270 days n = 25	≥271 days n = 27	All N = 124
1-2	--	--	--	--	1 (4%)	1 (<1%)
5-6	1 (8%)	--	--	--	--	1 (<1%)
7-8	--	--	2 (9%)	--	--	2 (2%)
9-10	12 (92%)	25 (93%)	17 (77%)	35 (100%)	22 (81%)	111 (90%)
>10	--	2 (7%)	3 (14%)	--	4 (15%)	9 (7%)

Table 14. Summary table of exposure for safety evaluation.

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Placebo-controlled	None	0	0	Not applicable
Active -controlled	None	0	0	Not applicable
Open studies	Two	124	111	Not applicable
Post marketing		Data not provided	Data not provided	Not applicable.
Compassionate use		Data not provided	Data not provided	Not applicable.

*In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure. For both studies, a total of 125 infants were enrolled and used for baseline demographic assessment (Figure 6).

Figure 8. Disposition of Patients (<1 year of age) from both studies (pooled)



* Patient No. 45 was excluded from study CASG114 due to lost follow-up after medication dispensed and is not included in this figure.

† Patient No. 234 was treated with 3 doses, but no safety follow-up. Thus, the safety population includes 124 patients.

‡ Based on the total number of doses taken < 9 (mt11).

One infant was excluded from the safety population (N=124) since no post baseline safety assessment was recorded. Of the infants enrolled in these studies, 120 infants completed at least 5 days of BID oseltamivir treatment.

In the pooled study population most infants were white (96 patients, 77%) compared with black (14 patients, 11%), and roughly half were male: 56% male, 44% female. The mean (SD) and median age were 167.1 (± 103.83) and 175.0 days, with half being over 6 months of postnatal age. The mean (SD) and median weight were 6.51 (± 2.16) and 6.40 kg, respectively. The majority of infants (74%) achieved at least full term (> 37 weeks).

Overall, 50 patients (40%) had fever (defined as temperature >38 °C) at baseline. More patients without fever at baseline were reported in all age sub groups. Eighty-one (65%) patients had symptoms for ≤48 hours prior to start of study medication, whereas 44 patients (35%) had symptoms ≥48 hours. More patients ≤ 90 days of age had duration of symptoms lasting no more than 48 hours. Most of the infants (99 patients, 79%) had influenza A and the remainder had either influenza B (20 patients, 16%) or were of an unknown influenza type (6 patients, 5%).

Overall, approximately half (64 patients, 51%) of the patients were located in inpatient non-ICU facilities with the rest from outpatient (50 patients, 40%) or inpatient ICU facilities (11 patients, 9%). This greater proportion of inpatient non-ICU patients was repeated in first 2 age sub groups (≤ 30 days and 31-90 days). However, in the 91-180 days, 181-270 days, and ≥270 days age subgroups, more were from an outpatient setting (11 patients, 50%; 22 patients, 63%; and 14 patients, 52%).

The following Table 15 shows the distribution of the main demographic characteristics of pooled subjects from the two PK studies:

Table 15. Demographic Data and Baseline Characteristics of the pooled data set

	Age Cohorts (Days)					
	≤30 D n=13	31–90 D n=28	91–180 D n=22	181–270 D n=35	≥270 D n=27	Total N=125
Sex (M)	9 (69%)	18 (64%)	13 (59%)	20 (57%)	10 (37%)	70 (56%)
Race (White)	12 (92%)	21 (75%)	17 (77%)	28 (80%)	18 (80%)	96 (77%)
Ethnicity (Hispanic)	9 (69%)	9 (32%)	5 (23%)	11 (31%)	2 (7%)	36 (29%)
Gestational Age (≤37 weeks)	1 (8%)	5 (18%)	8 (36%)	11 (31%)	8 (30%)	33 (26%)
Duration of Symptoms (≤48 hours)	10 (77%)	24 (86%)	11 (50%)	22 (63%)	14 (52%)	81 (65%)
Fever at Baseline (Yes)	6 (46%)	10 (36%)	8 (36%)	16 (46%)	10 (37%)	50 (40%)
Location of patients (ICU)	2 (15%)	5 (18%)	1 (5%)	--	3 (11%)	11 (9%)
Viral Type (Type B)	2 (15%)	2 (7%)	3 (14%)	5 (14%)	8 (30%)	20 (16%)
(Type A)	10 (77%)	24 (86%)	18 (82%)	30 (86%)	17 (63%)	99 (79%)
Log10 ($TCID_{50}$): Median						
- WP20749	3.6	3.8	3.3	3.5	4.3	3.8
- WP22849	4.0	2.5	2.8	3.8	3.5	3.3

Safety data for the additional 11 patients enrolled in study WP22849 during influenza season 2011–2012 were reported in an addendum clinical study report; and not included in the pooled safety population. Of those patients, seven were aged 30–90 days and four 91–<365 days.

Adverse events

In the pooled safety population (N=124), on-treatment AEs (reported during treatment with oseltamivir up to 3 days after the last treatment dose) occurred infrequently and with similar frequency across the age groups. AEs reported most frequently on treatment were vomiting (9%), diarrhoea (7%), dermatitis diaper (7%), and pyrexia (3%). All other on-treatment AEs occurred in ≤2% of patients overall. The occurrence of AEs in the pooled safety population is presented in Table 16.

Of the 11 additional patients enrolled in WP2249 during influenza season 2011–2012, five subjects were reported to have in total 7 AEs: vomiting (3), irritability (2), pyrexia (1), and seborrhoeic dermatitis (1).

Serious adverse event / deaths

SAEs reported (on-treatment) in the pooled safety population are tabulated below in table 17. Overall, 8 (6%) patients < 1 year of age of the pooled safety population had a total of 8 on-treatment AEs classified as a serious adverse event (SAE). Four of these SAEs were from study CASG114 and four were from study WP22849. Respiratory syncytial virus was the only SAE reported in more than one patient (2 patients from study WP22849).

No deaths were reported from these two studies (including the additional 11 patients enrolled in study WP22849 during the 2011-2012 influenza season).

Other significant events

In the pooled safety population, one patient withdrew from treatment due to an adverse event of hypersensitivity, which was severe in intensity and considered by the investigator related to treatment (Table 10, above). The patient was in the >=271 days age group and the event resolved with no sequelae.

While most AEs were mild or moderate in intensity, four patients reported four severe AEs (respiratory syncytial virus, pyrexia, hypersensitivity, and neutropenia). The neutropenia AE was considered

life-threatening but unrelated to treatment by the investigator and resolved with no dose adjustment or discontinuation.

Of the 89 AEs reported in the pooled safety population, most (85.4%) were considered by the investigator as not related to treatment. Thirteen (14.6%) AEs were considered related to treatment: vomiting, diarrhoea, pyrexia, dermatitis diaper, rash, rash maculo-papular, gastroenteritis norovirus, and hypersensitivity. Of these AEs, vomiting (4 patients), diarrhoea (2 patients), and pyrexia (2 patients) were reported in more than one patient with the rest being reported in one patient each. No trend was observed between the age subgroups.

No SAEs were reported for the 11 additional patients enrolled in WP2249 during influenza season 2011–2012.

