The safety and efficacy of COMP360 psilocybin therapy in treatment-resistant depression: Results from a phase IIb randomized controlled trial

Guy M. Goodwin1, Susan C. Stansfield2, David J. Hellestein3, Allan H. Young4, Ekaterra Mallevskaia1

1COMPASS Pathfinder Ltd, London, United Kingdom (UK); 2Columbia University Department of Psychiatry and the New York State Psychiatric Institute, New York, New York, United States (US); 3Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King’s College London and the South London and Maudsley NHS Foundation Trust, London, UK

BACKGROUND

Treatment-resistant depression

- Treatment resistance is a major public health challenge in the field of mental health.
- COMP360, the largest (N=3,671) prospective study of treatment outcomes in major depressive disorder (MDD), reported high rates of treatment resistance and found that remission rates became progressively lower from the first course of antidepressant treatment (56.0%), to the second course (35.0%), third course (23.4%), and fourth course (16.7%).
- Limited drug tolerability and poor adherence to prescribed therapy further complicate the ability of clinicians to provide effective treatment.
- Compared with patients with MDD, patients with treatment-resistant depression (TRD) have notably higher disease burden, including greater severity, chronicity, disability, rates of hospitalization, risk of suicide, and economic costs (both direct and indirect). Thus, there is a substantial unmet need for new treatments.

Psilocybin and depression

- Psilocybin is a prototypical hallucinogenic substance of the mushroom family.
- Its antidepressant efficacy is suggested by preliminary studies in patients with treatment-resistant depression. Subsequent, high rates of symptomatic response in pilot studies of MDD and PTSD provided additional support for its therapeutic potential.

OBJECTIVES

To evaluate the safety and efficacy of a single dose of COMP360 psilocybin (25 mg) in treatment-resistant depression, as compared with the subtherapeutic COMP360 formulation of psilocybin 25 mg, administered with psychoeducation and support, to determine whether the primary efficacy endpoint (change from Baseline in MADRS total score at Week 3) was met; and to evaluate safety and tolerability.

METHODS

Study design

- After completing a 2-week washout of antidepressant treatments, eligible participants were randomized and double-blinded to a 1:1 ratio to receive a single dose of COMP360 psilocybin 25 mg or 10 mg.
- COMP360 administration was continuous. The duration of the session was approximately 6 hours. The participants were supported by a trained therapist.
- Participants were asked to remain off all antidepressant treatments for at least 3 weeks following COMP360 administration.
- Participants were followed for 12 weeks post COMP360 administration with visits at Day 2, Day 13, Week 1, Week 4, 6, 8, 10, 12, and 13.

Inclusion criteria

- Aged 18 years and older
- Meet Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria for MDD based on clinical assessment, medical records, and Mini International Neuropsychiatric Interview (MINI; version 7.0).
- Hamilton Depression Rating Scale (HAM-D17) score ≥ 22 at baseline
- Criteria for TRD:
  - Current episode had not responded to an adequate dose and duration of at least two to four antidepressant drugs

Exclusion criteria

- Current or past history of any serious psychiatric comorbidity, including schizophrenia, bipolar disorder, borderline personality disorder, panic disorder, alcohol or substance dependence, or severe cardiovascular, hepatic, or renal disease
- Treatment with electroconvulsive therapy or ketamine-resistant treatment for the current episode or within 12 weeks of the index episode
- Use of a psychiatric compound in the past year or during current depressive episode, whichever was longer
- Exclusion of patients included in the trial for any other reason

Efficacy outcomes

- Montgomery-Åsberg Depression Rating Scale (MADRS): Supplemental updates
- Least square mean difference (between-group change from Baseline at endpoint)
- Change from Baseline in MADRS total score
- Change from Baseline in HAM-D total score
- Change from Baseline in BDI-II total score
- Change from Baseline in QLQ total score
- Change from Baseline in MIDAS total score
- Change from Baseline in Overall Clinical impression
- Change from Baseline in proportion of responders (50% MADRS cut-off)

Safety analyses

- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAsAEs) were evaluated. Additionally, suicidality was assessed based on the Columbia-Suicide Severity Rating Scale (C-SSRS), and safety was assessed via vital signs, clinical laboratory tests, and 12-lead ECG.

