# Dual-target gene therapy: Can it free Parkinson's patients from levodopa dependence?

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For decades, levodopa has been the cornerstone of Parkinson's disease management, but its long-term use inevitably leads to motor complications. The field has long sought a therapy that could restore autonomous dopamine synthesis, reducing reliance on exogenous levodopa and its associated fluctuations. A new gene therapy approach, targeting two critical enzymes in the dopamine pathway, offers a potential path forward.
A multicenter, open-label, dose-escalation Phase 1 trial evaluated BBM-P002, an adeno-associated virus vector designed to codeliver constitutively active tyrosine hydroxylase (TH) and aromatic L-amino acid decarboxylase (AADC), aiming to enable the brain to produce its own dopamine. The trial, published in Nature Medicine, focused on safety and tolerability over 12 months.1

**KEY TAKEAWAYS**

- The Pivot: A dual-target gene therapy, BBM-P002, aims to restore autonomous dopamine synthesis, moving beyond single-enzyme gene therapies that still require exogenous levodopa.
- The Data: BBM-P002 showed a favorable safety and tolerability profile over 12 months, with no dose-limiting toxicities or drug-related serious adverse events reported in 10 participants.
- The Action: This Phase 1 data supports continued clinical development for BBM-P002, but clinicians should await efficacy data from larger trials before considering its potential impact on practice.

Parkinson's disease, a progressive neurodegenerative disorder, primarily results from the loss of dopaminergic neurons in the substantia nigra. This neuronal loss leads to a severe deficiency of dopamine in the striatum, manifesting as motor symptoms such as bradykinesia, rigidity, tremor, and postural instability. Levodopa, a precursor to dopamine, remains the most effective symptomatic treatment, but its efficacy wanes over time, and its pulsatile delivery often leads to motor fluctuations and dyskinesias.1

Gene therapy has emerged as a promising strategy to address this unmet need by restoring dopamine synthesis directly within the striatum. Earlier monotherapies, primarily targeting AADC, aimed to enhance the conversion of exogenous levodopa into dopamine. While these approaches showed some success, they did not eliminate the need for levodopa, nor did they address the upstream deficiency in tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine synthesis. The challenge has been delivering multiple genes within the strict packaging limits of adeno-associated virus (AAV) vectors.1

## Designing a Dual-Target Approach

BBM-P002 represents a novel 'dual approach' designed to overcome the limitations of previous monotherapies. The therapy utilizes a new adeno-associated virus vector, AAVT42, engineered to codeliver two genes: constitutively active TH and AADC. This design aims to enable the striatal cells to autonomously synthesize dopamine from endogenous tyrosine, thereby reducing or potentially eliminating the reliance on exogenous levodopa. The rationale is that by providing both rate-limiting enzymes, the entire dopamine synthesis pathway can be reconstituted, offering a more complete and sustained therapeutic effect.1

The multicenter, open-label, dose-escalation Phase 1 trial (NCT05822739) enrolled 10 participants with moderate-to-advanced Parkinson's disease. These patients typically presented with significant motor symptoms and were likely experiencing levodopa-induced complications, though the abstract does not detail their specific UPDRS scores or duration of levodopa use. The trial's primary objective was to assess the safety and tolerability of bilateral intraputaminal infusions of BBM-P002 over 12 months. Secondary objectives, which will likely include efficacy measures, are not reported in this initial safety publication.1

## The Trial's Structure and Patient Cohorts

Investigators administered BBM-P002 through bilateral intraputaminal infusions, a common delivery route for gene therapies targeting Parkinson's disease, ensuring direct delivery to the affected brain region. The trial employed a dose-escalation design, starting with a single participant in the lowest dose cohort and progressively increasing the dose and cohort size. This standard Phase 1 methodology allows for careful monitoring of safety signals as exposure increases.1

The 10 participants were divided into four cohorts, receiving increasing doses of the gene therapy. Cohort 1 included 1 participant who received 4.0 × 1011 vg (vector genomes). Cohort 2 had 2 participants, each receiving 6.0 × 1011 vg. Cohort 3 also included 2 participants, treated with 1.0 × 1012 vg. The largest cohort, Cohort 4, comprised 5 participants, each receiving the highest dose of 1.2 × 1012 vg. This structured escalation allowed the researchers to evaluate dose-response relationships for safety and tolerability.1

The patient population in this trial, individuals with moderate-to-advanced Parkinson's disease, represents a group with significant unmet needs. These patients often struggle with motor fluctuations, dyskinesias, and the diminishing returns of conventional oral therapies. For many, the prospect of a therapy that could reduce their reliance on frequent levodopa dosing is compelling, as discussed in our previous coverage on dopamine agonists and their evolving role.1

## Safety and Tolerability Outcomes

The trial achieved its primary outcome, demonstrating a favorable safety and tolerability profile for BBM-P002 within 12 months post-treatment. This is a critical hurdle for any novel gene therapy, particularly one involving direct brain infusion. The absence of dose-limiting toxicities (DLTs) across all dose cohorts is reassuring. DLTs are typically defined as adverse events that are severe enough to prevent further dose escalation or require dose reduction, and their absence suggests a wide therapeutic window for the tested doses.1

