INPLASY

Trajectory of Treatment Responses Across Ulotaront Doses in Schizophrenia: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - Currently none.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 January 2025 and was last updated on 22 January 2025.

INTRODUCTION

Review question / Objective The optimal ulotaront dose for schizophrenia remains uncertain. This study examined its dose-response relationship for both efficacy and safety.

Condition being studied Schizophrenia treatment faces significant challenges, including limited effectiveness of current medications, treatment-resistant cases, and severe side effects that impact adherence. Many patients struggle to achieve full recovery, leaving unmet medical needs. Developing new drugs, such as ulotaront in this study, is crucial to address these gaps, offering innovative solutions to improve symptoms.

METHODS

Search strategy A comprehensive literature search was conducted across the following databases: PubMed, Embase, Cochrane Library, and ClinicalTrials.gov. The search used the keywords (SEP-363856 OR SEP-856 OR ulotaront) AND (psychosis OR psychotic disorder OR schizophreni* OR schizoaffective disorder OR delusional disorder) and included all relevant literature published up to January 22, 2025, without restrictions on language or geographic region.

Participant or population Schizophrenia spectrum disorder.

Intervention Ulotaront.

Comparator Placebo.

Study designs to be included Randomized controlled trial.

Eligibility criteria Studies meeting the following criteria were included: (1) participants had a diagnosis of schizophrenia spectrum disorder based on established diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders; (2) quantitative data on clinical outcomes, including the severity of psychotic

symptoms measured with a validated scale before and after medication administration (e.g., the Positive and Negative Syndrome Scale [PANSS]), were reported. The following exclusion criteria were applied: (1) non-RCTs or studies using comparators other than placebo. As this review assumes that placebo serves as a zero-dose baseline for ulotaront, trials comparing ulotaront with other drugs or those lacking a placebo arm were excluded, as they do not provide relevant data for dose-response analysis; (2) studies involving participants without a confirmed diagnosis of schizophrenia spectrum disorder based on established criteria, such as those diagnosed with bipolar disorder; (3) studies that did not report quantitative clinical outcomes appropriate for dose-response analysis; and (4) duplicate data from research protocols. In cases of multiple publications originating from the same research source, only the report with the largest sample size and the most comprehensive data was included.

Information sources A comprehensive literature search was conducted across the following databases: PubMed, Embase, Cochrane Library, and ClinicalTrials.gov.

Main outcome(s) Outcome data were classified into two primary domains: treatment efficacy and safety. For treatment efficacy, the primary outcome was the change in psychotic symptom severity between the placebo and treatment groups, assessed by the PANSS total scores. For treatment safety, the primary outcome was the dropout rate during the study period.

Additional outcome(s) Outcome data were classified into two primary domains: treatment efficacy and safety. For treatment efficacy, secondary outcomes included the PANSS positive symptom subscore, PANSS negative symptom subscore, and the Clinical Global Impression Scale-Severity (CGI-S). For treatment safety, secondary outcomes included adverse effect rates. Adverse effects were categorized into serious and non-serious events. Additionally, we examined key adverse events frequently reported in a prior study,1 such as headache, nausea, agitation, anxiety, insomnia, and somnolence.

Quality assessment / Risk of bias analysis The risk of bias for each included study was assessed using the Cochrane Risk of Bias Tool, Version 2 (RoB 2).

Strategy of data synthesis For PANSS and CGI-S, pre- to post-treatment changes were calculated and expressed as standardized mean differences (SMDs) with 95% confidence intervals (CIs). For dropout and adverse event, event counts were converted to risk ratios (RRs) with 95% CIs. To investigate whether ulotaront exhibited a dose-dependent relationship compared with placebo for both primary and secondary outcomes, a one-stage random-effects dose-response meta-analysis was conducted. Dose-response curves were modeled using restricted cubic splines with three knots placed at fixed percentiles (10%, 50%, and 90%). Model fit was assessed using goodness-of-fit statistics, with the coefficient of determination (R-squared) reflecting the proportion of effect-size variability explained by dose. Heterogeneity in the one-stage dose-response meta-analysis was evaluated using the variance partition coefficient, an extension of the I-squared statistic. All statistical analyses were performed in R version 4.3.2 (R Project for Statistical Computing). Two-sided tests were used, and p-values < 0.05 were considered statistically significant.

Subgroup analysis For the primary efficacy outcome, an additional analysis were conducted. We examined treatment efficacy over time by comparing ulotaront and placebo across varying doses. This analysis followed the same methodology as the primary dose-response analysis and was repeated accordingly.

Sensitivity analysis For the primary efficacy outcome, an additional analysis were conducted. A leave-one-out analysis was performed to assess the impact of excluding individual studies on the overall findings.

Language restriction No.

Country(ies) involved Taiwan.

Keywords ulotaront, efficacy, safety, schizophrenia.

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