# GT-02287 in Parkinson's Disease: Interim data from a Phase 1b study

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## Objective

To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of the brain-penetrant glucocerebrosidase (GCase) modulator GT-02287 in people with Parkinson's disease with and without a pathogenic GBA1 variant.

## Background

- Pathogenic variants in *GBA1*, which encodes for the lysosomal enzyme glucocerebrosidase (GCase), constitute the most common genetic risk factor for Parkinson's disease (PD) and are associated with more rapid motor and nonmotor progression
- *GBA1* variants impact folding and trafficking of GCase, which leads to endoplasmic reticulum (ER) stress, lysosomal and mitochondrial dysfunction, reduced GCase activity, alpha-synuclein aggregation, and neuroinflammation
- GT-02287 is an orally-bioavailable, brain-penetrant small molecule designed to bind to an allosteric site on GCase to facilitate protein folding in the ER and transport to lysosomes and mitochondria
- GT-02287 reduces ER stress, enhances lysosomal and mitochondrial function, increases GCase activity, decreases accumulation of sphingolipid substrates and aggregated alpha-synuclein, and reduces neuroinflammation
- In Phase 1 in healthy volunteers, GT-02287 was safe and well tolerated, produced therapeutic plasma and CSF levels, and increased GCase activity

## Methods

- This open-label Phase 1b study was designed to evaluate the safety, tolerability, and PK of GT-02287 13.5 mg/kg/day for 90 days in people with PD
- The incidence, nature, and severity of adverse events, and the incidence of clinically significant changes in vital signs, laboratory tests, physical examinations, body weight, C-SSRS scores, and 12-lead ECGs are used to evaluate safety and tolerability
- Exploratory endpoints include target-engagement and disease biomarkers in blood and CSF (GCase activity, glucosylsphingosine and glucosylceramide, inflammatory markers, neurofilament light chain, and α-synuclein), and clinical endpoints, including the MDS-UPDRS (Part III was assessed in the practically-defined OFF state)
- The target population consisted of individuals 30-85 years of age who had been diagnosed with PD within the last 7 years and who were treatment-naïve or on a stable regimen of dopaminergic therapy
- Participants were recruited at 7 sites in Adelaide, Brisbane, Melbourne, and Sydney that used their local databases to identify potential participants
- Gain Therapeutics partnered with Shake It Up Australia Foundation and QIMR Berghofer Medical Research Institute to identify potential participants with GBA1 variants from the Australia Parkinson's Genetics Study nationwide cohort
- In August 2025, a protocol amendment to extend dosing duration from 3 to 12 months was approved by the Australian regulatory authorities
- Participants can continue dosing for another 9 months (Part 2) after completing Part 1 (the first 90 days) to further evaluate safety and biomarkers

## Results

- 27 individuals were screened and 21 enrolled from March through September 2025; enrollment in Part 1 is now complete
- The 21 participants include 3 women and 18 men, 2 treatment-naïve, 2 on DBS, and 18 on levodopa +/- dopamine agonists and other PD drugs
- Mean age was 63.5 years (range 42-83), mean disease duration was 3.0 years (range 0.5-7.0), and the mean H&Y score was 1.6 (range 1-2.5)
- Genetic data are currently available in 15 participants: 2 have severe GBA1 variants and 1 has a mild GBA1 variant
- The mean MDS-UPDRS score at baseline was 5.8, 7.4, and 24.7 for Part I, II, and III, respectively
- Mean MDS-UPDRS Part II and Part III score decreased by Day 90; mean Part I scores remained unchanged
- Of the 21 enrolled participants, approximately half have indicated that they would like to continue dosing in Part 2

Adverse Events:

- 18 participants have experienced 93 treatment emergent adverse events (TEAEs) as of 03 Sep 2025
- The most common TEAEs were headache (n=6 participants), lab abnormalities (n=6), diarrhea (n=6), fatigue (n=4), and nausea (n=3)
- 85% of TEAEs were mild, 11% were moderate, and 5% were severe; there have been no treatment-emergent SAEs

Discontinuations:

- One participant discontinued from the study after 24 days due to panic attacks, nausea, and headaches

Dosing reduction

- One participant reduced the dose due to headaches
- Two participants reduced the dose due to lab abnormalities (see below)

Dosing interruptions:

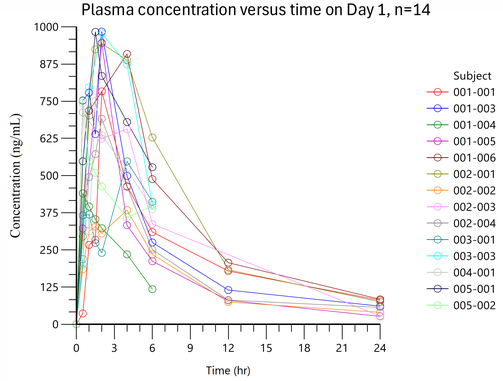
- One participant interrupted dosing for 7 days due to constipation
- One participant had dosing withheld for 30 days due to transient increases in ALT, ALP, and GGT; upon reinitiation of dosing at a lower dose, liver enzymes normalized and remained within normal limits thereafter
- One participant had dosing withheld for 4 days due to a transient increase in lipase; upon reinitiation of dosing at a lower dose, lipase levels had normalized and remained within normal limits thereafter

