

INTRODUCTION

- Levodopa-induced dyskinesia (LID) is a prevalent side effect of prolonged levodopa (L-DOPA) treatment, characterised by abnormal, involuntary movements affecting approximately 90% of PD patients by 9-15 years of treatment.
- LID represents a significant unmet clinical need in PD management as effective therapies remain limited and suboptimal.
- While the pathophysiology of LID is complex, a key factor is the severe loss of dopaminergic terminals and, consequently, of dopamine transporter (DAT) activity, which is critical for the physiological regulation of extracellular dopamine levels and dopaminergic neurotransmission.
- In this study, we tested the proposition that reinstating DAT activity by single intraputamenal administration of BGT-PD, an adeno-associated virus serotype-2 vector expressing the human DAT gene, could ameliorate or completely reverse LID in a unilateral parkinsonian rat model of LID.

MATERIALS & METHODS

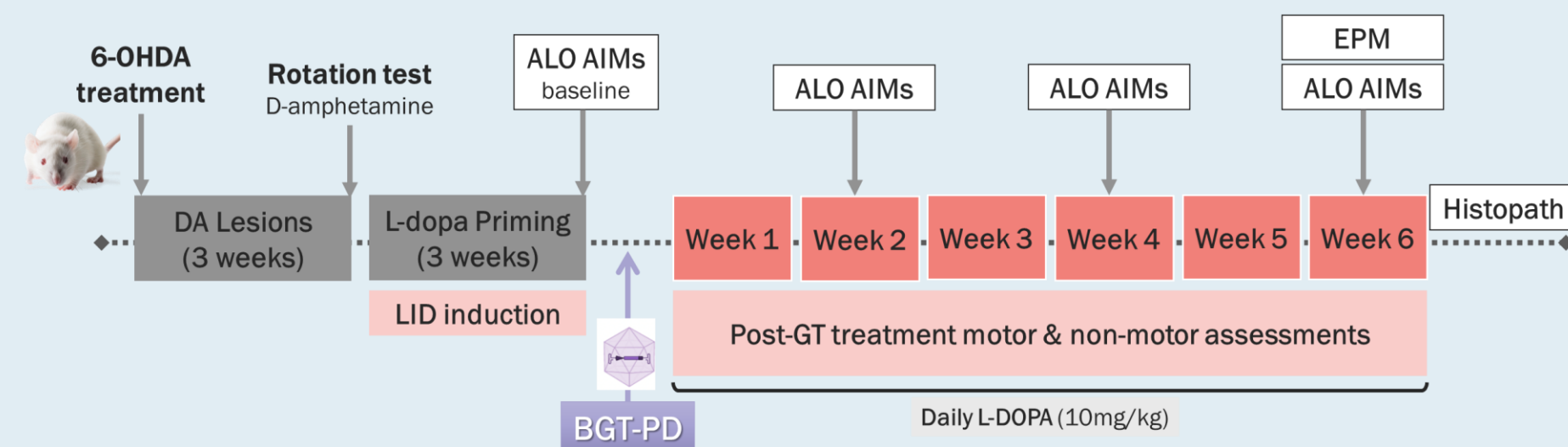


Figure 1: Experimental Design. Wild-type Wistar Han rats (9wo) were rendered hemi-parkinsonian by 6-OHDA injection followed by daily L-DOPA treatment to induce stable LID. Animals were then treated with a single intraputamenal injection of BGT-PD. LID severity was measured at 2-, 4- and 6-weeks post-treatment by ALO-AIMS rating. Anxiety-like behaviour was measured at 6 weeks post-treatment by EPM test. Extensive post-mortem brain histopathology assessment was conducted to confirm DAT colocalisation in neuronal subtypes (data not presented, publication in preparation). The study was conducted by QPS Austria (now Scantox Neuro GmbH) using vector material manufactured by Viralgen (Spain).

6-OHDA: 6-hydroxydopamine; **ALO AIMS:** Axial, limbs and oro-lingual (ALO) abnormal involuntary movements (AIMs); **EPM:** Elevated Plus Maze Test; **GT:** Gene Therapy.

