Psilocybin for Treatment-Resistant Depression

Revised Background and Scope

November 18, 2026

Background

Major depressive disorder (MDD) is common; about one-fifth of Americans will experience MDD.[1,2] Appropriate initial treatments include first-line antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), as well as psychotherapy.[3] Many Americans with MDD do not receive treatment at all, but among those who do, an estimated 2.8 million experience treatment-resistant depression (TRD).[1,2] Definitions for TRD vary,[4,5] but a common definition is inadequate response to two different antidepressant medications despite an adequate dose and duration of treatment. MDD accounts for annual United States (US) costs of more than $300 billion, about one-third of which are direct treatment costs and about two-thirds of which are workplace costs.[6] The annual national burden of TRD is estimated to account for 27%–41% of annual MDD costs.[2] For patients with MDD, the lifetime prevalence of suicide attempts is 31%, with 4% of women and 7% of men ultimately dying by suicide.[7,8] Patients with TRD have a greater than three-fold risk of death by suicide than patients with non-TRD MDD.[9]

The success of another course of antidepressant medications in TRD is much lower than in others with MDD; however, many patients with TRD are treated with additional trials of antidepressant medications.[10,11] Appropriate interventions in TRD include augmentation of medication therapy with an antipsychotic medication.[12] In patients with persistent symptoms, recommended options include esketamine (S-ketamine), ketamine (used off-label for TRD), or repetitive transcranial magnetic stimulation (rTMS, often referred to as simply "TMS"). Electroconvulsive therapy may be used in more severe cases.[13]

Recently, interest has grown in the use of psychedelic medications for TRD. Psilocybin, the psychedelic agent found in "magic mushrooms,"[14,15] is being evaluated for TRD. Although psilocybin is still a Schedule 1 substance (illegal under federal law), in some states, such as Oregon and Colorado, there are existing programs that allow individuals to receive psilocybin sessions at

licensed facilities. COMP360 is a synthetic preparation of psilocybin that has been developed by Compass Pathways. Compass Pathways was granted rolling review of its new drug application (NDA) for COMP360 by the Food and Drug Administration (FDA) in April 2026 and was also selected for the Commissioner's National Priority Voucher program, which potentially has a shortened one-to-two-month FDA review once the NDA is filed.[16]

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patient organizations, clinicians, researchers, and the manufacturer of the agent of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. We heard from multiple stakeholders about the importance of including IV ketamine as a comparator for TRD and some stakeholders suggested the addition of oral ketamine as a comparator. We heard about keeping work, function, and quality of life as important to considering effectiveness of treatment for TRD. Stakeholders emphasized the substantial work, expertise, and infrastructure needed to deliver psilocybin safely and effectively.

Report Aim

This project will evaluate the health and economic outcomes of psilocybin for treatment-resistant depression. The ICER Value Framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of

selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided in a research protocol published on the ICER website and registered in PROSPERO following the publication of the revised scope.

Populations

The population of focus for the review is adults aged 18 years and older with major depressive disorder, without psychotic features, and for whom two or more prior antidepressants prescribed at adequate dose and duration, during the current episode, have not resulted in adequate therapeutic benefit. As data permit, we also plan to examine subgroups of patients suggested by patients and clinical experts. These include subgroups defined by:

- Age (e.g., 18-64 vs. ≥65 years of age)
- Number of prior antidepressant trials (e.g., two, three, four)
- Episode of depression (e.g., first or recurrent)
- Comorbidity with other mental health conditions (e.g., anxiety, personality disorder, bipolar, post-traumatic stress disorder [PTSD])
- Concomitant use of medication for mental health (e.g., antidepressants, antipsychotics)
- Prior exposure to psychedelics

Intervention

The intervention of interest is:

- Psilocybin (25 mg)

Comparators

Data permitting, we intend to compare with:

- Esketamine (SPRAVATO®, Janssen)
- Intravenous (IV) ketamine, an anesthetic agent used off-label for TRD
- Repetitive Transcranial Magnetic Stimulation (rTMS)