Table 16. Number (%) of patients with AEs (on treatment) by body system in ≥2% of patients (pooled safety population).

	Age Cohorts (Days)					
	≤30 D n=13	31-90 D n=27	91-180 D n=22	181-270 D n=35	≥271 D n=27	Total N=124
Total Patients with at Least one AE (%)	6 (46%)	14 (52%)	7 (32%)	19 (54%)	15 (56%)	61 (49%)
Gastrointestinal Disorders						
Vomiting	-	2 (7%)	1 (5%)	5 (14%)	3 (11%)	11 (9%)
Diarrhea	1 (8%)	3 (11%)	3 (14%)	-	2 (7%)	9 (7%)
Regurgitation	1 (8%)	1 (4%)	-	-	1 (4%)	3 (2%)
Skin and Subcutaneous Tissue Disorders						
Dermatitis Diaper	3 (23%)	1 (4%)	1 (5%)	2 (6%)	2 (7%)	9 (7%)
Rash	-	1 (4%)	-	2 (6%)	-	3 (2%)
Rash Macular	-	-	-	2 (6%)	-	2 (2%)
Infections and Infestations						
Otitis Media	-	1 (4%)	-	2 (6%)	-	3 (2%)
Respiratory syncytial virus bronchiolitis	-	1 (4%)	-	-	2 (7%)	3 (2%)
Oral candidiasis	1 (8%)	1 (4%)	-	-	-	2 (2%)
Rotavirus infection	-	1 (4%)	-	1 (3%)	-	2 (2%)
General Disorders and Administration Site Conditions						
Pyrexia	-	-	-	2 (6%)	2 (7%)	4 (3%)
Eye Disorders						
Conjunctivitis	1 (8%)	-	1 (5%)	1 (3%)	-	3 (2%)
Blood and Lymphatic System Disorders						
Neutropenia	-	-	-	2 (6%)	-	2 (2%)

Table 17. SAEs on treatment (safety population, N = 124).

	Age Cohorts (Days)					
	≤30 D n=13	31-90 D n=27	91-180 D n=22	181-270 D n=35	≥271 D n=27	Total N=124
Total Pts with at Least one AE	-	1 (4)	2 (9)	2 (6)	3 (11)	8 (6)
Respiratory syncytial virus bronchiolitis	-	1 (4)	-	-	1 (4)	2 (2)
Cellulitis orbital	-	-	1 (5)	-	-	1 (<1)
Influenza	-	-	-	1 (3)	-	1 (<1)
Diarrhea	-	-	1 (5)	-	-	1 (<1)
Pyrexia	-	-	-	1 (3)	-	1 (<1)
Hypersensitivity	-	-	-	-	1 (4)	1 (<1)
Oxygen saturation decreased	-	-	-	-	1 (4)	1 (<1)

The safety profile in studies CASG114 and WP22849 was similar among age cohorts, with vomiting and diarrhoea as the most frequently reported AEs. The gastrointestinal side effects did not lead to withdrawal from study.

Serious AEs were few, occurring in 6% of patients and in no patient ≤ 30 days of age. There were no deaths and one withdrawal due to the AE of hypersensitivity. No new safety concerns were identified.

The safety profile of oseltamivir in infants below 1 year of age was consistent with the well-documented safety profile of oseltamivir in children aged 1 year and above, adolescents and adults.

The MAH did not provide a separate analysis of resistance in the two clinical studies in the perspective of safety, although some of these data are discussed along with the pharmacodynamic results. A consolidated safety analysis of the emergence of resistance should be presented by the MAH regarding the two clinical studies.

Other studies including infants below 1 year of age

- Study NV25182: Prospective observational safety study in children <2 years of age (N=1065) with specific reference to infants <1 year (exposed to oseltamivir N=161, no antivirals N=360).The reported AEs in NV25182 were consistent with those reported for older children in previous studies. Most commonly reported AEs were cough, rhinitis, fever and diarrhoea; and most commonly reported SAEs were pyrexia, bronchitis and pneumonia. The study setting does not allow for differentiation between symptoms of the treated disease and adverse reactions caused by the treatment.
- Additional previous observational prospective and retrospective studies from Japan (4 studies) and Germany (1 study) (total subjects <1 year of age: N=2362)

The submitted data for these independent studies was limited. The safety results were consistent with that in population >1 year of age.

Post marketing experience

Drug Safety Report No. 1060267 ”Adverse events entered with Tamiflu onto the Roche safety database in children less than 1 year of age (report excludes data from the two studies CASG 114 and WP 22849) for EU filing”, dated 24 June 2014, was prepared to support the filing of the application for the indication of Tamiflu for treatment of influenza in children less than one year of age in the European Union (EU).

DSR1060267 is not a stand-alone document and was reviewed in conjunction with the previous DSRs and with the information on the results of the two studies CASG 114/ WP20749 and WP22849 provided in the filing package. The DSRs that are mentioned in DSR1060267 are listed below:

- DSR No.1034695 on the overall available safety data in children <1 year of age, prepared in July 2009,
- DSR No. 1035178 on the safety profile of oseltamivir in children <6 months of age, written in September 2009,
- DSR No. 1036332 on the use of oseltamivir in premature children (age <37 post-menstrual week), completed in November 2009, and
- DSR No. 1050506, which reviewed cases that had been entered onto the Roche Safety database during the 2009 H1N1 influenza pandemic period.

The DSRs have been discussed within previous PSURs and other regulatory procedures. The DSRs include no robust data on oseltamivir treatment in new-born infants aged <2 weeks and do not include any data on safety or efficacy that would have consequences for the current variation.

Source of information

The company safety database records information on the following cases:

- Reports from clinical trials: All cases with serious adverse events or some designated non-serious adverse events, where oseltamivir is considered `suspect';
- Spontaneous reports: All cases (serious and non-serious) where oseltamivir is considered `suspect'.

The reporter's causality assessment is not considered as a criterion for recording adverse event information.

A pharmacovigilance agreement between Roche/Genentech and Chugai provides for safety data sharing, allowing Roche to maintain a global safety database for oseltamivir.

The electronic extraction of data from the company safety database for this report includes all serious (and non-serious) events: clinical trial and spontaneous reports (irrespective of reporter and company causality assessment). Validated extraction of Roche safety data for research reports is carried out by the PDS Data Management Group (PDS-DMG).

Cumulative Tamiflu cases, regardless of the adverse events reported in the cases, concerning infants less than one year of age reported from world-wide sources that have been entered in the Roche drug safety database up to 31 March 2014 were identified based on the age coded in the age screen of the cases. Reports from the two clinical studies WP22849 and CASG114 were excluded (based on the protocol number entered into the study screen), whereas cases that were reported from any other studies were included in the dataset, as well as spontaneous reports. Blinded study cases have been excluded from this analysis.

Overview

After exclusion of cases reported from WP22849 and CASG114, a total of 278 Tamiflu cases comprising 432 AEs and two comanifestations (comans) that had been entered onto the Roche Drug Safety database up to 31 March 2014 were identified that concern children <1 year of age. The two comanifestations were nasal congestion and pyrexia (reported once each) and are counted as and referred to as AEs in the rest of the document.