Investigators reported no drug-related serious adverse events (SAEs). SAEs are adverse events that result in death, are life-threatening, require inpatient hospitalization, result in persistent or significant disability, or are a congenital anomaly. The lack of such events strengthens the safety profile of BBM-P002. A total of 23 adverse events (AEs) occurred, but all were judged unrelated to BBM-P002. These AEs were primarily mild and transient, a common finding in early-phase

trials and often attributable to the surgical procedure or underlying patient comorbidities.1

Systemic toxicity was absent, indicating that the gene therapy remained localized to the target area without causing widespread adverse effects. Clinically meaningful immunogenicity was also not detected. This is a significant finding for AAV-based gene therapies, as immune responses against the viral vector can limit efficacy or cause adverse reactions. The lack of a significant immune response suggests that the AAVT42 vector may have a favorable immunogenic profile, which is important for long-term therapeutic success in maintaining the treatment's effect and avoiding adverse immune reactions.1

## The Mechanism of Action and Clinical Rationale

The core principle behind BBM-P002 is to re-establish the endogenous dopamine synthesis pathway. Tyrosine hydroxylase (TH) catalyzes the conversion of L-tyrosine to L-DOPA, which is the first and rate-limiting step in dopamine synthesis. Aromatic L-amino acid decarboxylase (AADC) then converts L-DOPA to dopamine. In Parkinson's disease, both enzymes are deficient due to the loss of dopaminergic neurons. By delivering both genes, BBM-P002 aims to bypass the need for exogenous L-DOPA and allow the transduced cells to produce dopamine continuously. This continuous, localized production could theoretically mimic the physiological release of dopamine more closely than oral levodopa, potentially mitigating motor fluctuations and dyskinesias.1

The choice of a constitutively active TH is also important. This modification ensures that the enzyme is always active, maximizing dopamine production without requiring additional regulatory signals that might be impaired in Parkinson's disease. The AAV vector ensures stable, long-term expression of these enzymes within the striatum, offering the potential for a durable therapeutic effect from a single administration. This approach contrasts with other investigational therapies, such as those targeting LRRK2, which aim to preserve synaptic function rather than directly restoring dopamine synthesis. Our coverage on LRRK2 inhibition in early Parkinson's highlights these alternative strategies.

## Limitations and Future Directions

The open-label design is the obvious caveat for this Phase 1 trial. While acceptable for initial safety assessments, it introduces potential for bias in reporting subjective outcomes, though this is less critical for objective safety endpoints like SAEs. The small sample size of 10 participants, particularly the single participant in Cohort 1, limits the generalizability of the safety findings. Larger Phase 2 and 3 trials will be necessary to confirm safety in a broader population and, to evaluate efficacy, which is the ultimate goal for patient benefit.1

The 12-month follow-up period is sufficient for initial safety, but the long-term durability of gene expression and potential late-onset adverse events remain unknown. Gene therapy, by its nature, aims for sustained effects, and monitoring for several years will be essential to fully understand the risk-benefit profile. The abstract does not detail the specific inclusion/exclusion criteria beyond 'moderate-to-advanced Parkinson's disease,' which could influence the applicability of these findings to different patient subgroups. For a comprehensive understanding of neurological conditions and their management, clinicians often consult resources like the Oxford Handbook of Neurology.

This trial focused solely on safety and tolerability. Efficacy data, such as changes in motor scores (e.g., UPDRS), levodopa equivalent daily dose (LEDD) reductions, or imaging biomarkers of dopamine synthesis, are not presented here. These will be the critical measures in subsequent trials to determine if BBM-P002 can indeed provide autonomous dopamine synthesis and translate into meaningful clinical benefits for patients. The success of this dual-target approach hinges

on its ability to improve motor symptoms and reduce levodopa-related complications, which were not assessed in this preliminary report.1

The trial's conclusion, that intraputaminal delivery of BBM-P002 was safe and well tolerated, supports continued clinical development. The next steps will undoubtedly involve Phase 2 trials designed to explore optimal dosing, confirm safety in a larger cohort, and provide initial efficacy signals. These trials will need to carefully select endpoints that capture both motor and non-motor improvements, as well as reductions in levodopa requirements. The potential for this therapy to offer a sustained, endogenous dopamine supply could represent a significant advance, but the journey from Phase 1 safety to widespread clinical adoption is long and fraught with challenges.

### CLINICAL IMPLICATIONS

This Phase 1 safety data for BBM-P002 is a necessary, but not sufficient, step for a gene therapy in Parkinson's disease. The concept of autonomous dopamine synthesis is highly attractive, with the potential to liberate patients from the levodopa roller coaster. But the absence of dose-limiting toxicities in 10 patients does not equate to clinical efficacy or long-term safety.

Clinicians should view these results as a green light for further investigation, not a signal for immediate practice change. The real test will come in Phase 2 and 3 trials, where reductions in levodopa equivalent daily dose, improvements in motor fluctuations, and sustained symptom control will be the true measures of success. Until then, current management strategies, including careful titration of existing dopaminergic therapies and consideration of advanced treatments for motor complications, remain paramount.

The industry will be watching closely. If BBM-P002 delivers on its promise by showing significant improvements in motor symptoms and quality of life, it could significantly alter the treatment landscape for moderate-to-advanced Parkinson's disease, potentially reducing the burden of polypharmacy and improving quality of life. But the high cost and specialized delivery of gene therapies mean that even successful treatments face significant hurdles in accessibility and reimbursement.

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### REFERENCES

1. 1. Niu M, Guo J, Yang Y. Dual-target gene therapy in Parkinson's disease: a multicenter phase 1 trial. Nat Med. 2026.

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