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Changes in depressive symptoms (e.g., Montgomery–Åsberg Depression Rating Scale [MADRS])
    - Rate of response, remission, and relapse
    - Changes in functional outcomes (e.g., Sheehan Disability Scale [SDS])
    - Changes in other mental health symptoms (e.g., anxiety, positive and negative emotions)
    - Changes in health-related quality of life (e.g., EuroQol 5-Dimension 5-Level [EQ-5D-5L])
    - Changes in cognition
    - Impact on employment and education
    - Time burden on patients from treatment
    - Adverse events including but not limited to
        - Serious adverse events including acute events requiring higher-level medical care
        - Suicidal ideation, behavior, and self-harm
        - Prolonged visual hallucinations (i.e., hallucinogen persisting perception disorder [HPPD])
        - Psychotic symptoms
        - Cardiovascular effects
- Other Outcomes
    - Adverse events including
        - Discontinuation due to adverse events
    - Effects associated with abuse potential (e.g., euphoria, hallucinations and other perceptual distortions, alterations in cognition, and changes in mood)

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical

effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There are particular obligations to people with this condition because of disease severity and/or unmet need with currently available therapies.
There are particular obligations to people with this condition because it disproportionately affects those from a racial/ethnic group that have not been equitably served by the health care system.
Apart from issues around disease severity/unmet need and race/ethnicity, there are other particular obligations to people with this condition.
The treatments are likely to improve caregivers' quality of life and/or ability to pursue their own education, work, and family life.
If payment/cost were not an issue, the treatments are likely to improve access to treatment because of its method of delivery and/or treatment setting.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on January 22, 2027. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the cost-effectiveness of COMP360 relative to esketamine and rTMS, and to IV ketamine if data permit. The base-case analysis will use a five-year time horizon, reflecting uncertainty in the durability of treatment effects and the limited evidence available to support longer-term extrapolation. A lifetime analysis will be explored if available evidence supports credible extrapolation of longer-term effectiveness and outcomes. The model structure will be based in part on a literature review of prior published models of TRD and available evidence for COMP360 and the comparators. Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts (e.g., patient and caregiver productivity, patient and caregiver time burden associated with treatment delivery) and other indirect costs will be considered in a separate modified societal perspective analysis. This analysis will be considered as a co-base case when relevant direct data on societal effects and/or costs are available, and at least one of these two conditions is met: (1) the impact of treatment on available societal effects/costs is

judged to be substantial; (2) the contribution of societal effects/costs to the total effects/costs associated with the condition is judged to be substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per evLY or QALY gained, or when the result crosses the threshold of $100,000 or $150,000 per evLY or QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of COMP360 on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

The target population will consist of adults ages 18 years and older with major depressive disorder, without psychotic features, and for whom two or more prior antidepressants prescribed at adequate dose and duration during the current episode have failed, termed TRD. The model structure and cycle length will be determined based on the available evidence. The model is expected to capture treatment response, remission, non-response, relapse, and subsequent treatment given available data to populate and transition between states. As data permit, the model will account for retreatment following relapse or loss of response and subsequent therapy following non-response or relapse. Depression severity is also expected to be characterized using categories based on the MADRS, as supported by available evidence.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using a network meta-analysis.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of rates of response, remission, and relapse, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLY). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events, and other clinically significant acute events, as data permit. The model will include direct medical costs, including but not limited to drug costs, resources associated with the anticipated care model for COMP360 and comparator treatments (e.g., preparation, administration and monitoring, and follow-up care, as applicable), condition-related care, and serious adverse events and acute events requiring higher-level medical care. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLY gained, cost per life-year gained, and cost per case of remission gained.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation

between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by psilocybin (e.g., psychiatric hospitalization), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of MDD beyond the potential offsets that arise from a new intervention.

From open input submissions from the public, we heard that trials of first-line antidepressants in patients who have not responded to multiple earlier trials of first-line antidepressants are an example of a low-value intervention in TRD care.

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