Thirty-two of the 278 cases originate from studies (comprising 52 adverse events), 17 cases (with 37 AEs) were literature reports, 208 cases were spontaneous reports (comprising 317 AEs), while 21 cases (with 28 AEs) were reported from other sources (Table 18)

Two hundred and thirty-five of the 278 cases were reported by health care professionals (mainly physicians: n=141 and pharmacists: n=66). Forty-three cases were reported by consumer/other non-health care professional (comprising 66 adverse events).

The majority of the 278 cases were reported from Japan (n=110), USA (n=54) and UK (n=45).

Table 18. Distribution of case reports by primary reporting source.

Source	N Cases	N Serious Cases	N Adverse Events
Spontaneous	208	47	317
Study	32	27	52
Literature	17	11	37
Other	21	21	28
Total	**278**	**106**	**434**

Of the 278 subjects 122 were male and 107 female. Gender was not reported in 49 cases.

The mean age of the 278 subjects was 0.51 year, and the median age was 0.5 year (range 0 days to 0.92 years).

Table 19. Case reports by age and gender.

Age Groups	Female	Male	Unknown / Not specified	Total Cases
0 to < 3 months	16	20	18	54
3 to < 6 months	22	25	10	57
6 to < 9 months	32	45	15	92
9 to <12 months	37	32	6	75
Total	107	122	49	278

Table 20. Case reports by age class and gender

Age Groups	Female	Male	Unknown/Not specified	Total No. Cases
Neonate	8	8	9	25
Infant	99	114	40	253
Total	**107**	**122**	**49**	**278**

Neonate: Birth to <1 month, Infant: ≥1 month to <2 years, Child: ≥2 years to <12 years

Six subjects were indirectly exposed to oseltamivir taken by the lactating mother through breast milk. Furthermore, there were 14 cases where the route of Tamiflu dosage was entered as transplacental or an adverse event PT indicating pregnancy (the babies were indirectly exposed in utero because Tamiflu was taken by the pregnant mother). In another five cases the oseltamivir formulation/route of administration was reported as intravenous (reported from the clinical trial NP25138). The dosage route and formulation of the remaining cases was either oral (capsules or syrup/oral suspension) or unknown. For most of the 278 cases the mg/kg dosage regimen was not reported and cannot be calculated due to missing information.

Summary of AEs

Majority of the cases were classified as non-serious (n=172), while 106 cases were serious (comprising 149 SAEs).

The System Organ Class (SOC) most commonly concerned is the SOC General disorders and administration site conditions (18.0% of the 434 AEs), followed by Gastrointestinal disorders (15.9%), Skin and subcutaneous tissue disorders (14.3%), Injury, poisoning an procedural complications (11.1%), and Infections and infestations (10.6%). Majority of the 149 serious AEs had been reported under the SOC Infections and infestations (25.5%), followed by Nervous system disorders (14.1%), General disorders and administration site conditions (12.1%) and Respiratory disorders (10.7%). (Table 21)

Table 21. Summary table of AEs by SOC.

System Organ Class	No. Patients with at least 1 AE/SOC	Serious Adverse Events		Total Adverse Events	
		N	%	N	%
Infections and infestations	39	38	25.5	46	10.6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0.0	0	0.0
Blood and lymphatic system disorders	3	1	0.7	3	0.7
Immune system disorders	2	1	0.7	2	0.5
Endocrine disorders	0	0	0.0	0	0.0
Metabolism and nutrition disorders	5	2	1.3	6	1.4
Psychiatric disorders	14	5	3.4	23	5.3
Nervous system disorders	24	21	14.1	28	6.5
Eye disorders	3	0	0.0	3	0.7
Ear and labyrinth disorders	0	0	0.0	0	0.0
Cardiac disorders	5	3	2.0	5	1.2
Vascular disorders	4	0	0.0	4	0.9
Respiratory, thoracic and mediastinal disorders	24	16	10.7	25	5.8
Gastrointestinal disorders	61	11	7.4	69	15.9
Hepatobiliary disorders	6	4	2.7	6	1.4
Skin and subcutaneous tissue disorders	57	11	7.4	62	14.3
Musculoskeletal and connective tissue disorders	1	1	0.7	1	0.2
Renal and urinary disorders	0	0	0.0	0	0.0
Pregnancy, puerperium and perinatal conditions	2	0	0.0	2	0.5
Reproductive system and breast disorders	2	2	1.3	2	0.5
Congenital, familial and genetic disorders	6	6	4.0	7	1.6
General disorders and administration site conditions	69	18	12.1	78	18.0
Investigations	10	7	4.7	14	3.2
Injury, poisoning and procedural complications	47	2	1.3	48	11.1
Surgical and medical procedures	0	0	0.0	0	0.0
Social circumstances	0	0	0.0	0	0.0
Total	**N/A**	**149**	**100.0**	**434**	**100.0**

Of the total 434 AEs (serious and non-serious) reported in the 278 cases, the most frequently reported AE PTs were the following: Vomiting (n=27), rash (n=26), diarrhoea (n=20), hypothermia (n=19), no adverse event (n=16), convulsion (n=12), and overdose (n=10).

An AE coded to a PT possibly suggestive of the presence of an oseltamivir overdose was reported in sixteen cases: PT accidental overdose n=6, and overdose: n=10. Furthermore, the available information in the cases reporting the PTs drug dispensing error (n=1), drug prescribing error (n=1), incorrect dose administered (n=5), and medication error (n=5) was reviewed to determine where an overdose had been reported in these cases.

Outcome

The majority of the 434 events was reported to have the outcome 'recovered/resolved (with or without sequelae)' (n=134) or 'recovering/resolving' (n=45). The outcome was unknown /not reported for 167 AEs. The outcome was 'not recovered/not resolved' for 48 AEs.

Deaths

Of the 434 AEs a fatal outcome was reported for 14 cases (16 AEs): Acute respiratory distress syndrome (n=2), multi organ failure (n=2), bronchitis, cerebral ischemia, death, disseminated tuberculosis, H1N1 influenza, influenza, peritoneal haemorrhage, pneumonia viral, respiratory distress, respiratory failure, abdominal compartment syndrome, and sudden infant death syndrome (reported once each).

Eleven of the 14 subjects with fatal outcome were influenza infected, while in one case the indication was reported as viral infection. In two cases the Tamiflu indication was reported as prophylaxis: a baby with pre-existing disseminated tuberculosis died of progression; and a baby with a medical history of peritoneal haemorrhage, abdominal compartment syndrome, congenital diaphragmatic eventration, and pulmonary sequestration died of peritoneal haemorrhage and abdominal compartment syndrome.

The age distribution of the 14 infants who died was as follows: 0 to <3 months: n=4, 3 to <6 months: n=4, 6 to <9 months: n=3, and 9 to <12 months: n=3.

The review of the narratives does not indicate a causality of oseltamivir as the possible cause of death , but related to the influenza infection and/or the pre-existing underlying disease (such as disseminated tuberculosis, peritoneal haemorrhage and abdominal compartment syndrome), or the case cannot be assessed due to lack of relevant information.

