

143

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 (Δ QTcF) 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 Δ QTcF (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 Δ QTcF \geq 10 msec) can be excluded for olanzapine and samidorphan concentrations up to

\approx 110 and \approx 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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144

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 (\geq 50% decrease from baseline on Montgomery-Asberg Depression Rating Scale [MADRS] total score), acute remission (MADRS scores \leq 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

response with esketamine+AD vs AD+placebo at endpoint (rates 63.4% vs 49.5%, respectively) yielded an NNT value of 8, and MADRS remission at endpoint (48.2% vs 30.3%) resulted in a NNT vs AD+placebo of 6. NNH values vs AD+placebo were <10 for the adverse events (AE) of dissociation (26.1% vs 3.7%), vertigo (26.1% vs 2.8%), nausea (26.1% vs 6.4%), dizziness (20.9% vs 4.6%), and dysgeusia (24.3% vs 11.9%), the NNH values were 5, 5, 6, 7, and 9, respectively. Discontinuation rates due to AE (7.0% vs 0.9%) yielded a NNH of 17. LHH comparing MADRS remission vs discontinuation was 17/6, or approximately 3. The pattern of results was similar for the other acute studies and for the pooled data combining all 3 acute studies. Maintenance use of esketamine (dose 56-84 mg once-weekly or once-every-other-week) plus an oral AD demonstrated NNT values <10 for relapse and/or maintenance of remission in favor of esketamine+AD vs AD+placebo, a NNT of 4 was observed for outcome of relapse in patients with stable response at the time of randomization (relapse rates were 25.8% vs 57.6%, respectively). In the maintenance study, discontinuation rates due to an AE (2.6% vs 2.1%) yielded a non-significant NNH value of 178.

CONCLUSION: The low NNT values <10 for efficacy outcomes suggest potential benefits of esketamine+AD for both acute and maintenance use. LHH was favorable: esketamine+AD was 3 times more likely to result in acute remission vs discontinuation due to an AE.

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145 Incidence and Characteristics of Akathisia and Restlessness During Cariprazine Treatment for Bipolar I Disorder

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ABSTRACT: Study Objective: Akathisia and restlessness are common adverse events associated with atypical antipsychotic use; in severe cases, symptoms may lead to treatment discontinuation. Cariprazine, a dopamine D3/D2 receptor partial agonist with preferential binding to D3

receptors, is approved for the treatment of schizophrenia (1.5–6 mg/d), and manic or mixed (3–6 mg/d) and depressive episodes (1.5–3 mg/d) associated with bipolar I disorder. Pooled post hoc analyses were conducted to characterize the incidence and severity of cariprazine-related akathisia and restlessness in patients who participated in bipolar disorder studies.

METHOD: All studies were Phase II/III multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in patients with bipolar I disorder who were currently experiencing a manic/mixed (NCT00488618, NCT01058096, NCT01058668) or depressive (NCT01396447, NCT02670538, NCT02670551) mood episode. Patients received flexibly dosed cariprazine 3-12 mg/d (day 1: 1.5 mg; day 2: 3 mg; subsequent up-titration in 3-mg increments if needed) or placebo in the bipolar mania studies and fixed-dose cariprazine 1.5 mg/d, 3 mg/d (slow titration to 1.5 mg [day 8] and 3 mg [day 15]) or initiation at 1.5 mg with escalation to 3 mg on day 15), or placebo in the bipolar depression studies. The incidence, severity, and timing of treatment-emergent adverse events (TEAEs) of akathisia and restlessness were evaluated in this analysis.

RESULTS: In the bipolar mania studies (N=1065), TEAEs of akathisia occurred in 20.2% of cariprazine-treated patients and 4.8% of placebo-treated patients; 2.4% of cariprazine-treated patients discontinued due to akathisia. TEAEs of restlessness occurred in 6.7% and 2.3% of cariprazine- and placebo-treated patients, respectively, and caused discontinuation of 0.3% of cariprazine-treated patients. In the bipolar depression studies (N=1407), akathisia occurred in 2.1%, 5.5%, and 9.6% of patients in the placebo, cariprazine 1.5 mg/d, and cariprazine 3 mg/d groups, respectively; <2% of patients in each group discontinued due to akathisia. Restlessness occurred in 3.2% of placebo-treated patients and 2.1% and 6.6% of patients in the 1.5 and 3 mg/d groups, respectively; discontinuations due to restlessness occurred in 0.2% and 1.1% of patients in the 1.5 and 3 mg/d groups. Akathisia and restlessness in cariprazine-treated patients was generally mild or moderate in severity (>92% in both populations). Most akathisia events in the bipolar mania studies were reported for the first time within the first 2-3 weeks of treatment.

CONCLUSIONS: In these post hoc analyses, the incidence of akathisia and restlessness were generally higher with cariprazine than with placebo. However, most incidences were mild or moderate in severity, and infrequently led to discontinuation. Akathisia appears to be dose related in both mania and depression, suggesting lower doses and slower titration may reduce occurrence.

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