GT-02287, a clinical-stage GCase enhancer, improves activities of daily living and cognitive performance in a preclinical model of GBA1 Parkinson's disease

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Objective

To investigate the ability of GT-02287 to rescue nest-building behaviour following delayed administration in a mouse model of GBA1-Parkinson's disease (GBA1-PD).

Background

Nest building is a non-invasive test to study activities of daily living and cognitive performance in rodent models. GT-02287 is an orally bioavailable, brain penetrant, small-molecule structurally targeted allosteric regulator that binds to glucocerebrosidase (GCase), stabilizes it, and increases its function by chaperoning it to the lysosome. It is currently in Phase 1 clinical development for the treatment of GBA1-PD.

Methods

C57BL/6 mice underwent intra-striatal injection of alpha-synuclein preformed fibrils (PFFs) on day 1 with or without low-level chronic intraperitoneal administration of irreversible GCase inhibitor, conduritol beta-epoxide (CBE), for 28 days to model GBA1-PD and idiopathic PD, respectively. GT-02287 was administrated orally once daily starting 8 days after the initial toxic insult. Nest-building performance was assessed by scoring the quality of the nest and motor function was tested in the wire hang test. Plasma NfL levels were assessed by ELISA, and aggregated α-synuclein, Iba-1, and GFAP levels were measured by immunohistochemistry on the day of sacrifice.

Results

In this delayed treatment paradigm, GT-02287 improves nest-building performance, as well as motor performance (as measured by wire hang test and shown previously) in a mouse model of GBA1-PD and this is correlated with a reduction in plasma levels of NfL, an emerging biomarker of neurodegeneration, as well as a reduction in levels of aggregated α-synuclein, GFAP (a marker of astrogliosis) and Iba-1 (a marker of microgliosis) in the substantia nigra (Fig. 1). Interestingly, in the idiopathic PD model (intra-striatal injection of PFFs but no CBE treatment) deficits in nest building behaviour and increases in plasma NfL levels had not developed by the end of the experiment (Fig. 2), suggesting that deficits in complex behaviour, which are correlated with increased plasma NfL levels, take longer to develop than deficits in motor behaviour in the absence of lowering of GCase activity. These results suggests that GT-02287 can rescue deficits in complex behaviours in which cognitive function is involved in a GBA1-PD model in addition to improving motor function deficits in this model as reported previously.