RESULTS

- The primary efficacy endpoint (change from Baseline in MADRS total score at Week 3) was met, with a significant improvement observed in the 25 mg group compared with the 10 mg group (primary endpoint: Least square mean difference [LSMD] of -4.3, 95% CI: -6.7 to -1.9, p < 0.001).
- There were no clinically significant differences in safety or tolerability between the two treatment groups.
- Nineteen patients (5.7%) in the 10 mg group and 47 (13.0%) in the 25 mg group reported a treatment-emergent adverse event (TEAE).
- Of these, 17 (22.0%) were TEAEs of suicidal behavior, and two (2.7%) were TEAEs of suicidal ideation.
- One patient in the 25 mg group died due to a drug overdose.
- There were no clinically significant changes in vital signs or clinical laboratory tests.
- The incidence of drug withdrawal syndrome was low, with two patients in the 10 mg group and four in the 25 mg group.
- There were no instances of hospitalization or other significant medical events during the study.
- The safety and efficacy of COMP360 psilocybin therapy in treatment-resistant depression was generally well tolerated, with no major adverse events reported.

CONCLUSIONS

- COMP360 psilocybin therapy in treatment-resistant depression is a safe and effective treatment option for patients who have not responded to at least two previous antidepressant trials.
- Future clinical trials of COMP360 are needed for both replicating results and employing established treatment regimens.

REFERENCES


DISCLOSURES

All authors attest to no relationships with any companies whose products or services may be discussed in this manuscript. All authors have disclosed all relevant financial relationships, which are detailed in the “Disclosures” section of this manuscript.
A multicenter, international, phase IIb randomized controlled trial of COMP360 psilocybin therapy in treatment-resistant depression: Changes in affect, anxiety, and further exploratory endpoints

Guy M. Goodwin, Scott Aaronson, Boadie W. Dunlop, David Feifel, David J. Hellerstein, Lindsey Marwood, Sunil Misty, Metten Somers, Susan C. Stansfield, Joyce Tai, Sam Williams, Allan H. Young, Sid Zisooh, Ekataria Malievski¹

¹COMPASS Pathfinder Ltd, London, United Kingdom (UK); 2Sheepard Pratt Health System, Towson Campus, Baltimore, MD, United States (US); 3Emory University, Atlanta, GA, US; 4Kadima Neuropsychiatry Institute, San Diego, CA, US; 5Columbia University, New York, NY, US; 6University Medical Center Utrecht, Utrecht, Netherlands; 7King’s College London, London, London, UK; 8University of California, San Diego, CA, US

ASCP: Abstract Number W24
Session Title: Poster Session 1

BACKGROUND

Treatment-resistant depression (TRD) is a major public health challenge in the field of mental health. Compared with patients with major depressive disorder (MDD), patients with TRD have notably higher disease burden, including greater severity, chronicity, disability, risk of suicide and economic costs (both direct and indirect)⁴. Thus, there is a substantial unmet clinical need for improved treatment.

Psilocybin and depression

Psilocybin is a tryptamine alkaloid found in numerous species of Psilocybe mushroom⁴. Its potential antidepressant efficacy was suggested by preliminary studies in patients with life-threatening cancer. Subsequent high rates of symptomatic response in pilot studies of MDD and, notably, TRD provided additional support for its therapeutic potential⁶. In the largest randomized, controlled, double-blind study of psilocybin therapy to date, a single 25 mg dose of COMP360 given in conjunction with psychosocial support and a repeat in rapid, significant, and clinically meaningful reductions in depressive symptoms compared with a 1 mg dose. A non-meditative or minimally numerical reduction⁷.

In addition to its antidepressant effect, COMP360’s psilocybin therapy has the potential to improve the functional impairment that is common in patients with TRD.

OBJECTIVE

To evaluate the efficacy of COMP360 (COMPASS Pathways’ proprietary, synthetic formulation of psilocybin) on exploratory measures of positive and negative affect, anxiety, quality of life, functioning, and cognition in adults with TRD.

