The novel glucocerebrosidase chaperone GT-02287 in development for GBA-PD is safe and well tolerated in healthy volunteers at oral doses that produce plasma exposures in the projected therapeutic range

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Objective

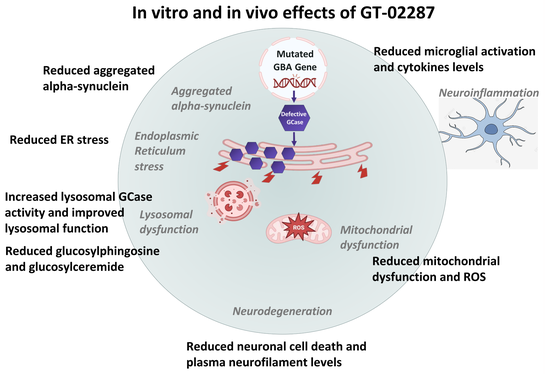
To characterize the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of single and multiple doses of GT-02287 in a Phase 1 first-in-human study in healthy volunteers.

Background

Pathogenic variants in *GBA1*, the gene that 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 progression and higher risk of developing dementia and other nonmotor symptoms.

GBA1 variants impact endolysosomal trafficking of GCase, which leads to endoplasmic reticulum (ER) stress, lysosomal and mitochondrial dysfunction, impaired autophagy, reduced lysosomal GCase activity, alpha-synuclein aggregation, and neuroinflammation.

GT-02287 is an orally-bioavailable, brain-penetrant molecule designed to bind to an allosteric site on GCase to facilitate protein folding and transport from the ER to lysosomes and mitochondria. This reduces ER stress, enhances lysosomal function and GCase activity, and decreases accumulation of glucosylsphingosine and glucosylceramide.

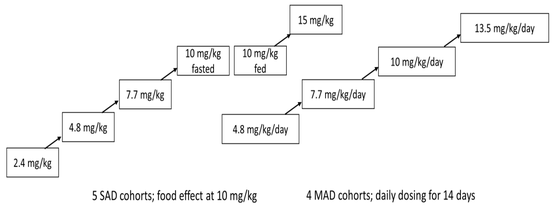


Methods

Healthy men (n=40) and women (n=33) were randomized in a 3:1 ratio to GT-02287 or placebo within each cohort of 8 subjects.

Single oral doses of 2.4, 4.8, 7.7, 10.0, and 15.0 mg/kg (Part 1 SAD) and multiple oral doses of 4.8, 7.7, 10.0, and 13.5 mg/kg once daily for 14 days (Part 2 MAD) were evaluated.

Safety and tolerability were evaluated with clinical laboratory tests, vital signs, ECGs, and adverse events (AEs). Plasma samples of GT-02287 were collected to characterize PK parameters. Change from baseline in GCase activity in blood was used as a biomarker of target engagement.



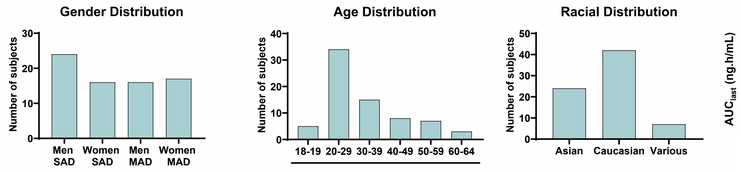
Results

The single and multiple dose levels tested were safe and generally well tolerated. Over 90% of AEs were mild and of short duration. The most common AEs were nausea and headache. No serious AEs or AEs of CTCAE Grade 3 or higher occurred, and no safety signals in ECGs or vital signs were observed. One subject had a transient, mild increase in AST and ALT after receiving a single dose of GT-02287. The PK profile of GT-02287 was linear across the tested dose ranges, and plasma exposures were within the projected therapeutic range. GT-02287 was measurable in cerebrospinal fluid (CSF), demonstrating CNS exposure. GCase activity increased in subjects who received active GT-02287 but not in those who received placebo, demonstrating target engagement.

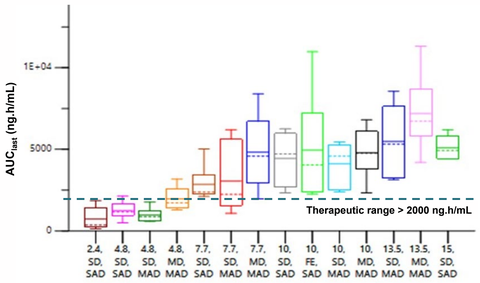
Conclusions

- **In this Phase 1 study in healthy volunteers, the novel GCase-targeting small molecule GT-02287 was safe and generally well tolerated after single and multiple oral doses.**
- **Dose levels of 7.7 mg/kg/day and above produced plasma exposures in the projected therapeutic range.**
- **CNS exposure and peripheral target engagement were demonstrated.**
- **These results support continued development of GT-02287 as a potential disease-slowing treatment for PD.**
- **A Phase 1b study in patients with GBA1-PD and idiopathic PD is planned to start by year-end.**

