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A Combination of Olanzapine and Samidorphan Has No Clinically Relevant Effect on QT Prolongation up to Supratherapeutic Doses

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ABSTRACT: Background: ALKS 3831, a combination of olanzapine and samidorphan (OLZ/SAM) in development for schizophrenia, is intended to mitigate olanzapine-associated weight gain. This thorough QT (tQT) study evaluated OLZ/SAM effects on electrocardiogram parameters.

METHODS: In this randomized, double-blind, parallel-group study, 100 patients with stable schizophrenia were randomized 3:2 to either receive OLZ/SAM 10/10 mg (therapeutic dose) on days 2–4, 20/20 mg on days 5–8, and 30/30 mg (supratherapeutic dose) on days 9–13 with moxifloxacin-matching placebo on days 1 and 14, or a single dose of moxifloxacin 400 mg and matching placebo on days 1 and 14 (nested crossover design). Drug concentration relation to change from baseline in Fridericia-corrected QTc (ΔQTcF) was evaluated using a linear mixed-effect concentration-QTc (C-QTc) model. Adverse events were assessed.

RESULTS: The slope (90% CI) of the C-QTc was not significant for olanzapine or samidorphan (0.03 [−0.01, 0.08] and 0.01 [−0.01, 0.04] msec per ng/mL, respectively). Predicted placebo-corrected ΔQTcF (90% CI) was 2.33 (−2.72, 7.38) and 1.38 (−3.37, 6.12) msec at the observed geometric mean maximal concentration of olanzapine (62.6 ng/mL) and samidorphan (75.1 ng/mL), respectively, on day 13. A clinically relevant QT effect (ie, placebo-corrected ΔQTcF ≥10 msec) can be excluded for olanzapine and samidorphan concentrations up to ≈110 and ≈160 ng/mL, respectively. Assay sensitivity was confirmed by the C-QTc relationship of moxifloxacin. OLZ/SAM was well tolerated.

CONCLUSIONS: OLZ/SAM, in doses and plasma concentrations up to supratherapeutic levels, was well tolerated and had no clinically relevant effects on electrocardiogram parameters, including QT interval, in patients with schizophrenia.

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Esketamine Nasal Spray for Management of Treatment-Resistant Depression: Number Needed to Treat, Number Needed to Harm, Likelihood to be Helped/Harmed

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ABSTRACT: Background: Targeting of glutamate receptors is a novel approach for the treatment of major depressive disorder (MDD). This study aimed to review the usefulness for esketamine nasal spray for the management of treatment-resistant depression (TRD) using the tools of evidence-based medicine: number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH).

METHODS: Data sources were four completed Phase 3 randomized, double-blind, placebo-controlled, studies, including two pivotal registration studies of esketamine nasal spray in TRD in non-elderly adults (acute flexible-dose study NCT02418585, maintenance study NCT02493868) Efficacy outcomes included acute response (≥50% decrease from baseline on Montgomery-Asberg Depression Rating Scale [MADRS] total score), acute remission (MADRS scores ≤12; and other thresholds using the MADRS and Clinical Global Impressions-Severity [CGI-S] scales), categorical shifts in MADRS and CGI-S scores, and avoidance of relapse/recurrence (observed relapse rates). NNT, NNH and LLH are calculated for combination of esketamine nasal spray and oral antidepressant (esketamine+AD) vs AD+placebo in patients with TRD.

RESULTS: In the acute flexible-dose study of esketamine nasal spray (56-84 mg twice-weekly for 4 weeks), MADRS

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