



BPL-003

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Major depressive disorder continues to be one of the most prevalent and disabling psychiatric conditions worldwide. Treatment-resistant depression, typically defined as failure to respond to at least two adequate antidepressant trials, affects a substantial proportion of individuals with major depressive disorder. Approximately 30 % of individuals with depression are affected by treatment-resistant depression. These individuals tend to experience longer illness duration, higher rates of comorbid psychiatric disorders, and a significantly increased risk of suicide [1].

BPL-003 is an investigational psychedelic drug under development for the treatment of treatment-resistant depression. It belongs to a class of compounds known as serotonergic psychedelics, acting primarily through serotonin receptor agonism. Its active ingredient, 5 - methoxy - N, N - dimethyltryptamine (5 - MeO - DMT), exerts a broad serotonergic profile with higher affinity at 5 - HT_{1A} than 5 - HT_{2A} receptors. The pharmacodynamic effects of BPL-003 are rapid in onset and typically resolve within 45 to 90 minutes post-administration [2]. The BPL-003 formulation is being developed for a 2-hour clinic visit, mirroring intranasal esketamine, and is accompanied by preparatory and integrative psychological support [3].

Although classic psychedelics are often summarized as 5-HT_{2A} agonists, 5 - MeO - DMT shows preferential binding at 5-HT_{1A}, with 300 - 1000× higher selectivity for 5 - HT_{1A} than 5 - HT_{2A} in binding assays. It is rapidly inactivated by monoamine oxidase to 5 - methoxyindoleacetic acid and can be O - demethylated by CYP2D6 to bufotenine (an active metabolite), yet bufotenine expo-

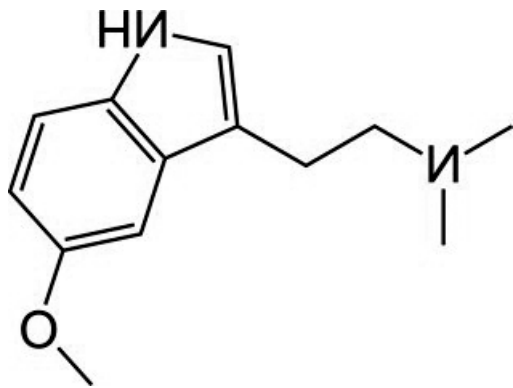
sure after intranasal BPL-003 was negligible in plasma. This receptor profile is often linked to comparatively fewer complex visuals and more pronounced ego-dissolution phenomena, though the clinical importance of these differences is still being clarified [4].

In a double-blind, placebo-controlled, single-ascending-dose study (n = 44; 1 - 12 mg), BPL-003 produced rapid absorption and a short terminal half-life (< 27 min), with subjective effects resolving in 45 - 90 minutes. Systemic exposure rose dose-proportionally, and subjective drug intensity closely tracked plasma 5 - MeO - DMT concentrations. On validated psychometric scales, 60 % of participants at 10 - 12 mg reported a “complete mystical experience” (MEQ - 30), and Ego Dissolution Inventory scores increased with dose. These findings support a brief, in-clinic dosing paradigm [4].

Current pharmacological strategies for treatment-resistant depression, including augmentation with atypical antipsychotics and newer agents like esketamine, have shown promise but are limited by side effects, cost, and modest remission rates. The introduction of newer therapies, such as BPL-003 represents a potential paradigm shift. These treatments aim to induce rapid symptom relief after one or two sessions, in contrast to the daily dosing required by traditional antidepressants. The drug is believed to modulate cortical connectivity and induce a transient state of enhanced neuroplasticity. In fact, in vivo two-photon imaging in mice revealed that 5 - MeO - DMT markedly boosts dendritic spine formation in the medial frontal cortex, resulting in a sustained increase in spine density (5). The chemical structure of BPL-003 is shown in Figure 1.