Demographics



Plasma PK



Adverse Events

System Organ Class Preferred Term Severity	Part 1 Total GT-02287 (N=30) n (%)	 Placebo (N=10) n (%)	Part 2 Cohort 1 GT-02287 (N=6) n (%)	 Placebo (N=2) n (%)	Cohort 2 GT-02287 (N=7) n (%)	 Placebo (N=2) n (%)	Cohort 3 GT-02287 (N=6) n (%)	 Placebo (N=2) n (%)	Cohort 4 GT-02287 (N=6) n (%)	 Placebo (N=2) n (%)	Total GT-02287 (N=25) n (%)	 Placebo (N=8) n (%)
Number of Participants with at Least One TEAE	17 (56.7%)	4 (40.0%)	5 (83.3%)	1 (50.0%)	3 (42.9%)	1 (50.0%)	2 (33.3%)	0	6 (100%)	2 (100%)	16 (64.0%)	4 (50.0%)
Mild	15 (50.0%)	4 (40.0%)	5 (83.3%)	1 (50.0%)	3 (42.9%)	1 (50.0%)	2 (33.3%)	0	6 (100%)	2 (100%)	16 (64.0%)	4 (50.0%)
Moderate	4 (13.3%)	1 (10.0%)	2 (33.3%)	0	0	0	1 (16.7%)	0	1 (16.7%)	2 (100%)	4 (16.0%)	2 (25.0%)
Severe	0	0	0	0	0	0	0	0	0	0	0	0

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Number of Participants with at Least One TEAE	17 (56.7%)	4 (40.0%)	5 (83.3%)	1 (50.0%)	3 (42.9%)	1 (50.0%)	2 (33.3%)	0	6 (100%)	2 (100%)	16 (64.0%)	4 (50.0%)
Gastrointestinal disorders	7 (23.3%)	1 (10.0%)	1 (16.7%)	1 (50.0%)	2 (28.6%)	0	2 (33.3%)	0	5 (83.3%)	0	10 (40.0%)	1 (12.5%)
Nausea	5 (16.7%)	1 (10.0%)	1 (16.7%)	0	1 (14.3%)	0	2 (33.3%)	0	4 (66.7%)	0	8 (32.0%)	0
Diarrhoea	0	0	0	1 (50.0%)	0	0	1 (16.7%)	0	2 (33.3%)	0	3 (12.0%)	1 (12.5%)
Abdominal pain	0	0	0	1 (50.0%)	0	0	0	0	2 (33.3%)	0	2 (8.0%)	1 (12.5%)
Abdominal discomfort	1 (3.3%)	0	0	0	0	0	0	0	0	0	0	0
Abdominal pain upper	0	0	0	0	1 (14.3%)	0	0	0	0	0	1 (4.0%)	0
Angular cheilitis	0	0	0	0	0	0	0	0	1 (16.7%)	0	1 (4.0%)	0
Constipation	0	0	0	1 (50.0%)	0	0	0	0	0	0	0	1 (12.5%)
Dry mouth	1 (3.3%)	0	0	0	0	0	0	0	0	0	0	0
Gastrooesophageal reflux disease	0	0	0	0	1 (14.3%)	0	0	0	0	0	1 (4.0%)	0
Hyperaesthesia teeth	0	0	0	0	1 (14.3%)	0	0	0	0	0	1 (4.0%)	0
Salivary hypersecretion	0	0	1 (16.7%)	0	0	0	0	0	0	0	1 (4.0%)	0

CNS exposure

CSF levels of GT-02287 are in the therapeutic range

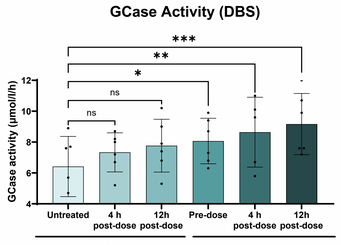
Species	Mean CSF level (ng/mL)	Total brain level (ng/g)	Mean plasma Cmax (ng/mL)	Timepoint	Dose (mg/kg)
Human	3.1	No data	850	Day 13	13.5 PO
Mouse	4.0	6592	2414	15 min	10 IV
Rat	3.0	2441	680	1 hour	30 PO

CSF levels in human, mouse, and rat are similar after administration of GT-02287.

In humans who received multiple doses of 13.5 mg/kg/day, the mean CSF level on Day 13 was 3.1 ng/mL, which is similar to CSF levels in mice and rats that received pharmacologically effective doses of GT-02287.

CSF levels are low in all species due to low aqueous solubility and high protein binding. Total brain levels in rodents are 2-8 times higher than total plasma levels, and free brain levels measured with microdialysis in rat are several-fold above the EC_{50} for GCase binding.

Target engagement



GCase activity in dry blood spots was measured with a 4-methylumbelliferyl fluorometric assay. In GT-02287 subjects, 5 out of 6 had increased GCase activity in dry blood spots, demonstrating target engagement. No increase in GCase activity was observed in placebo subjects (data not shown).

One-way, paired, repeated-measures ANOVA. *p < 0.05; **p < 0.01; ***p < 0.001