Reporting rate among infants <1year vs. children 1 to 12 years of age

A summary tabulation of the 434 AEs by SOC reported in the 278 Tamiflu cases concerning infants less than one year of age is provided in Table 22. Data from the Roche drug safety database on the 8407 AEs reported in Tamiflu cases concerning patients aged 1-11 years is also included in this table for comparison.

The SOCs for which there are differences between infants <1 year of age and children ≥ 1 year of age, with a greater incidence in infants < 1 year of age compared with the older children (i.e. ≥ 1 year of age) were the following (applying a 2% cut-off in the <1 year old group):

- SOC General Disorders and Administration Site Conditions (infants <1 year of age: 18.0%; older children: 9.6%)
    - The most common preferred terms (PTs) in the SOC General Disorders and Administration Site Conditions for infants <1 year of age were ‘no adverse event’ (16 events), hypothermia (19 events), pyrexia (9 events), and drug ineffective (8 events).
- SOC Skin and subcutaneous tissue disorders (infants <1 year of age: 14.3%; older children: 10.6%)
    - The most common PTs in the Skin and subcutaneous tissue disorders SOC for infants <1 year of age were rash (26 events), five events each of erythema multiforme and urticaria, and 4 events each of rash generalized, rash macular, and rash maculo-papular.
- SOC Injury, poisoning and procedural complications (infants <1 year of age: 11.1%; older children: 3.8%)
    - The most common PTs in the Injury, poisoning and procedural complications SOC for infants <1 year of age were overdose (10 events), accidental overdose (6 events), 5 events each of medication error and incorrect dose administered, and 4 events of maternal exposure timing unspecified.
- SOC Infections and Infestations (infants <1 year of age: 10.6%; older children: 2.6%),

- The most common PTs in the Infections and Infestation SOC for infants <1 year of age were pneumonia (8 events), pathogen resistance (7 events), gastroenteritis rotavirus (5 events) and bronchitis (4 events).

- SOC Respiratory, thoracic and mediastinal disorders (infants <1 year of age: 5.8%; older children: 4.8%)
- The most common PTs in the Respiratory, thoracic and mediastinal disorders SOC for infants <1 year of age were respiratory failure and asthma (4 events each).
- SOC Investigations (infants <1 year of age: 3.2%; older children: 1.2%).
- Apart from the PT Waist circumference increased (n=2), none of the 14 AEs reported in the infants <1 year of age in the Investigations SOC was reported more than once.

Table 22. Summary tabulation of AEs by SOC comparing children <1 year of age with children 1-11 years of age.

	Age < 1		Age 1 to 11	
System Organ Class	Serious AEs N	All AEs N	Serious AEs N	All AEs N
Infections and infestations	38	46	126	217
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1	1
Blood and lymphatic system disorders	1	3	40	59
Immune system disorders	1	2	23	38
Metabolism and nutrition disorders	2	6	11	40
Psychiatric disorders	5	23	673	2811
Nervous system disorders	21	28	241	649
Eye disorders	0	3	12	177
Ear and labyrinth disorders	0	0	6	30
Cardiac disorders	3	5	32	48
Vascular disorders	0	4	13	33
Respiratory, thoracic and mediastinal disorders	16	25	93	407
Gastrointestinal disorders	11	69	116	1558
Hepatobiliary disorders	4	6	28	35
Skin and subcutaneous tissue disorders	11	62	115	890
Musculoskeletal and connective tissue disorders	1	1	29	115
Renal and urinary disorders	0	0	19	55
Pregnancy, puerperium and perinatal conditions	0	2	0	0
Reproductive system and breast disorders	2	2	0	9
Congenital, familial and genetic disorders	6	7	2	3
General disorders and administration site conditions	18	78	203	809
Investigations	7	14	41	97
Injury, poisoning and procedural complications	2	48	20	322

The differences in AEs reported in the two age groups are not suggestive of any safety concern and the events entered onto the Roche Drug Safety database in children <1 year of age are in line with the well-established safety profile reported in children aged one year of age and older.

Overdose

The MAH gives case summaries of all reported AEs with possible overdose of oseltamivir. There were total 16 cases possibly suggestive of overdose: PT Accidental overdose n=6, and Overdose: n=10. Additionally 14 AE PTs reported for additional 12 cases were reviewed: PTs Drug dispensing error (n=1), Drug prescribing error (n=1), Incorrect dose administered (n=5), Medication error (n=5), Accidental exposure to product (n=1), Accidental exposure to product by child (n=1). Of all these cases 19 were considered to represent a true

overdose (>2 fold); in nine of the cases no AE was reported. In three cases, only the PT Overdose and Accidental overdose was reported. The remaining seven cases were reported to have experienced PT Diarrhoea (n=5), Waist circumference increased (n=2), and Abnormal behaviour, Lethargy, Crying, Malaise, Feeling abnormal, and Dyspnoea (n=1, each).

Neuropsychiatric adverse events (NPAE)

No difference in NPAE reporting rates between oseltamivir and placebo was found in Phase III treatment studies (0.5% vs 0.6%). Analysis of US healthcare claims databases showed the risk of NPAEs in oseltamivir-treated patients was no higher than those not receiving antivirals. Of note, only one instance of NPAE has been reported in the two main clinical studies.
Hypothermia was reported more frequently in infants <1 year of age. Hypothermia in infants receiving oseltamivir has been assessed previously.

The MAH was requested as part of the Tamiflu EU License Renewal to submit all available PK, efficacy and safety data collected during the H1N1 pandemic influenza. The safety data collected during the 2009 H1N1 pandemic for children less than one year of age comprised a total of 94 Tamiflu cases (initial reports) with 141 adverse events, 5 of which (3.5%) related to the preferred term “hypothermia”. Therefore, the MAH was requested to provide case narratives of the five patients with H1N1 pandemic influenza with reported hypothermia.

The MAH responded by submitting DSR “Hypothermia following Tamiflu exposure” (Report No 1056191, dated 27 June 2013), evaluating the cumulatively available information including analyses of the Roche global safety database, preclinical data, epidemiology data, clinical study data and review of the published literature; in addition to the requested case narratives and a review on hypothermia.

The CHMP conclusion on that report was the following: “There is no credible evidence that oseltamivir has a pharmacodynamic effect leading to hypothermia. The extensive data retrieved and analysed by the MAH regarding potential relationship between oseltamivir and hypothermia do not suggest a causal relationship, even though such relationship cannot be entirely ruled out. If oseltamivir causes hypothermia, the incidence seems to be very low based on the available information.”

As regards overdose, also more frequently reported for infants < 1 year of age, none of the cases reported were fatal. Two accidental overdose events in infants < 1year of age were considered SAE. The risk of erroneous dosing is expected to be lower now that the 6 mg/ml oral liquid, easier to administer, is on market. Moreover, the SmPC has been updated within recent years to clarify dosage based on User Testing results. Within Variation II/0096 Section 4.9 of the SPC was updated to reflect available post-marketing safety data on overdose with oseltamivir. The comprehensive analysis by the MAH on all available data on overdose did not reveal any unexpected tolerability issues or dose-response relationship between overdose and occurrence of AEs; or any specific action to be recommended in case of overdose. However, the MAH was requested to add in the product information a remark that overdose has been observed more frequently in children to alert the Health Care Professionals and parents to exercise caution in administration of Tamiflu to children.

