A NOVEL CHEMICAL SERIES, DIFFERENT FROM THE CLINICAL-STAGE ALLOSTERIC GCASE MODULATOR GT-02287, FOR THE TREATMENT OF PARKINSON'S DISEASE

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Objective

Impaired glucocerebrosidase (GCase) function is implicated in both GBA1 and idiopathic Parkinson's disease (PD). GT-02287, a small molecule, allosteric GCase chaperone, is showing promise in an ongoing Phase 1b trial in people with PD with and without a GBA1 mutation. The aim of the current study was to develop a structurally distinct back-up series for the treatment of PD and other conditions in which GCase deficit may play a role.

Methods

We applied our proprietary Magellan™ drug discovery platform to identify a second hit series with a scaffold distinct from GT-02287, which was then further optimized.

Results

A novel chemical series, represented by the advanced lead GT-04686, has displayed activity in both *in vitro* and *in vivo* models, including increase in GCase activity and lipid substrate depletion in patient fibroblasts harboring both mutated and WT GBA1, as well as restoration of motor and non-motor function in an animal model of GBA1 PD.

Conclusions

Gain Therapeutics' proprietary Magellan™ drug discovery platform has demonstrated its ability to identify multiple distinct chemical scaffolds to serve as starting points for lead optimization. Further development through medicinal chemistry has yielded a new, orally bioavailable, brain penetrant chemical series able to restore key biological activities impaired in Parkinson's disease, supporting the advancement of these compounds toward the clinic.

GT-04686 ENHANCES GCASE ACTIVITY AND DEPLETES ENDOGENOUS SUBSTRATE IN PATIENT-DERIVED FIBROBLASTS

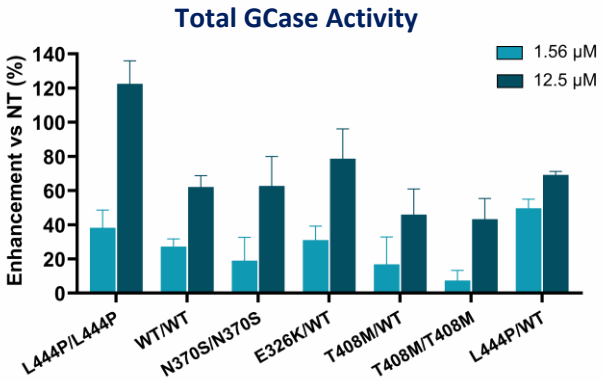


Figure 1. Fibroblasts were treated with GT-04686 for 4 days and GCase activity measured using 4-MU-β-D-glucopyranoside substrate, at 37°C for 1h. NT: not treated.

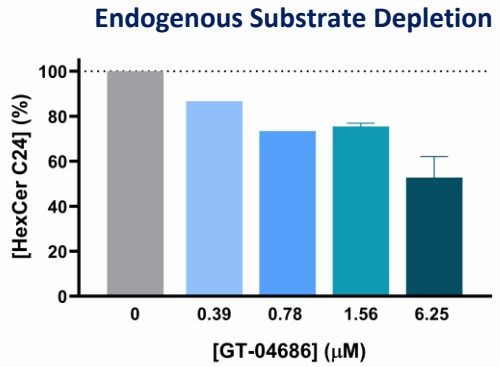


Figure 2. L444P/L444P fibroblasts were treated with GT-04686 for 10 days (with compound renewal). Hexosylceramide was measured by UPLC tandem MS.

GT-04686 SHOWS GOOD BRAIN PENETRATION

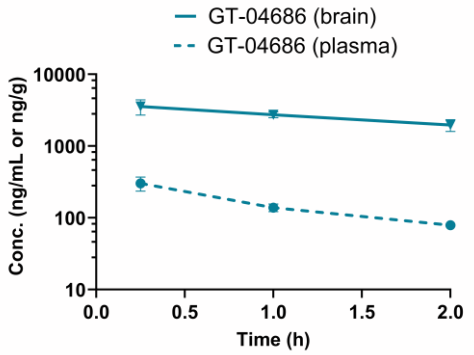
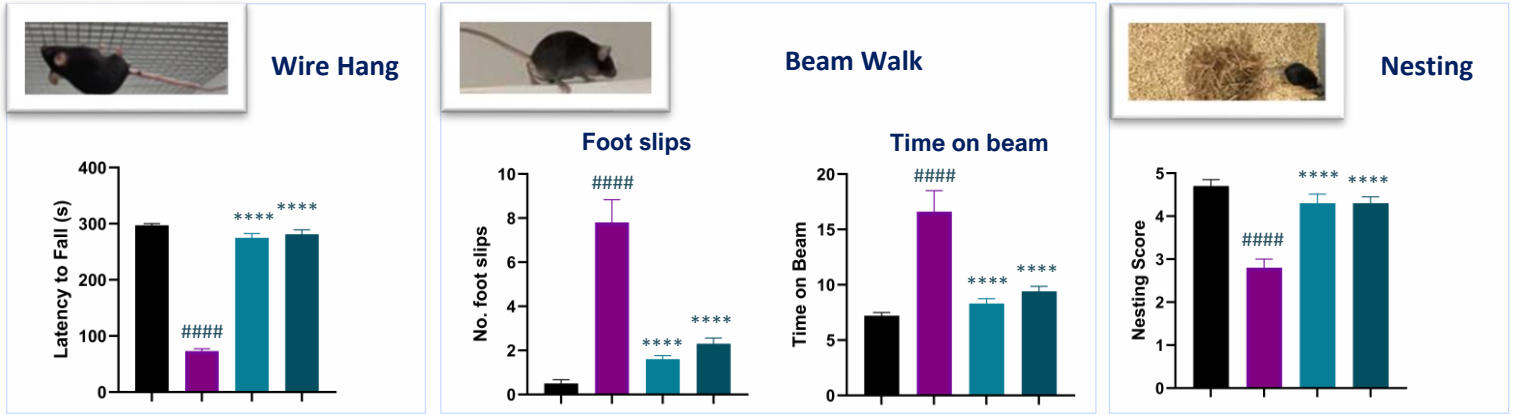


Figure 3: Plasma and brain levels of GT-04686 following IV admin. at 10mg/kg, in C57BL/6 mice, measured by LC/MS, n=3.

GT-04686 IMPROVES MOTOR IMPAIRMENT AND NEST BUILDING PERFORMANCE IN THE CBE/PFF GBA1 PD MOUSE MODEL



Data shown as mean ± SEM, n= 10. # Sig diff. compared to sham control. *Sig. diff. compared to CBE /PFF alone. One-way ANOVA followed by Dunnett's multiple comparison test. ####/**** P< 0.0001

Figure 4: In vivo studies: Mice were injected with α-syn PFFs (5 ug/1uL /mouse, intra-striatal, bilateral) on D1 and chronic low-level CBE for 27 days (50 mg/kg, i.p. QD). GT-04686 was administrated orally once daily starting at D8, once disease activity was manifest. Data are shown for D28.