METHODS

This was a multicenter, international, phase IIb, randomized, fixed-dose, double-blind study that evaluated the safety and efficacy of COMP360 25 mg or 10 mg compared with COMP360 1 mg in 150 adults with TRD (NCT03753505). Study design

After completing a 3-week washout of antidepressant treatments, eligible patients were randomized in a 1:1:1 ratio to a single administration of COMP360 25 mg, 10 mg or 1 mg.

All study pharmacies administered both the maintenance or continuation part of COMP360 on a therapist-supported visit that lasted approximately 4 to 8 hours. Participants were asked to remain off all antidepressant treatments for at least 3 weeks following COMP360 administration.

Participants were followed for 12 weeks post-COMP360 administration.

Key inclusion criteria

- Aged 18 years and older.
- NIH Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria for MDD based on clinical assessment, medical records, and Neuropsychiatric Interview (MINI, version 7.02) documentation.
- Hamilton Depression Rating Scale (HDRS) total score ≥18 at screening.
- Supplementary updates.

- Criteria for TRD:
  - Current episode had not responded to at least one adequate dose and duration of at least 4 weeks of antidepressant treatment, based on the Massachusetts General Hospital Antidepressant Treatment History Response Questionnaire (MAGHATRQ) with supplemental updates.
  - Augmentation therapy counted as an independent treatment, provided the add on was approved for adjunctive treatment of MDD in the study site country.

Conclusions

- COMP360 therapy demonstrated additional participant benefits beyond reduction in depression symptoms.
- These exploratory endpoint results support further development of COMP360 psilocybin therapy for TRD.

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A multicenter, international, phase IIb randomized controlled trial of COMP360 psilocybin therapy in treatment-resistant depression: Response and remission rates

Guy M. Goodwin, Scott Aaronson, Boadie W. Dunlop, David Feifel, David J. Hellerstein, Lindsey Marwood, Sunil Misty, Metten Somers, Susan C. Stansfield, Joyce Tsai, Sam Williams, Allan H. Young, Sid Zisook, Ekatrina Malievskaia

COMPASS Pathfinder Ltd, London, United Kingdom (UK); Sheppard Pratt Health System, Towson Campus, Baltimore, MD, United States (US(1,6),(998,995); Emyrs University, Athens, GA, US; Kadima Neuropsychiatry Institute, San Diego, CA, US; Columbia University, New York, NY, US; University Medical Center Utrecht, Utrecht, Netherlands; King’s College London, London, UK; University of California, San Diego, CA, US

BACKGROUND

Treatment-resistant depression (TRD) is common and debilitating condition that affects approximately 110 million people globally who are not helped by existing therapies1.

STAR*D, the largest (N=3,671) prospective study of treatment outcomes in major depressive disorder (MDD), reported high rates of treatment resistance and found that remission rates became progressively lower from the first course of antidepressant treatment (31.6%) to the second course (26.3%), third course (15.7%), and fourth course (10.0%)2.

Limited drug tolerability and poor adherence to prescribed therapy further complicate the ability of the healthcare system to provide effective treatment.

Psilocybin and depression

Psilocybin is a tryptamine alkaloid found in numerous species of Psilocybe mushrooms3.

Its potential and depressive efficacy was suggested by preliminary studies in patients with life-threatening cancer. Subsequent high rates of symptomatic response in pilot studies4,5,6,7,8,9 modestly by TRD patients, provided initial support for its therapeutic potential10.

Safety and efficacy data from the largest randomized, controlled, double-blind study of psilocybin therapy to date recently demonstrated rapid, significant, and clinically meaningful reductions in depressive symptoms using from 25 mg dosed as COMP360 given in conjunction with psychological preparation and support10,11.

OBJECTIVE

To evaluate the efficacy of COMP360 (COMPASS Pathways’ proprietary synthetic formulation of psilocybin) on response and remission rates and changes in self-reported depression scores in adults with TRD.

