Back to the Future of Psychopharmacology

Archives of Psychiatry Research 2026;62:191-194

DOI:10.20471/sept.2026.62.02.12
Received February 24, 2026
Accepted after revision April 7, 2026

ABBV-932 - DCAR (Desmethyl Cariprazine Prodrug)

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Bipolar disorder and generalized anxiety disorder (GAD) remain leading contributors to disability, with depressive and anxiety symptoms often persisting despite first-line pharmacotherapy. In bipolar depression, residual anhedonia, low motivation, and cognitive/functional impairment are frequent even when mood episodes remit, and tolerability barriers (weight gain, sedation, metabolic effects, prolactin elevation, extrapyramidal symptoms) can limit sustained use of many agents. Contemporary development strategies therefore increasingly target symptom dimensions linked to reward and salience processing and pharmacologic profiles that may be easier to combine with antidepressant therapy without amplifying classic adverse-effects.

ABBV-932 is an investigational, orally administered compound being developed by AbbVie (with origins in a CNS collaboration with Gedeon Richter) for neuropsychiatric indications including bipolar depression and adjunctive treatment of GAD. While public scientific literature on ABBV-932 itself is still sparse, trial records and public research summaries indicate that ABBV-932 is a prodrug of desmethyl-cariprazine (DCAR), designed to deliver a dopamine D3 - preferring D3/D2 receptor partial agonist exposure profile [1]. This mechanistic framing places ABBV-932 in the broader family of "dopamine receptor partial agonists," which is a class that includes cariprazine and that is of interest for disorders in which dopaminergic circuit dysfunction intersects with affective symptoms.

Dopamine D3 receptors are highly expressed in limbic regions and have been implicated in motivational salience, reward learning, and stress-related behavioural phenotypes. Reviews synthesizing preclinical and translational data argue that more selective or preferential modulation of D3 signalling may offer a route to influencing negative-affect and reward-related symptoms while potentially differentiating from predominantly D2 - driven antipsychotic effects [2]. In parallel, clinical experience with existing dopamine partial agonists suggests that partial agonism can reduce risks tied to full D2 blockade (e.g., prolactin elevation) but may introduce other liabilities such as akathisia and restlessness, with meaningful between-drug differences in pharmacodynamics and pharmacokinetics [3].

The "prodrug of DCAR" design is especially noteworthy because DCAR is a major active metabolite in the cariprazine system, and the kinetics of parent drug vs. active metabolites can influence onset, titration, and washout behaviour. Population pharmacokinetic work in cariprazine highlights that active metabolites (including DCAR and didesmethyl-cariprazine) substantially shape total active exposure over time [4]. From a development perspective, a DCAR prodrug could plausibly aim to reduce reliance on metabolic conversion from a parent compound, shape the time course of active moiety exposure, and/or improve interindividual predictability. That said, the specific clinical advantage intended for ABBV-932 (e.g., onset, tolerability, exposure stability)

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has not yet been demonstrated in publicly available peer-reviewed efficacy/safety reports, so these remain mechanistic expectations rather than established clinical facts.

A key enabling step for dopaminergic CNS drugs is establishing central target engagement at tolerable doses. For ABBV-932, an open-label Phase 1 PET study evaluated dopamine D2/D3 receptor occupancy using the D3 -preferring radiotracer [11C] - (+) - PHNO after up to 14 days of once-daily oral dosing in healthy volunteers in the United Kingdom [5]. The use of [11C] - (+) - PHNO is methodologically coherent with a D3 - preferring hypothesis, because the tracer provides sensitivity to D3 - rich regions relative to purely D2 - weighted ligands. While the publicly accessible summaries emphasize design and objectives rather than numeric occupancy results, the very conduct of such a study shows an intent to calibrate dosing to central engagement, which is an important translational bridge before pursuing symptom endpoints in heterogeneous clinical populations.

ABBV-932 has advanced into Phase 2 evaluation for depressive episodes in bipolar I or II disorder. Public trial listings describe a randomized, placebo-controlled, multi-arm design with approximately 161 participants, daily oral dosing for 6 weeks, and a 4-week follow-up period; enrolment began in October 2024 and the study is listed as completed (completion December 2025). Eligibility criteria include DSM-5-TR bipolar I/II disorder (without psychotic features) and a minimum baseline depression severity threshold (e.g., HAMD - 17 criteria) [6].

Currently, public sources accessible do not provide posted outcome data (effect sizes, response/remission rates, symptom-domain patterns, or detailed adverse-event tables) for this completed Phase 2 study. The absence of results reporting does not imply failure, as late posting is common, but it does limit interpretation. The most defensible conclusion at present is that ABBV-932 has been positioned for bipolar depression as a fixed-dose, placebo-controlled signal-seeking program grounded in a D3/D2 partial agonist mechanism, with target engagement work supporting dose selection [1,5,7].

In parallel, a longer-duration study has been described as an open-label assessment of safety/tolerability over 26 weeks in adults with bipolar I/II depressive episodes, targeting about 200 participants across the United States and Puerto Rico [8]. Longer exposures are particularly informative for dopamine partial agonists because akathisia/restlessness, sleep disruption, and functional effects may evolve over time, and discontinuation patterns can differ meaningfully from short-term trials. Evidence from the related compound cariprazine suggests that akathisia and related extrapyramidal-spectrum symptoms are among the most clinically salient tolerability issues to track in bipolar depression populations [9]. Whether ABBV-932 reproduces, attenuates, or reshapes this profile remains an empirical question.

ABBV-932 is also being tested as adjunctive therapy added to antidepressant treatment for adults with GAD and inadequate response to adequate antidepressant therapy. A Phase 2 randomized study is listed as recruiting, with an intended sample size of approximately 315 participants, 6 weeks of adjunctive dosing, and follow-up thereafter. Notably, inclusion criteria explicitly require ongoing use of guideline-relevant antidepressants (e.g., escitalopram, paroxetine, duloxetine, venlafaxine ER) and inadequate response, while excluding substantial concurrent depressive symptom burden (e.g., MADRS threshold), which helps sharpen the anxiety-specific signal [10].

Mechanistically, this program can be read as testing whether dopaminergic modulation, particularly via D3 -weighted D3/D2 partial agonism, can improve anxiety outcomes in patients who remain symptomatic despite serotonergic/noradrenergic antidepressants. Neuroimaging findings across anxiety disorders suggest dopaminergic-system alterations, although results are heterogeneous across diagnoses and modalities. Preclinical work also supports a role for D3 receptors in amygdala microcircuits relevant to anxiety-like behaviour. At a systems level, anxiety has been conceptualized in terms of dysregulated approach – avoidance valuation and conflict processing within cortico-limbic/striatal circuitry. Dopaminergic signalling contributes not only to reward learning but also to threat safety learning processes that can shape avoidance behaviour and functional impairment. Still, until controlled outcomes are available, both clinical relevance and combination tolerability should be treated as provisional [11-14].

All in all, if ABBV-932 demonstrates clinically meaningful benefit with an acceptable tolerability profile, its most plausible differentiators would be symptom-domain, combination-friendly profile and kinetic advantage. For now, ABBV-932 should be viewed as a translationally grounded, mid-stage investigational molecule aiming to extend D3/D2 partial agonism into bipolar depression and adjunctive GAD treatment, with PET occupancy work supporting central engagement and multiple Phase 2 efforts defining its clinical signal and tolerability envelope.

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