RESULTS

Single injection of BGT-PD shows significant anti-dyskinetic effect compared to vehicle-treated control, with complete suppression of ALO AIMs observed at 6 weeks post-treatment.

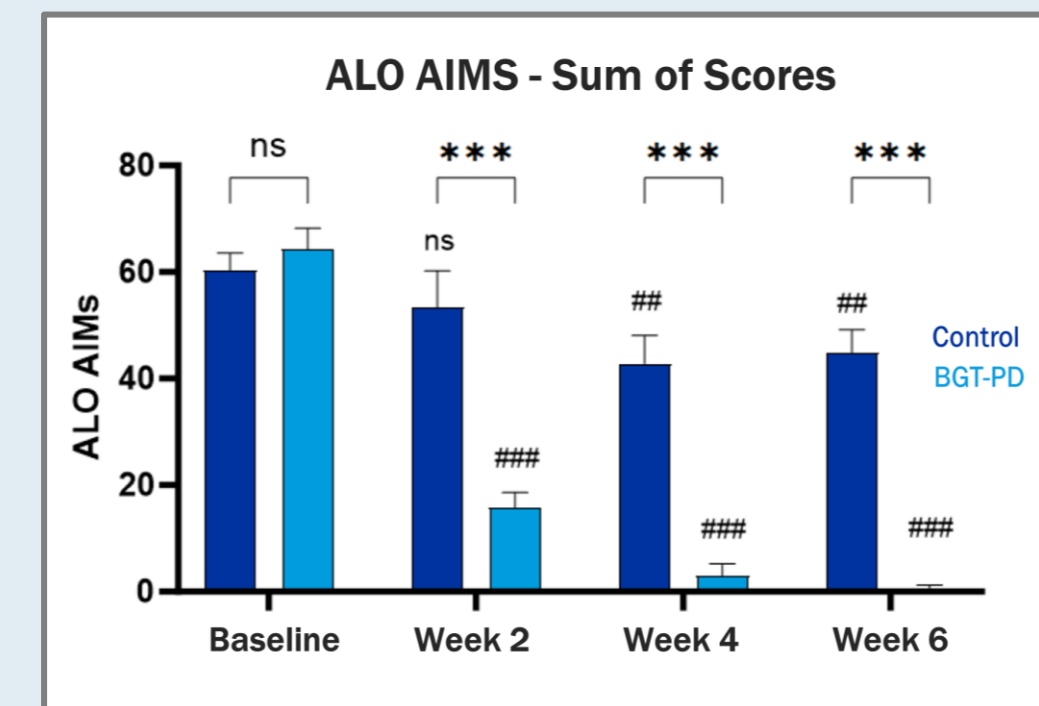


Figure 2: Sum of ALO AIMS scores over the entire observation period at baseline, week 2, week 4 and week 6 post BGT-PD treatment (n=15/group/time point; mean ± SEM). Mixed-effects analysis followed by Bonferroni's multiple comparisons test (ns, not significant; *** p<0.001). Mixed-effects analysis followed by Bonferroni's post hoc test comparing baseline vs week 2, week 4 and week 6 (## p<0.01; ###p<0.001).