The current application includes updated dosage recommendations for infants aged 0 to 1 year and a new plastic oral dispenser of 3 ml. There remain issues regarding dosage in this age group. These are discussed elsewhere in this Overview.

The higher prevalence of infections and infestations in infants aged <1 year than in older children is regarded as reflection of a more severe baseline disease in infants.

Prophylaxis cases

In 21 of the total 278 cases the indication of Tamiflu was reported as prophylaxis of influenza infection. One of the 21 cases (PTs Foetal exposure during pregnancy, and Underweight) concerns a baby transplacentally

exposed to Tamiflu taken by the pregnant mother for influenza prophylaxis. Two subjects died (Death due to progression of pre-existing disseminated tuberculosis; and death due to worsening of pre-existing peritoneal haemorrhage and abdominal compartment syndrome). Several of the AEs reported in subjects with prophylaxis concerned gastrointestinal symptoms (vomiting 4, diarrhoea 4, flatulence 1, rectal haemorrhage 1); dosing errors or difficulties such as capsule physical issue, expired drug administered, under- and overdose (7). Other reported AEs in this subgroup were fontanelle bulging (1), waist circumference increased (2), pyrexia (1) and anger (1).

Immunocompromised children

Based on the medical history reported in the 278 cases, three subjects were immunocompromised, with medical history of 1) salmonellosis, congenital immunodeficiency, and H1N1 influenza; 2) influenza, immunodeficiency, and interstitial lung disease; and 3) Omenn syndrome. The events reported in the three cases are not unexpected for this patient population: pathogen resistance, drug resistance, decreased drug effect, drug ineffective, respiratory failure, neurotoxicity and graft versus host disease.

The data do not indicate any immunosuppressive effect by oseltamivir.

Serious adverse events

Amongst the 149 SAEs, the most frequently reported serious AE PTs were the following: convulsion (n=12), pneumonia (n=8), pathogen resistance (n=6), drug ineffective (n=6), gastroenteritis rotavirus (n=4), respiratory failure (n=4), H1N1 influenza (n=3), bronchitis (n=3), asthma (n=3), diarrhoea (n=3), and erythema multiforme (n=3).

In the comparison of AEs by SOC between children <1 year of age and children 1–11 years of age, there were 149 SAEs (34 %) in a total of 434 AEs reported for infants below 1 year of age, and 1846 SAEs (22 %) in a total of 8407 AEs reported for children aged 1 to 11 years. The data do not allow for reliable assessment of relatedness of the reported SAEs with oseltamivir. Many of the reported AEs can also be symptoms of influenza.

No unexpected AEs/SAEs were detected in this analysis.

2.5.2. Conclusions on clinical safety

In the pooled safety population from the pivotal studies CASG114 and WP22849 (the 2010-2011 influenza season, the pooled number of evaluable patients <1 year of age yielded a safety dataset of 124 infants. In this dataset, there were 61 patients (49 %) with at least one reported AE: 23 reports of gastrointestinal AEs (vomiting, diarrhoea, regurgitation), 14 reported skin and subcutaneous tissue disorders (dermatitis diaper, rash, rash macular); 10 reports of infections and infestations (otitis media, respiratory syncytial virus bronchiolitis, oral candidiasis, rotavirus infection), 4 reports of pyrexia, 3 of conjunctivitis, and two of neutropenia. Eight subjects had 8 AEs classified as SAEs: respiratory syncytial virus bronchiolitis (2), cellulitis orbital, influenza, diarrhoea, pyrexia, hypersensitivity, and oxygen saturation decreased (1 of each). Concerning diarrhoea, this AE has not occurred more frequently in oseltamivir than in placebo arms of previous paediatric studies, thus diarrhoea was recently deleted from the paediatric ADR list in section 4.8 of the SmPC for Tamiflu. Based on the overall existing data for older children, adolescents and adults, it could be assumed that diarrhoea is not related to oseltamivir also in infants but there is no certainty due to lack of controlled studies. Therefore as precaution diarrhoea was included in the ADRs reported for infants below 1 year of age in Section 4.8 of the SmPC; information on diarrhoea and diaper rash in infants was also reflected in section 4 of the PL.

No SAEs were reported for the additional 11 patients enrolled in study WP22849 during influenza season 2011-2012.

The prospective observational safety study (NV25182) enrolled infants 24 months of age and younger, who were treated as outpatients with oseltamivir for suspected influenza (n = 340), oseltamivir for prophylaxis of influenza (n= 13), and infants with suspected influenza not treated by antiviral therapy (n=711). Subjects below 1 year of age constituted 50 % of the study population (n = 530). Of the subjects below 1 year of age, 161 were exposed to oseltamivir. In NV25182, AEs were reported in 49% of subjects treated with oseltamivir, 55% of subjects not treated with antiviral therapy, and 43% of patients with oseltamivir prophylaxis. The reported AEs were consistent with those reported for older children in previous studies. Most commonly reported AEs were cough, rhinitis, fever and diarrhoea; and most commonly reported SAEs were pyrexia, bronchitis and pneumonia. The study setting does not allow for differentiation between symptoms of the treated disease and adverse reactions from the treatment.

To complement the safety data from the two pivotal studies (CASG114 and WP22849), the MAH reviewed available data from the post-marketing experience of Tamiflu in children < 1 year of age (DSR1060267 - The post-marketing surveillance adverse events). After exclusion of cases reported from the two submission studies WP22849 and CASG114/WP20749, a cumulative total of 278 Tamiflu cases comprising 434 AEs that had been entered onto the Roche Drug Safety database up to March 31, 2014 were identified that concern children <1 year of age. Of the 278 cases, 32 originated from studies (comprising 52 AEs); 17 cases (with 37 AEs) were literature reports; 208 cases were spontaneous reports (comprising 317 AEs); and 21 cases (with 28 AEs) were reported from other sources. Forty-two of the 278 cases were non-medically confirmed and/or consumer reports, comprising 66 AEs. The 278 cases include six infants who were exposed to oseltamivir through breast milk. Furthermore, there were 14 cases where the route of Tamiflu dosage was entered as transplacental. Overall, the reported AEs for infants < 1 year of age were similar to those reported for older children. However, there were more reports on General Disorders and Administration Site Conditions, Skin and Subcutaneous Tissue Disorders, Injury, Poisoning and Procedural Complications, Infections and Infestations, Respiratory, thoracic and mediastinal disorders and Investigations in children below 1 year of age. The differences were not marked, and can be partly due to more severe influenza in infants. No unexpected findings were noted.

The MAH also submitted previous prospective and retrospective surveillance data from Japan and Germany. In those studies, oseltamivir was well tolerated. Moreover, previous DSRs that were already assessed have been taken into consideration for this procedure; the results did not affect the known safety profile of the drug.

