GT-02287, a brain-penetrant structurally targeted allosteric regulator of glucocerebrosidase shows evidence of pharmacological efficacy in conduritol β-epoxide (CBE) models of Parkinson's disease

B. Guzman[1], N. Pérez[1], A. M. García-Collazo[1], E. Cubero[1], X. Barril[1], M. Bellotto[1], A. Henriques[2], L. Rouviere[2], R. Maj[1]

[1] *Gain Therapeutics, Lugano (Switzerland) and Barcelona (Spain).*

[2] *Neuro-sys, Gardanne (France)*

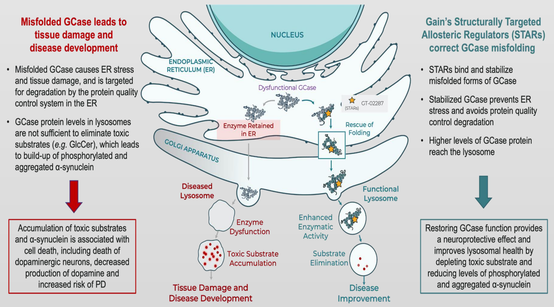
International Parkinson and Movement Disorder Society

Objective

To investigate the ability of the structurally targeted allosteric regulator, GT-02287, which is a candidate for the treatment of Parkinson's disease (PD), to protect against CBE-induced neurotoxic effects in cultured dopaminergic neurons and in CBE plus α-synuclein preformed fibril (PFF)-treated mice.

Background

GBA1 encodes the lysosomal enzyme glucocerebrosidase (GCase), deficiency in which has been linked to increased alpha-synuclein pathology, as well as to lysosomal, mitochondrial and endoplasmic reticulum stress, key pathophysiological features in PD. Importantly, *GBA1* mutations also increase the risk factor for PD.



Methods

Gain Therapeutics applied its innovative proprietary drug discovery platform, Site-directed Enzyme Enhancement Therapy (SEE-Tx™), to the development of small-molecule structurally targeted allosteric regulators (STARˢ) that stabilize GCase avoiding its degradation whilst facilitating its maturation and trafficking to the lysosomes. CBE, a covalent inhibitor that reacts with the catalytic site of GCase and inactivates the enzyme, was used to cause a partial defect of GCase activity comparable to heterozygotes GBA-PD patients. CBE-based models represent an additional tool to study pathophysiological pathways in PD under GCase defect and are considered relevant for the development of treatments for the disease.

Conclusions

SEE-Tx™ is a fast and cost-effective solution that has allowed us to develop structurally targeted allosteric regulators (STARˢ) of the GCase enzyme that are orally bioavailable and brain-penetrant.

Enhancement of lysosomal GCase activity by GT-02287 protects against key pathophysiological hallmarks of PD, including neurite and lysosomal pathology, as well as locomotor deficits. Therefore, STARˢ therapy represents a novel pharmacological tool for the treatment of PD, warranting further development towards the clinic.

Results

GT-02287 reduces CBE-induced pathology in rat mesencephalic neurons

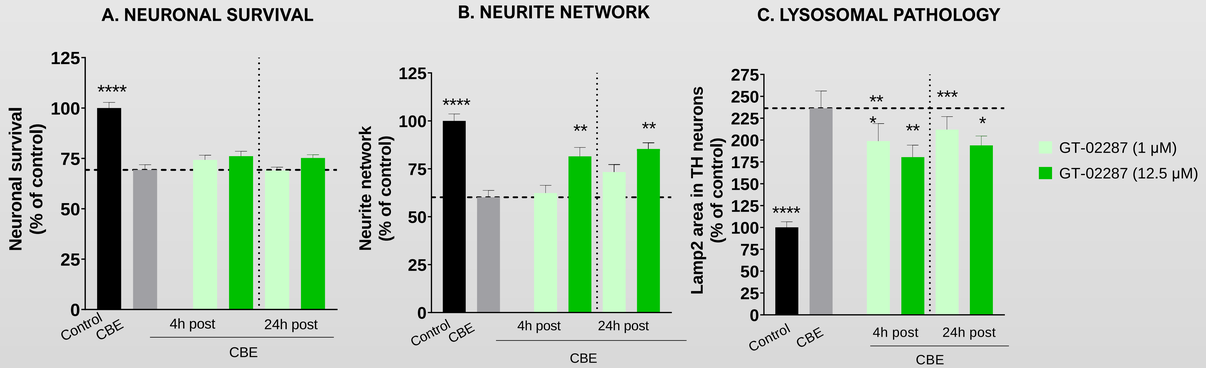


Fig.1 GT-02287 shows a therapeutic, post-injury effect on neurite network (B) and lysosomal health (C), 4 and 24 hours after CBE was applied to rat mesencephalic neurons. Effects on neuronal survival (A) were not statistically significant.
CBE (100 μM) was applied and 4 hours or 24 hours later, GT-02287 was added at two different doses. Three days after CBE treatment, the culture was fixed and stained for tyrosine hydroxylase (TH), a marker for dopaminergic neurons. Neuronal survival, neurite network and lysosomal LAMP-2 parameters were evaluated. **** p≤0.0001, *** p≤0.001, ** p≤0.001, * p≤0.05 versus Untreated CBE. One-way ANOVA followed by Dunnett's Multiple Comparison Test.

GT-02287 improves CBE plus α-syn PFF-induced locomotor impairment in mice

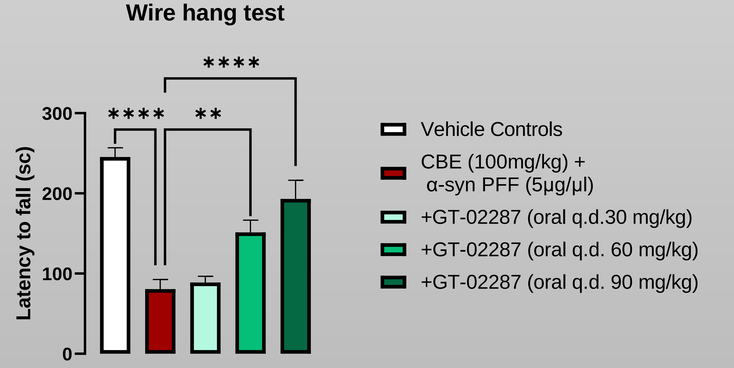


Fig.2. Differences in fine locomotor skills performance in the Wire Hang test were observed in vehicle controls (white bar), CBE + PFF injured (red bar) and in CBE + PFF injured mice treated with GT-02287 for 14 days (green bars).
Data is shown as Mean ± S.E.M. (n=9-10), One-way ANOVA followed by Dunnett's Multiple Comparison Test
* Significant difference as compared to CBE + PFF group. *P < 0.05,**P < 0.01, ***P < 0.001, ****P < 0.0001