## Demographics and baseline characteristics

| Participant | Genotype | Sex | Age (y) | Disease duration (y) | H&Y | Parkinson's treatment | MDS-UPDRS at Baseline | | Genetic variant details |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Part III | Total | |
| 001-001 | Other | M | 62 | <1 | 1.5 | None | 19 | 29 | *PRKN* Arg275Trp, pathogenic, early-onset PD |
| 001-003 | Idiopathic | M | 68 | 1.5 | 1.5 | Levodopa, pramipexole | 18 | 32 | |
| 001-004 | Other | M | 53 | 1 | 2.5 | Levodopa, rotigotine, safinamide | 17 | 27 | *PLA2G6* Arg635Ter; loss of function |
| 001-005 | Idiopathic | F | 64 | <1 | 1 | Levodopa, pramipexole | 9 | 16 | |
| 001-006 | Idiopathic | M | 60 | 2 | 2 | Levodopa, rotigotine | 19 | 28 | |
| 002-001 | Idiopathic | M | 55 | 4 | 1.5 | Levodopa, rasagiline, opicapone | 31 | 37 | |
| 002-002 | Other | M | 73 | 1 | 2 | Levodopa | 19 | 25 | *ZFYVE26* Pro1634Ser; unknown significance |
| 002-003 | Idiopathic | M | 55 | 4.5 | 2 | Levodopa, pramipexole | 15 | 19 | |
| 002-004 | Idiopathic | M | 69 | 2.5 | 2 | Levodopa, safinamide | 27 | 41 | |
| 003-001 | GBA1 severe | M | 42 | 7 | 1.5 | Levodopa, DBS | 66 | 86 | *GBA1* Thr362Ile; severe |
| 003-003 | Pending | F | 46 | 1 | 1 | Levodopa, rasagiline | 16 | 38 | |
| 003-005 | Pending | M | 59 | 1.5 | 1.5 | Levodopa, safinamide | 37 | 58 | |
| 003-007 | Pending | M | 83 | 3 | 1 | Levodopa | 17 | 36 | |
| 003-008 | Pending | M | 73 | 5.5 | 2 | DBS | 55 | 94 | |
| 003-009 | Pending | M | 63 | 4 | 1 | Levodopa | 9 | 27 | |
| 004-001 | GBA1 severe | M | 60 | 5 | 2 | Levodopa, safinamide | 37 | 65 | *GBA1* Asp448His and Leu422Terfs; both severe |
| 005-001 | Idiopathic | M | 64 | 5 | 2 | Levodopa, rasagiline | 18 | 22 | |
| 005-002 | Idiopathic | F | 69 | 5 | 2.5 | Levodopa, opicapone | 24 | 37 | |
| 005-003 | Pending | M | 70 | <1 | 1 | None | 9 | 11 | |
| 006-001 | Other | M | 69 | 4 | 2 | Levodopa, pramipexole | 33 | 34 | *SPG11* Arg1207His; unknown significance |
| 007-001 | GBA1 mild | M | 77 | 4 | 1.5 | Levodopa | 24 | 39 | *GBA1* Asn409Ser; likely pathogenic |
| **Mean (SD)** | | | **63.5 (9.9)** | **3.0 (1.9)** | **1.6 (0.5)** | | **24.7 (14.6)** | **38.1 (21.3)** | |

## Plasma PK

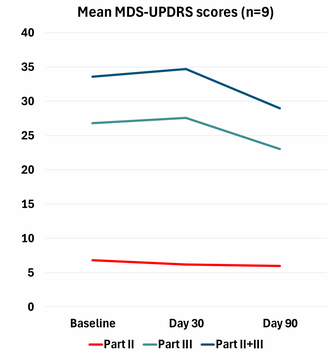
Plasma concentration versus time on Day 1, n=14




## MDS-UPDRS changes

MDS-UPDRS changes for participants (n=9) who have completed their Day 90 visit

| Participant | Change BL to Day 30 | | | Change BL to Day 90 | | |
|---|---|---|---|---|---|---|
| | Part II | Part III | II+III | Part II | Part III | II+III |
| 001-001 | -3 | 3 | 0 | -4 | 0 | -4 |
| 001-003 | -3 | 4 | 1 | -1 | +2 | +1 |
| 001-004 | -2 | -5 | -7 | -2 | -3 | -5 |
| 002-001 | 1 | -2 | -1 | 0 | -4 | -4 |
| 002-002 | 1 | 11 | 12 | +1 | -12 | -11 |
| 003-001 | 1 | 11 | 12 | -1 | -15 | -16 |
| 003-003 | -3 | 4 | 1 | +5 | +6 | +11 |
| 004-001 | 0 | no data | | -4 | -1 | -5 |
| 005-001 | 3 | -9 | -6 | -1 | -7 | -8 |
| **Mean** | **-0.6** | **2.1** | **1.5** | **-0.8** | **-3.8** | **-4.6** |




## Conclusions

- **In this ongoing Phase 1b study, the novel GCase-targeting small molecule GT-02287 appears safe and generally well tolerated for 90 days of dosing**
- **Most adverse events were mild; only 1 participant discontinued due to poor tolerability; more than half of participants have agreed to continue for another 9 months in Part 2**
- **Plasma exposures were within the projected therapeutic range and comparable to exposures observed in healthy volunteers in Phase 1**
- **Several participants experienced an improvement in their UPDRS Part II and Part III scores by Day 90**
- **These interim results support continued development of GT-02287 as a potential disease-slowing treatment for PD; a Phase 2 study in people with PD is planned for 2026**