Overall, the safety data from the two pivotal studies CASG114 and WP22849 (135 patients aged below 1 year) and the updated post-marketing surveillance data of Tamiflu in children <1 year of age (278 Tamiflu cases comprising 434 AEs) showed a similar tolerability and safety profile of Tamiflu as the previous data from the prospective observational safety study (NV25182) with 161 subjects aged below 1 year exposed to oseltamivir and additional previous prospective and retrospective surveillance data from Japan and Germany. Except for diarrhoea and diaper rash, the new safety data in infants aged 1 year and below submitted for the current variation did not include AEs probably or possibly related to oseltamivir (ADRs) that would not already be present in the currently approved SmPC and PL or require changes in the frequency information.

The MAH did not provide a separate analysis of resistance in the two clinical studies in the perspective of safety, although some of these data are discussed along with the pharmacodynamic results. A consolidated safety analysis of the emergence of resistance regarding the two clinical studies assessed in this variation should be presented by the MAH via a post-authorisation commitment (LEG).

Some data exist on oseltamivir use in neonates from independent studies. The study data submitted for this variation included no data on new-born infants aged <2 weeks. Therefore, benefit-risk in this age group is completely extrapolated from older children. The safety data so far does not indicate any such risks that would overcome the clinical need for antiviral treatment for influenza in new-born babies. Young children are

more prone to being hospitalised due to influenza, e.g. in the US, and the reported hospitalisation rate is 4.5 per 1000 children under the age of 6 months (Poehling KA et al. New Vaccine Surveillance Network; The under recognized burden of influenza in young children. *N. Engl. J. Med.* 2006). Small children are at high risk for influenza-related complications such as sinusitis, otitis media, croup, bronchitis, and pneumonia (Ruf BR, Szucs T. Reducing the burden of influenza-associated complications with antiviral therapy. *Infection*, 2009).

Overall the acceptable safety profile of Tamiflu is confirmed also in the age group of full term infants below 1 year of age.

The section safety specification of the current RMP adequately characterizes the safety profile of the medicinal product and the MAH's proposed safety concerns for Tamiflu were endorsed. No new safety concern had been identified since the previous RMP update, hence no RMP update was required in this application.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II statement related to the PSUR refers to the EURD list, which remains unchanged.

2.6. Risk management plan

No RMP was provided with this variation by the MAH. The PRAC agreed that the currently adopted version is applicable.

2.7. Type IA_{IN} included in the grouped variation

As a consequence of extension of indication, a 3 ml plastic oral dispenser was proposed to be added to the Tamiflu 6 mg/ml powder for oral suspension outer carton (in addition to the already included 10 ml plastic oral dispenser), to enable the accurate dosing in infants below 1 year of age. This 3 ml oral dispenser is proposed in response to a CHMP request as part of the line extension for 6 mg/ml (EMEA/H/C/402/X/0085).

Sufficient documentation to support the variation has been submitted. The dispenser is CE marked. It is acceptable that no compatibility studies are provided for the oral dispenser. The contact time of Tamiflu reconstituted drug product with the 3 ml oral dispenser is short (in the range of minutes). Compatibility of the Tamiflu suspension with the press-in bottle adapter (PIBA) has been presented and assessed as part of the line extension of Tamiflu 6 mg/ml. After storage of the reconstituted suspension for 4 and 10 days upside down at room temperature no leaching compounds could be detected by HPLC. It was therefore concluded that there is no significant leaching occurring from the adapter. Consequently, it can be accepted that no compatibility studies are provided for the oral dispenser.

However, during the procedure the MAH was asked to clarify how the doses of 3.3 ml, 3.8 ml, 4.3 ml and 4.8 ml are intended to be administered. A 10 ml syringe with a 0.5 ml graduation was selected in the original MAA to administer higher doses (for infants 91 days and older) and the MAH declared that the dosing schedule from 3.5 ml to 5.0 ml is in 0.5 ml (3 mg) steps. It is also reminded that both in the SPC and PL of the Tamiflu capsules it is advised to use oral dispenser of 5 ml (graduation 0.1 ml) to administer 3–5 ml of pharmacy compounded and home prepared Tamiflu suspension.

Because the doses of 3,3 ml, 3,8 ml, 4,3 ml and 4,8 ml cannot be accurately administered with the 10 ml dispenser the MAH proposed to introduce a weight categorization with 1.0 kg increments above 6 kg body weight. This result in amounts of suspension of 3.5 ml, 4.0 ml, 4.5 ml and 5 ml to be withdrawn to dose

children of 6-10 kg body weight. It is agreed with the MAH that using the 10 ml dispenser once would lead to a more accurate dosing instead of using the 3 ml oral dispenser twice. The proposed categorizing of the dose recommendation for children with a bodyweight of 6 kg and higher will result in a slightly higher dose than 3 mg/kg for some cases. It can be agreed that the slightly higher dose of Tamiflu 6 mg/ml suspension administered for children with a bodyweight of 6 kg and higher is acceptable from a safety point of view.

2.8. Update of the Product information

As a consequence of the new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The major changes are reported below.

- **Changes to section 4.1** (new text underlined; deleted text strikethrough)

Treatment of influenza

Tamiflu is indicated in adults and children including full term neonates ~~In patients one year of age and older~~ who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms. ~~This indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A (see section 5.1).~~

~~Tamiflu is indicated for the treatment of infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).~~

~~The treating physician should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure there is a potential benefit to the child.~~

- **Changes to section 4.2**

Posology

Tamiflu hard capsules and Tamiflu suspension are bioequivalent formulations. 75 mg doses can be administered as either

- *one 75 mg capsule or*
- *one 30 mg capsule plus one 45 mg capsule or*
- *by administering one 30 mg dose plus one 45 mg dose of suspension.*

Commercially manufactured Tamiflu powder for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. ~~Adults, adolescents or infants and children (1 year of age or older) who are unable to swallow capsules may receive appropriate doses of Tamiflu suspension.~~

(..)

Infants 0 – 12 months of age ~~less than 1 year~~

~~In the absence of a suitable formulation, a pharmacy compounded preparation should preferentially be used as the syringe provided in the Tamiflu 12 mg/ml powder for oral suspension pack (with mg markings) does not allow for appropriate dose adjustments and commercially available syringes (with ml markings) may lead to unacceptable dosing inaccuracies (see section 6.6)~~

Treatment: The recommended treatment dose for infants ~~less than 1 year~~ 0 - 12 months of age ~~is between 2 mg/kg twice daily and~~ 3 mg/kg twice daily ~~during a pandemic influenza outbreak~~. This is based upon pharmacokinetic and safety data indicating that this dose in infants 0 - 12 months provides plasma concentrations of the pro-drug and active metabolite that are anticipated to be clinically efficacious with a

safety profile comparable to that seen ~~provide plasma drug exposures in the majority of patients similar to those shown to be clinically efficacious~~ in older children and adults (see section 5.2). The following ~~age-adjusting~~ dosing regimen is recommended for treatment of infants ~~below 1 year~~ 0 - 12 months of age:

Body weight*	**Recommended dose for 5 days**
3 kg	9 mg twice daily
4 kg	12 mg twice daily
5 kg	15 mg twice daily
6 kg	18 mg twice daily
7 kg	21 mg twice daily
8 kg	24 mg twice daily
9 kg	27 mg twice daily
10 kg	30 mg twice daily

* This table is not intended to contain all possible weights for this population. For all patients under the age of 1 year, 3 mg/kg should be used to determine dose regardless of the weight of the patient.