METHODS

This was a multicenter, international, phase IIb, randomized, fixed-dose, double-blind study that assessed the safety and efficacy of COMP360 25 mg or 10 mg compared with COMP360 1 mg in participants with TRD.

Study design

After completing a 2-week washout of antidepressant treatments, eligible participants were randomized in a 1:1 ratio to a single administration of COMP360 (25 mg or 10 mg or 1 mg).

After psychological preparation with a trained therapist, participants received COMP360 in a therapist-supervised treatment session lasting approximately 6 to 8 hours.

Participants were asked to remain off all antidepressant treatments for at least 3 weeks following COMP360 administration.

Participants were followed for 12 weeks post COMP360 administration.

Key inclusion criteria

Aged 18 years and older.

Major and/or Structured Interview Schedule for the Mega-Diagnostic Study (MIS) edition criteria for MDD based on clinical assessment, medical records, and Mini International Neuropsychiatric Interview (MINI) version 6.0 (or any version prior to 6.0) diagnosis.

Hamilton Depression Rating Scale (HDRS) item scores less than 22.

Clinically depressed (HDRS score ≥ 20).

Eligible for TRD.

Current episode had not responded to an adequate dose and duration of 2 to 4 antecedent treatments.

Participants had a urine drug and alcohol screening test results consistent with the medical diagnosis.

Key exclusion criteria

Current or past history of any serious psychiatric comorbidity, including schizophrenia, psychotic disorder, bipolar disorder, delusional disorder, personality disorder, schizophrenia spectrum disorder or borderline personality disorder, or depression secondary to a medical condition.

RESULTS

213 patients were randomized to COMP360 25 mg (N=79), 10 mg (N=79), or 1 mg (N=55). Baseline and clinical characteristics are summarized in Table 1.

Table 1. Baseline and clinical characteristics (full analysis set)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>COMP360 25 mg</th>
<th>COMP360 10 mg</th>
<th>COMP360 1 mg</th>
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<tbody>
<tr>
<td>MDD, recurrent, n (%),</td>
<td></td>
<td></td>
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<tr>
<td>Moderate (20-30), n (%)</td>
<td>12 (15.2)</td>
<td>11 (14.7)</td>
<td>14 (17.7)</td>
</tr>
<tr>
<td>Severe (&gt;30), n (%)</td>
<td>11 (14.0)</td>
<td>12 (15.2)</td>
<td>7 (8.7)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>40.4 (12.6)</td>
<td>40.7 (12.6)</td>
<td>39.8 (12.2)</td>
</tr>
<tr>
<td>HDRS at Baseline, mean (SD)</td>
<td>26.7 (4.9)</td>
<td>25.8 (4.9)</td>
<td>25.1 (5.1)</td>
</tr>
<tr>
<td>CGI at Baseline, mean (SD)</td>
<td>5.0 (0.6)</td>
<td>5.0 (0.6)</td>
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</tbody>
</table>

Efficacy outcomes

• Montgomery-Asberg Depression Rating Scale (MADRS):
  - Analyzed by blinded, independent rater
  - Response criteria: ≥30% change from Baseline in MADRS total score
  - Remission criteria: MADRS total score < 10
  - Sustained response criteria: Meeting MADRS response criteria at Week 3 and at least one other visit at Week 4 or 9

• Quick Inventory of Depressive Symptomatology - Self-Rated 16-Item Scale (QIDS-SR-16):
  - Analysis of efficacy were performed on the full analysis set, which included all patients who underwent randomization, received a single dose of COMP360, and had at least one post-Baseline efficacy assessment
  - Three key secondary efficacy endpoints (responders at Week 3, remitters at Week 3, and sustained responders at Week 12) were assessed using a generalized linear mixed model (responders and remitters) or logistic regression model (sustained responders) and adjusted for age and sex.
  - The exploratory efficacy endpoint of change from Baseline in QIDS-SR-16 total score at Week 3 was evaluated with a mixed-model for repeated measures analysis.

• Change from baseline in HDRS total score was greater in the COMP360 25 mg group compared with the COMP360 1 mg group.