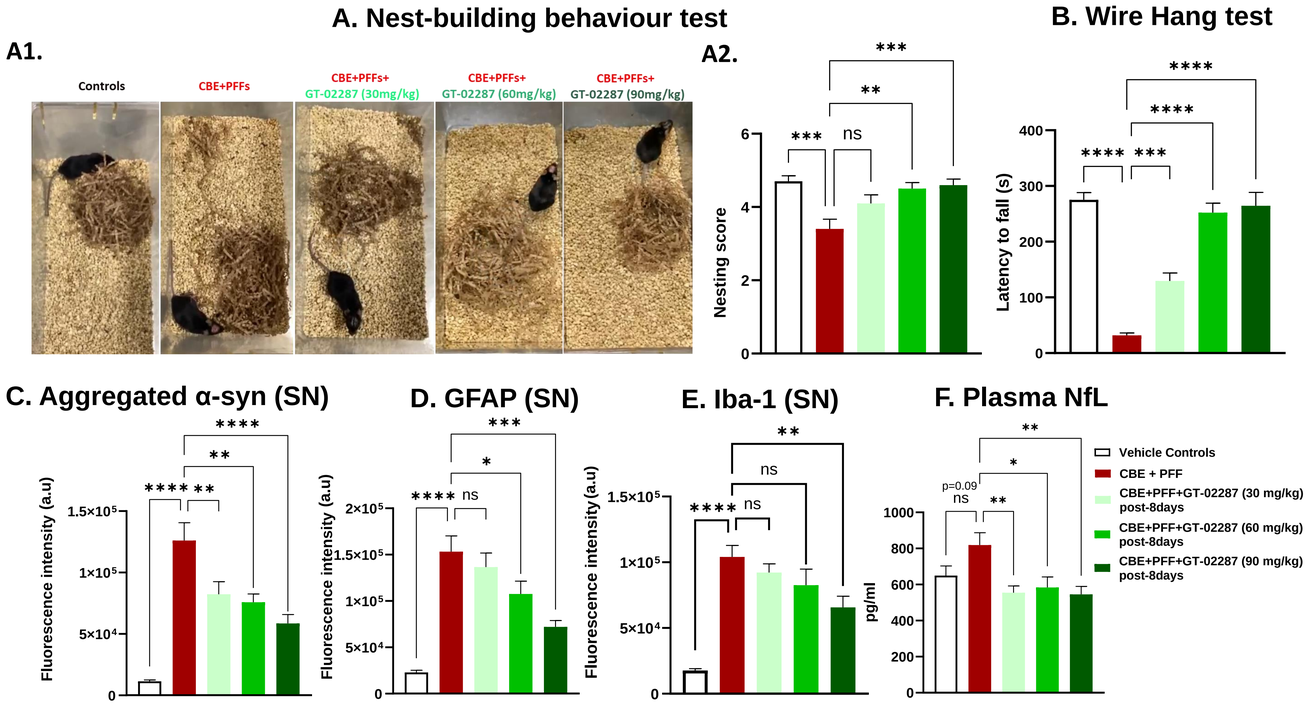

Fig.1 Representative pictures (A1) and scoring (A2) of the nest-building behaviour test (A), and wire hang test (B), assessed at day 28, as well as levels of aggregated α-synuclein (C), GFAP (D) and Iba-1 (E) in substantia nigra, and plasma levels of neurofilament light chain (NfL) (F) assessed at sacrifice (day 28) are shown for controls (white bars), CBE + PFFs-injured (red bars) and CBE + PFFs-injured mice treated with GT-02287 at (30 (light green), 60 (mid green) and 90 (dark green bars) mg/kg oral q.d.) starting 8 days after the initial combined toxic insult. Data is shown as mean ± S.E.M. (n=8-10), one-way ANOVA followed by Dunnett's multiple comparison test. Significant difference as compared to CBE + PFFs.*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

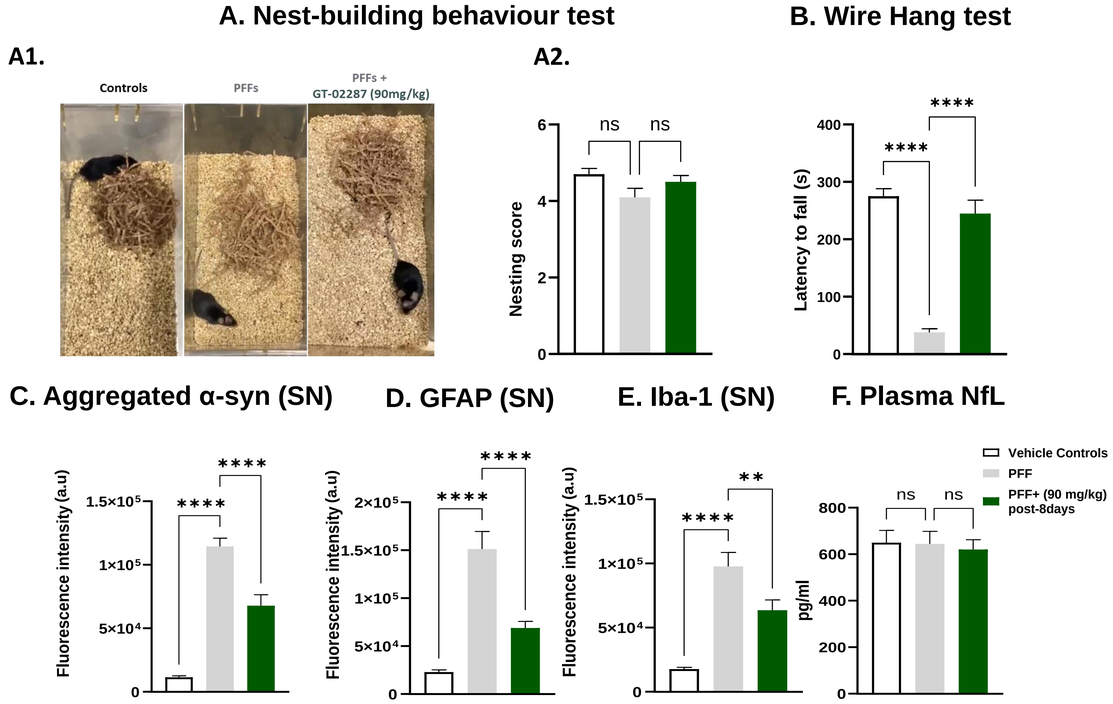

Fig.2 Representative pictures (A1) and scoring (A2) of the nest-building behaviour test (A), and wire hang test (B), assessed at day 28, as well as levels of aggregated α-synuclein (C), GFAP (D), and Iba-1 (E) in substantia nigra, and plasma levels of neurofilament light chain (NfL) (F) assessed at sacrifice (day 28) are shown for controls (white bars), PFFs-injured (grey bars) and PFFs-injured mice treated with GT-02287 at (90 mg/kg oral q.d. (dark green bars) starting 8 days after the initial combined toxic insult. Data is shown as mean ± S.E.M. (n=8-10), one-way ANOVA followed by Dunnett's multiple comparison test. Significant difference as compared to PFFs.*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

Conclusions

These data further support the potential of GT-02287 as a disease-modifying therapy for the treatment of GBA1-PD that is already clinically established, including improvement in activities of daily living and cognition.