~~**Age**~~	~~**Recommended dose for 5 days**~~
~~0 to 1 month*~~	~~2 mg/kg twice daily~~
~~> 1 month to 3 months~~	~~2.5 mg/kg twice daily~~
~~> 3 months to 12 months~~	~~3 mg/kg twice daily~~

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza. This ~~age based~~ dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual ~~postmenstrual~~ age less than ~~37~~ 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Post-exposure prevention: The recommended prophylaxis dose for infants less than 1 year of age during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical data in infants and children 1 year of age or older and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza. The following age-adjusted dosing prophylaxis regimen ~~are~~ is recommended for infants ~~below 1 year~~ 0 - 12 months of age:

Age	***Recommended dose for 10 days***
0 - 12 months	*3 mg/kg once daily*
~~*0 to 1 month**~~	~~*2 mg/kg once daily*~~
~~*> 1 month to 3 months*~~	~~*2.5 mg/kg once daily*~~

~~*There is no data available regarding the administration of Tamiflu to infants less than one month of age.*~~

This ~~age based~~ dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual ~~postmenstrual~~ age less than ~~37~~ 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children 0-12 months of age ~~below 12 years~~.

For instructions on preparing the extemporaneous formulation, see section 6.6.

In addition, changes related to section 6.5 of the SmPC have been introduced with regard to variation type IA_{IN} submitted within this group of variations.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s), which were reviewed and accepted by the CHMP.

During the procedure, the CHMP requested further changes as some inaccuracies and discrepancies remained in the proposed PI. The information on adverse events in infants below one year of age, the total number of infants below one year of age in studies CASG114 and WP22849, and information regarding

dosage and use of the new oral dispenser required amendments or justifications (please see attachments 1 and 2 to this assessment report).

2.8.1. User consultation

The results of a user consultation with target patient groups on the package leaflet were submitted by the MAH via a different procedure and were under review at the time that this variation was finalised.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The clinical effect of oseltamivir in the currently approved age groups has been already ascertained by the CHMP, insofar as it has been recognized that the duration of clinical illness may be reduced by a median of one-day in subjects treated with oseltamivir, provided treatment is initiated early in the course of the infection.

There is an unmet clinical need for antiviral treatment also for infants below 1 year of age. Children less than 1 year of age are at higher risk of influenza complications than older children. Although fatalities are rare in children, complications are common and include upper respiratory tract infections, acute otitis media, febrile convulsions and asthma exacerbations. Children also play a central role in spreading influenza in the community, by virtue of their relative serosusceptibility and consequent higher attack rate of infection.

In general, transplacental acquisition of protective antibodies begins at 28 weeks of gestation, and increases until the time of birth. The antibody level of term neonate is believed to be similar to the antibody level of the mother. Antibody levels decline rapidly after birth but generally persist up to the age of 6 months, after which, transplacental immunity has waned. For pandemic strains of influenza virus, transplacental immunity may not exist. The maternal immunity against seasonal strains of influenza virus is also variable and may not be sufficient on its own to prevent clinical influenza in the infant.

The current variation to extend the use in infants less than 1 year of age in the treatment of influenza is based on PK/PD modelling from studies CASG114 and WP22849. The MAH has used pharmacokinetic data, modelling and simulation to support the dosage of oseltamivir in infants <1 year of age. More than 600 oseltamivir and OC concentrations in 133 infants were measured, which is an impressive amount of data in this population. The population PK model was developed and evaluated using acceptable methods. The simulations indicate that a 3 mg/kg BID regimen in infants <1 year of age is predicted to provide OC exposures that exceed those observed with marketed doses in adults on 75 mg BID and children 1-5 years of age. The highest and most variable exposure is predicted for infants < 1 month of age. OC exposures are, however, not anticipated in any infant group to exceed those observed with dosage 150 mg BID in adults, which was the alternative, well tolerated dosage in pivotal phase 3 studies in adults and adolescents. It is predicted that with a lower dosage (e.g. 2.5 mg/kg BID) the target OC levels will not be achieved in all patients. Predicted oseltamivir exposures are anticipated to be similar to some of the exposures that have been shown to be tolerated across the oseltamivir clinical pharmacology program. Both the simulated data and the NCA PK results of individual studies suggest similar trends by age group of OC and oseltamivir exposure in infants <1 year of age.

Uncertainty in the knowledge about the beneficial effects

The emergence of resistant strains during oseltamivir treatment has been observed more frequently in the youngest age groups in general. Furthermore, in the two clinical trials herewith assessed, the exposure of

the younger age group <1 year of age was associated with treatment-induced emergence of viral resistance, with no demonstrated effect on the duration of viral shedding. It is not known if this is unequivocally related to exposure to the drug, but it has been hypothesized that the higher risk of resistance may be linked to the longer time of viral shedding seen in infants. Although this is a theoretical explanation, it is recommended that the dosage in infants be on therapeutic level in order to minimise the risk of resistance. Albeit limitedly, the risk of resistance triggers some concern since there is a recognized epidemiologic role for this age group in the transmission of the infection across family members and other exposed individuals. However the impact of virus resistance to oseltamivir on the severity and magnitude of an influenza epidemic is currently not known. However this issue does not affect the benefit-risk evaluation of Tamiflu in the newly proposed indication, and in addition further investigations have been requested to the MAH post-approval in order to gain further reassurance.

Relationships between exposure to OC and efficacy endpoints (e.g. resolution of fever and viral shedding) or safety parameters were not established in clinical studies in infants <1 year of age. As all infants were expected to receive an effective dose in the studies, the variability in exposure was obviously not large enough to demonstrate exposure-dependent differences in safety or efficacy results.

One of the issues related to the dosage discussed in this application is the highly variable exposure to OC observed in the youngest infants (<1 month of age). It is apparent that, if the dosage per kg of body weight is the same, the average exposure to OC will be highest in the youngest infants because the maturation of the renal function is not completed yet. It is also apparent that the youngest infants have the most variable exposure regardless of the dosage. Clinical data on oseltamivir use (treatment) in patients <2 weeks of age are sparse. Insufficient data are available to recommend a posology for preterm infants, and an extrapolation from full term neonates cannot be made because nephrogenesis is incomplete and postnatal maturation of GFR may be less rapid in preterm compared to term infants.

Risks

Unfavourable effects

The most frequently observed AEs in patients exposed to oseltamivir are vomiting and/or diarrhoea, and vomiting is regarded as related to oseltamivir. Diarrhoea was reported as AE in 7% (9/124; including one SAE) of patients in the pooled safety population of CASG114 and WP22849, and there were 20 case reports in the post-marketing experience. There is no evidence of increased CNS events in infants.

A substantial amount of safety data is overall available on the use of oseltamivir for treatment of influenza in infants below 1 year of age. Based on the available information, the safety profile of oseltamivir is similar between infants below 1 year of age and older children. Overall, tolerability to oseltamivir is acceptable.