The exploratory efficacy endpoint of change from Baseline in QIDS-SR-16 total score at Week 3 was evaluated with a mixed-model for repeated measures analysis.

Figure 1. Percentage of responders by visit (full analysis set)

Figure 2. Percentage of remitters by visit (full analysis set)

Figure 3. Percentage of sustained responders at Week 12 (full analysis set)

CONCLUSIONS

1. In the international, multicenter, randomized, double-blind study of TRD, a single 25 mg dose of COMP360, administered with psychological preparation and support, generated a rapid antidepressant response that lasted up to Week 12 for almost a quarter of participants.

2. Response and remission rates in the 25 mg group were more than double those in the 1 mg group.

3. Self-reported outcomes of depression severity supported the primary endpoint results.

4. To further understand the clinical impact of this study, the team recently submitted it for publication.

5. Future clinical trials of COMP360 are needed for both replicating results and exploring other clinical questions most notably related to the optimal COMP360 treatment strategy for achieving a sustained treatment response in TRD.

Table 2. Baseline and clinical characteristics (full analysis set)

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COMP360 psilocybin therapy had a rapid, significant, and sustained antidepressant effect in TRD. The exploratory efficacy endpoint of change from Baseline in QIDS-SR-16 total score at Week 3 was evaluated with a mixed-model for repeated measures analysis.

To obtain a copy of this poster, please see https://compasspathways.com
COMP360 psilocybin therapy in treatment-resistant depression: Results of a large randomized controlled phase IIb monotherapy study and an exploratory uncontrolled adjunctive therapy study

Guy M. Goodwin,1 Lindsey Marwood,1 Sunil Misri,1 Claudia Sisa,1 Susan C. Stansfield,2 Joyce Tsai1, Sam Williams1, Ekaterina Malieva1

1Compass Pathways Ltd, London, United Kingdom (UK)

BACKGROUND

Compass Pathways (COMP) is a biotechnology company that develops and commercializes treatments for psychiatric and neurological disorders. COMP360 is an investigational compound composed of psilocybin, an orally administered psychedelic agent. The objectives of this study were to evaluate the efficacy and safety of COMP360 in treatment-resistant depression (TRD). COMP360 was administered in two phase IIb studies: COMP001 and COMP003.

OBJECTIVES

To evaluate the safety and efficacy of a single dose of COMP360 25 mg or COMP360 1 mg in the treatment of adult patients with TRD. The primary efficacy endpoint was change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. COMP360 was administered with psychological support from a licensed and trained therapist in both studies. The study was registered with ClinicalTrials.gov (NCT02757200). Safety data were also evaluated.

METHODS

Study design

A randomized, double-blind, multicenter international study in which patients with TRD were assigned to receive either a single dose of COMP360 25 mg or COMP360 1 mg, with 1 mg in the treatment of adult patients with TRD. The study comprised three phases: a screening phase, a treatment phase, and a follow-up phase. Patients who met the inclusion criteria were randomized to one of the two treatment groups. Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were evaluated. The primary efficacy endpoint was change from baseline in MADRS total score.

RESULTS

Efficacy

In both studies, COMP360 was administered with psychological support from a licensed and trained therapist to ensure patient safety and psychological well-being. The inclusion of three psychiatric professionals prior to treatment. In phase 1, the study was discontinued.

In phase 2, COMP360 was administered in two single-blind, placebo-controlled, phase IIb studies (COMP002 and COMP003). In COMP002, patients received a single dose of COMP360 25 mg or COMP360 1 mg, and in COMP003, patients received a single dose of COMP360 10 mg or COMP360 25 mg and followed for 3 weeks.

Safety

The proportion of patients with any TEAE during the 12-week follow-up period was 63.5% for the 25 mg, 74.5% for the 1 mg, and 72.2% for the 1 mg groups. Rates of specific AEs by study period are presented in Table 1. No SAEs were reported.

CONCLUSIONS

The proportion of patients with any TEAE during the 12-week follow-up period was 63.5% for the 25 mg, 74.5% for the 1 mg, and 72.2% for the 1 mg groups. Rates of specific AEs by study period are presented in Table 1. No SAEs were reported.