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Figure 1. Chemical structure of BPL-003



Initial clinical evaluation began with a Phase 2a open-label study in individuals with moderate-to-severe treatment-resistant depression. A single 10 mg dose of BPL-003 resulted in rapid reductions in depressive symptoms, with more than half of participants achieving remission at four weeks post-dose. These findings set the stage for a larger and a more rigorous trial. Starting in 2023, a multinational, randomized, controlled Phase 2b trial (Study BPL-003 - 201) was conducted across 38 sites in six countries. A total of 193 patients with treatment-resistant depression were enrolled. Participants were randomized to receive a single intranasal dose of 0.3 mg (control), 8 mg, or 12 mg BPL-003. The study's primary endpoint was change in Montgomery – Åsberg Depression Rating Scale (MADRS) score from baseline to Day 29. Key secondary endpoints included symptom changes

at Days 2, 8, and 57, as well as safety and tolerability outcomes. The results were promising: both the 8 mg and 12 mg doses produced rapid and statistically significant improvements in MADRS scores. By Day 2, patients in the active dose groups had already shown substantial reductions in depressive symptoms compared to control. These effects persisted at Day 29 and were largely maintained through Day 57. Interestingly, the 8 mg dose demonstrated similar efficacy to the 12 mg dose but with fewer adverse events, encouraging its selection for future Phase 3 trials [2,3].

BPL-003 was generally well tolerated. No treatment-related serious adverse events were reported. Common side effects included transient headache, nausea, anxiety, and nasal discomfort. The majority of these effects occurred during or shortly after dosing and resolved within the observation period. Most patients were deemed fit for discharge approximately 90 minutes after administration [3].

The successful outcome of the Phase 2b trial marked a significant milestone in the development of BPL-003. Plans are underway to begin Phase 3 trials later in 2025. If further trials confirm the compound's safety and efficacy, BPL-003 could become one of the first psychedelic medications approved for clinical use, and especially in treatment-resistant depression. Its fast-acting nature and single-dose administration make it appealing for patients who have exhausted other options. More broadly, BPL-003 reflects a re-emergence of interest in psychedelic compounds as legitimate tools in biological psychiatry and offers a new possible therapeutic avenue in pharmacotherapy.

References

1. Howes OD, Thase ME, Pillinger T. Treatment resistance in psychiatry: state of the art and new directions. *Mol Psychiatry*. 2022;27:58-72.
2. Kuntz L. BPL-003 for Treatment-resistant depression: phase 2b patient enrollment completed [Internet]. Cranbury (USA): Psychiatric Times; 2025 [updated; cited August 25th]. Available from: <https://www.psychiatrictimes.com/view/blp-003-for-treatment-resistant-depression-phase-2b-patient-enrollment-completed>
3. GlobeNewswire. Atai life sciences and beckley psytech announce positive topline results from the phase 2b study of BPL-003 in patients with treatment-resistant depression [Internet]. Los Angeles (USA): GlobeNewswire; 2025 [updated 2025; cited 2025 August 25th] Available from: <https://www.globenewswire.com/news-release/2025/07/01/3108164/0/en/atai-Life-Sciences-and-Beckley-Psytech-Announce-Positive-Topline-Results-from-the-Phase-2b-Study-of-BPL-003-in-Patients-with-Treatment-Resistant-Depression.html>
4. Rucker JJ, Roberts C, Seynaeve M, Young AH, Suttle B, Yamamoto T, et al. Phase 1, placebo-controlled, single ascending dose trial to evaluate the safety, pharmacokinetics and effect on altered states of consciousness of intranasal BPL-003 (5-methoxy-N,N-dimethyltryptamine benzoate) in healthy participants. *J Psychopharmacol*. 2024;38:712-23.
5. Weiss F, Magnesa A, Gambini M, Gurrieri R, Annuzzi E, Elefante C, et al. Psychedelic-induced neural plasticity: a comprehensive review and a discussion of clinical implications. *Brain Sci*. 2025;15:117.