Uncertainty in the knowledge about the unfavourable effects

In the absence of controlled safety studies it is difficult to detect any potential differences in safety and tolerability of oseltamivir between infants below 1 year of age and adults or older children. However, no post-authorisation signals have been detected that would indicate age-specific safety issues in infants.

Clinical data on oseltamivir use (treatment) in patients <2 weeks of age are sparse. The exposure to OC observed in the youngest infants (<1 month of age) is highly variable.

A consolidated safety report on the emergence of resistance in the two clinical PK studies related to this variation should be submitted as a post-authorisation commitment (LEG) along with any updated data from the resistance surveillance program.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Seasonal influenza is usually a mild-to-moderate, self-limiting illness that does not necessarily need to be medically treated. However, more pathogenic zoonotic influenza viruses can often cross species barriers and infect humans. Regardless of the strain pathogenicity, however, infants are more susceptible to complications of influenza such as upper and lower respiratory tract infections and otitis. The currently approved antiviral medicinal products are in general not indicated in infants. Oseltamivir has been already granted an indication in children aged 2 weeks and above in the United States. Oseltamivir is also recommended by the WHO for treatment of avian influenza, as a marked reduction in mortality has been demonstrated in subjects infected with avian influenza viruses and treated with oseltamivir.

The safety data gathered so far indicate a similar safety profile of oseltamivir in children below 1 year of age vs. older children. Therefore, the indication of oseltamivir was already extended in 2009 to cover infants below 1 year of age during a pandemic. The current PK/PD analysis has been carried out to further define the correct dosage in infants and to grant an extension of indication to treat infants also outside an influenza pandemic. In individual subjects, the severity of influenza disease or severe underlying conditions may indeed require antiviral treatment of influenza to avoid complications and even death.

Benefit-risk balance

The benefit-risk balance of oseltamivir in infants below 1 year of age and with a post-conceptual age of at least 36 weeks is regarded as favourable. Insufficient data are available for premature infants, for whom a different dosing may be required due to the immaturity of the renal function, therefore a posology recommendation could not be made for this population.

Discussion on the Benefit-Risk Balance

The benefit-risk is dependent on the individual patient condition, on the severity of influenza and on the pathogenicity of the virus strain. As influenza can be even life-threatening and also carries risk of complications, and on the other hand, no major safety concerns have been noted in infants, the overall benefit-risk of oseltamivir in the treatment of influenza in infants <1 year of age also in a non-pandemic situation is regarded to be favourable.

Oseltamivir is generally well tolerated, and the available data do not indicate a different profile in infants.

The dosage recommendation proposed by the MAH in the current variation for the youngest infants is higher than the currently approved dosage during a pandemic outbreak. The proposed dosage is based on a substantially larger PK dataset and more accurate PK modelling and simulation. The CHMP concluded that the new dosage will more reliably ensure an efficacious exposure to oseltamivir in all treated patients, in spite of the larger inter-individual variability in exposure among young infants compared to older infants or children. This is regarded as beneficial because youngest infants tend to require longer time to stop viral shedding due to their immature immune system. This may also be linked with more frequent emergence of resistance mutations during treatment, as mentioned. The higher exposures in infants receiving 3 mg/kg BID do not exceed those in adults receiving a dose of 150 mg BID; this exposure was well tolerated in adults in the pivotal phase 3 studies.

Although not decisive for the benefit-/risk balance of oseltamivir in the proposed indication, the MAH should provide further reassurance that the emergence of resistant strains in patients aged <1 year exposed to the proposed dose and regimen of oseltamivir is not potentiated by under exposure to the compound. Hence the CHMP requested i) to discuss in future PSURs the epidemiologic relevance of emergence of resistant mutations and any potential increased risk of transmission of resistant viral mutants within the environment, which could be associated to the dosing regimen approved in this application; to investigate and discuss if there is any information concerning different dosages and emergence of resistance in this age group; ii) to

submit a consolidated safety report on the emergence of resistance in the two clinical PK studies that were assessed in this application, along with any updated data from the resistance surveillance program. This second request should be addressed via a post-authorisation commitment (LEG, legally binding measure).

As data on preterm infants is very limited, the newly granted indication does not cover preterm babies (i.e. post-conceptual age less than 36 weeks).

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations requested		**Type**	**Annexes affected**
B.IV.1.a.1	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IAin	I, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a new population for Tamiflu (infants below 1 year of age not limited to an pandemic outbreak with dosing regimen 3 mg/kg twice daily for 5 days). Consequentially, addition of a 3 ml plastic oral dispenser, within the Tamiflu 6 mg/ml powder for oral suspension outercarton only (in addition to the already included 10 ml plastic oral dispenser), to enable the accurate dosing in infants below 1 year of age. This 3 ml oral dispenser is proposed following CHMP request as part of the line extension for 6 mg/ml (EMEA/H/C/402/X/0085 - European Commission Decision: November 2011).

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC were updated to reflect the new data. The Package Leaflet and Labelling are updated in accordance.

Furthermore, the PI is being brought in line with the latest QRD template.

The requested group of variations procedure proposed amendments to the SmPC, Labelling and Package Leaflet.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP/0062/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include a new population for Tamiflu (infants below 1 year of age not limited to an pandemic outbreak with dosing regimen 3 mg/kg twice daily for 5 days). Consequentially, addition of a 3 ml plastic oral dispenser, within the Tamiflu 6 mg/ml powder for oral suspension outer carton only (in addition to the already included 10 ml plastic oral dispenser), to enable the accurate dosing in infants below 1 year of age. This 3 ml oral dispenser is proposed following CHMP request as part of the line extension for 6 mg/ml (EMEA/H/C/402/X/0085 - European Commission Decision: November 2011).

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC were updated to reflect the new data. The Package Leaflet and Labelling are updated in accordance.

Furthermore, the PI is being brought in line with the latest QRD template.

Summary

The current variation to extend the use in infants less than 1 year of age in the treatment of influenza is based on PK/PD modelling from studies CASG114 and WP22849. The MAH has used pharmacokinetic data, modelling and simulation to support the dosage of oseltamivir in infants <1 year of age. The simulations indicate that a 3 mg/kg BID regimen in infants <1 year of age is predicted to provide OC exposures that exceed those observed with marketed doses in adults on 75 mg BID and children 1-5 years of age. The highest and most variable exposure is predicted for infants < 1 month of age. OC exposures are, however, not anticipated in any infant group to exceed those observed with dosage 150 mg BID in adults, which was the alternative, well tolerated dosage in pivotal phase 3 studies. It is predicted that with a lower dosage (e.g. 2.5 mg/kg BID) the target OC levels will not be achieved in all patients. Predicted oseltamivir exposures are anticipated to be similar to some of the exposures that have been shown to be tolerated across the oseltamivir clinical pharmacology program. As data on preterm infants is very limited, the newly granted indication does not cover preterm babies (i.e. post-conceptual age less than 36 weeks). Based on the data assessed, the safety profile of oseltamivir in infants below 1 year of age is acceptable. As a consequence of extension of indication, a 3 ml plastic oral dispenser was proposed to be added to the Tamiflu 6 mg/ml powder for oral suspension outer carton (in addition to the already included 10 ml plastic oral dispenser), to enable the accurate dosing in infants below 1 year of age.