NOVEL ALLOSTERIC GCASE MODULATOR GT-04686 REDUCES NEUROPATHOLOGY AND IMPROVES MOTOR AND NON-MOTOR FUNCTION IN A PRECLINICAL MODEL OF GBA1 PARKINSON'S DISEASE

Joanne Taylor[1], Ana Trapero[2], Ana Ruano[2], Jokin Carrillo[2], Elena Cubero[2], Natàlia Pérez-Carmona[2], Ana Maria García-Collazo[2]

[1]Gain Therapeutics Inc, Bethesda, Maryland, USA [2]Gain Therapeutics Sucursal En España, Barcelona, Spain

Objective

To evaluate the in vivo efficacy of GT-04686 in a CBE/PFFs mouse model of GBA1-PD.

Background

Impaired glucocerebrosidase (GCase) function appears to broadly contribute to Parkinson's disease (PD) pathogenesis, even in non GBA1 mutation carriers, making enhancement of GCase activity a promising therapeutic strategy. Rexaceract, an allosteric GCase modulator developed from Gain Therapeutics' Magellan™ virtual screening platform, is currently in clinical development as a potential disease modifying therapy for PD. Magellan™ virtual screening also identified several structurally diverse hit chemical series of putative GCase modulators. GT-04686 originates from one of these series, structurally distinct from rexaceract, and was optimized through medicinal chemistry for robust activity in in vitro and in vivo PD models.

Methods

GT-04686 is a novel, orally bioavailable, brain penetrant small-molecule structurally targeted allosteric GCase regulator. To model GBA1-PD, C57BL/6 mice received a single intra-striatal injection of α-synuclein preformed fibrils (PFFs) on day 1 combined with a chronic low-level intraperitoneal administration of conduritol β-epoxide (CBE), a covalent GCase inhibitor, at 50 mg/kg every other day from day 1. In a delayed treatment paradigm, oral once daily GT-04686 dosing started on day 8 and continued for 13 days. Motor and non-motor function were assessed at various time points (wire hang, beam walk, nesting, and smell test). In a different experiment, brain was collected for biomarker and neuropathology analysis following 22 days of treatment.

Results

Delayed administration of GT-04686 in the CBE/PFFs mouse model of GBA1-PD improved motor function, rescued nest-building performance (a complex behavior involving cognitive function) and reduced olfactory deficit. These behavioral benefits were accompanied by modulation of several biomarkers of PD pathology such as reduced α-synuclein aggregation, preserved TH+ neurons in substantia nigra and increased striatal dopamine. Cortical neurons were also preserved (NeuN staining).

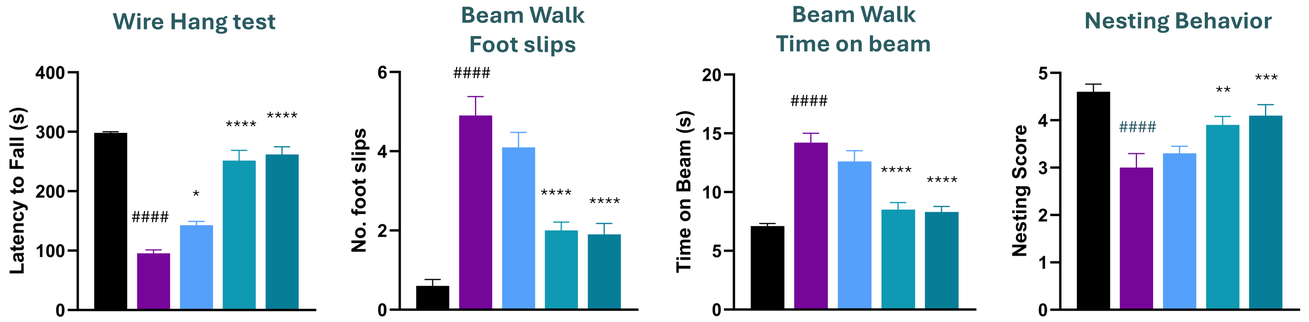
Conclusions

A new chemical series of GCase modulators has yielded GT-04686, a novel compound ready for IND-enabling studies for the treatment of Parkinson's disease and potentially other conditions involving GCase deficit.

Acknowledgements

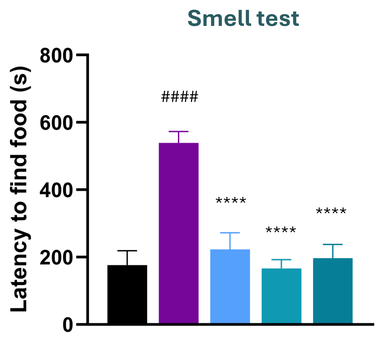
We would like to thank Sai Life Sciences for their collaboration in conducting these experiments.

GT-04686 improves motor and non-motor behavior



Mice were treated from day 0 to day 21.

Ameliorates olfactory deficit

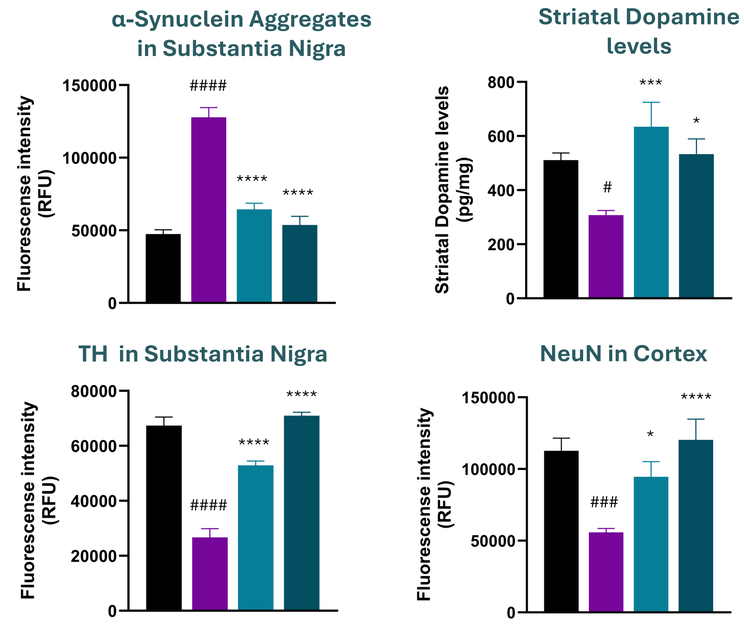


Control CBE+PFFs + GT-04686 7.5 mg/kg
+ GT-04686 15 mg/kg + GT-04686 30 mg/kg
+ GT-04686 60 mg/kg

***In vivo* effect of GT-04686 in a CBE/PFFs mouse model**

Data is shown as mean ± SEM, n = 10 per group.
Significant difference as compared to sham control * Significant difference as compared to CBE+PFFs vehicle control. One-way ANOVA followed by Dunnett's multiple comparison test. #/* P < 0.05; ##/** P < 0.01; ###/*** P < 0.001, ####/**** P < 0.0001.

Modulates biomarkers of neurodegeneration



Mice were treated from day 0 to day 30.