Sustained Efficacy with Long-term Treatment with AXS-05: Results from the COMET Phase 3 Trial, a Long-term, Open-label Study Evaluating the Efficacy and Safety of AXS-05 for the Treatment of MDD

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Introduction

• Major depressive disorder (MDD) is a serious disorder. MDD is chronic, disabling, and life threatening. Despite major advances in treatment and diagnosis, the majority of these patients do not achieve remission.1

• Need for mechanistically novel approaches: Current approved antidepressants either do not address the disease mechanism or are associated with prolonged time to clinically meaningful response (4–8 weeks) and adverse events that can impact adherence to treatment.2

• The COMET trial was a Phase 3, multi-center, open-label study conducted in the United States (US). The primary objective of the COMET trial was to evaluate the long-term efficacy and safety of AXS-05 in the treatment of major depressive disorder.2

Trial Objective

The objective of the COMET Phase 3 trial was to evaluate the long-term efficacy and safety of AXS-05 in the treatment of major depressive disorder.

Trial Design

• The COMET trial was a Phase 3, multi-center, open-label U.S. trial

• Subjects were treated with AXS-05 (105 mg dextromethorphan-105 mg brompheniramine) twice daily for up to 12 months

• The study enrolled both subjects completing a prior AXS-05 study and newly enrolled subjects

• A total of 611 subjects were treated with AXS-05, including 61 newly enrolled subjects

• Marked or moderate improvement in depressive symptoms after treatment with AXS-05 was achieved by 84.6% of patients

Safety and Tolerability

• AXS-05 was generally safe and well-tolerated in the study

• The most commonly reported adverse events (AEs) were dizziness, nausea, headache, dry mouth, and decreased appetite

• The most common AEs resulting in discontinuation were dizziness (3.8%), nausea (1.7%), and headache (1.9%)

Efficacy Results

Improvement in Depressive Symptoms over Time

Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>AXS-05</th>
<th>MADRS</th>
<th>CGI-2</th>
<th>SDS</th>
<th>Nausea</th>
<th>Insomnia</th>
<th>Weight Gain</th>
<th>Dry Mouth</th>
<th>Headache</th>
<th>Dizziness</th>
<th>Anorexia</th>
<th>Constipation</th>
<th>Nausea</th>
<th>Insomnia</th>
<th>Weight Gain</th>
<th>Dry Mouth</th>
<th>Headache</th>
<th>Dizziness</th>
<th>Anorexia</th>
<th>Constipation</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>42.4 (14.5)</td>
<td>58.5 (17.0)</td>
<td>43.6 (16.4)</td>
<td>38.9 (15.8)</td>
<td>52.1 (17.0)</td>
<td>45.9 (16.4)</td>
<td>40.3 (15.8)</td>
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Adverse Events Occurring in ≥20% of Subjects

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>AXS-05</th>
<th>MADRS</th>
<th>CGI-2</th>
<th>SDS</th>
<th>Nausea</th>
<th>Insomnia</th>
<th>Weight Gain</th>
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<tbody>
<tr>
<td>Dizziness</td>
<td>3.2%</td>
<td>4.3%</td>
<td>2.0%</td>
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<td>Nausea</td>
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<tr>
<td>Insomnia</td>
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References


Conclusions

• AXS-05 resulted in rapid and substantial reduction in symptoms of depression and improvement in functioning, which were durable over 12 months of treatment

• Rates of clinical response and remission on the MADRS, and functional response on the SSSR were substantial

• AXS-05 was generally safe and well-tolerated in this trial. The most commonly reported adverse events were dizziness, nausea, and headache

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AXS-05: A Novel, Oral NMDA Receptor Antagonist with Multimodal Activity

AXS-05 is a novel, oral investigational NMDA receptor antagonist with multimodal activity, which is a mechanistically novel approach for the treatment of major depressive disorder. AXS-05 is a novel, oral investigational NMDA receptor antagonist with multimodal activity, which is a mechanistically novel approach for the treatment of major depressive disorder.

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Safety and Tolerability

AXS-05 was a novel, oral investigational NMDA receptor antagonist with multimodal activity.2

• The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, a synaptic glutamate receptor, and a ion channel receptor.3

• These actions modulate glutamatergic transmission.

• The brompheniramine component serves primarily to increase the bioavailability of dextromethorphan, and it is a nonsedating and daytime-use antihistamine inhibitor of histamine H1 receptors.

Dextromethorphan (DM) and brompheniramine (DM) Plasma Concentration

The COMET trial was a Phase 3, multi-center, open-label U.S. trial.

Subjects were treated with AXS-05 (105 mg dextromethorphan-105 mg brompheniramine) twice daily for up to 12 months.

The study enrolled both subjects completing a prior AXS-05 study and newly enrolled subjects.

A total of 611 subjects were treated with AXS-05, including 61 newly enrolled subjects.

Marked or moderate improvement in depressive symptoms after treatment with AXS-05 was achieved by 84.6% of patients at Week 1, 80.7% of patients at Week 2, 79.5% of patients at Week 3, and 77.0% of patients at Week 4.

Clinical response after 6 months of treatment with AXS-05 was achieved by 86.7% and 93.1% of patients, respectively.

Clinical response after 12 months of treatment with AXS-05 was achieved by 84.6% and 83.3%, respectively.