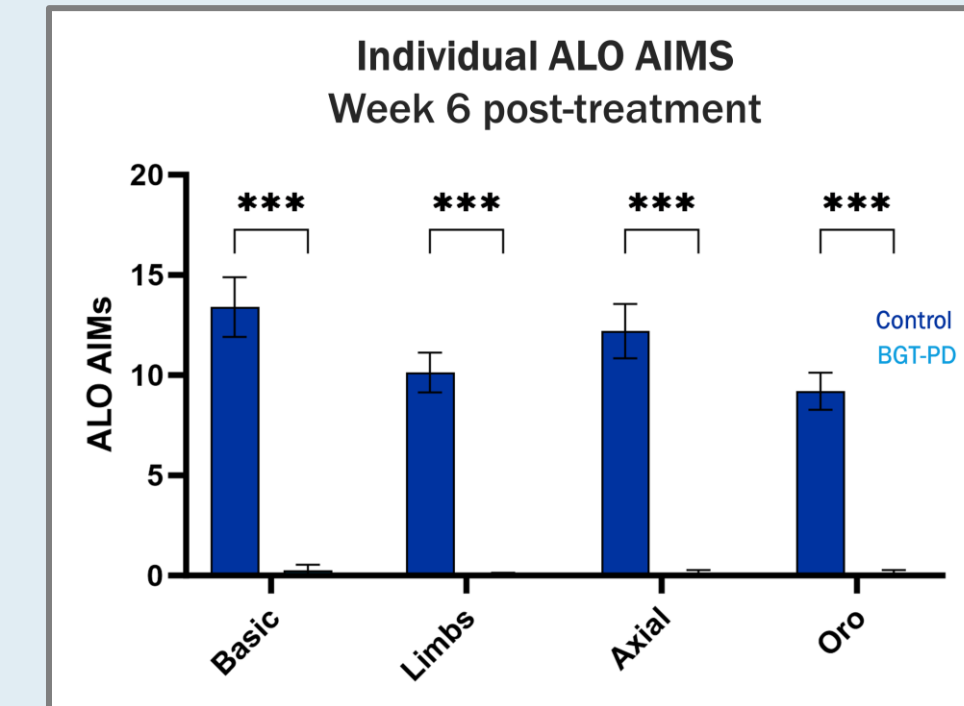


Figure 3: Individual ALO AIMS scores at week 6 post BGT-PD treatment (n=15/group/time point; mean ± SEM). In all four categories (basic, limbs, axial and orolingual), BGT-PD treatment significantly reduced ALO AIM scores in comparison to vehicle-treated animals, indicating a generalised treatment effect rather than limited effects to specific. AIMS. 2-Way ANOVA, followed by Bonferroni's multiple comparisons test (*** p<0.001).

ALO AIMS - Longitudinal

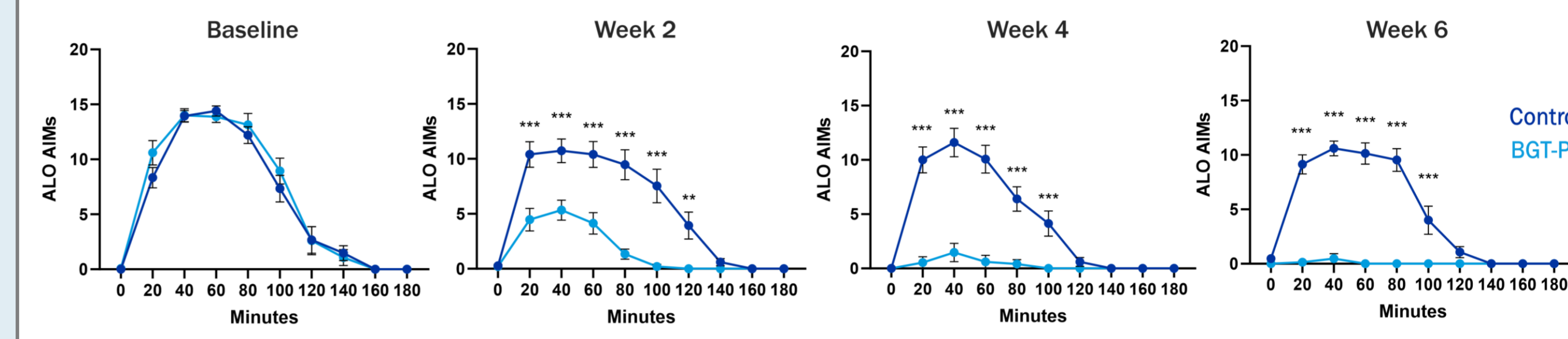


Figure 4: Time course of abnormal involuntary movement severity following L-DOPA administration. Sum of ALO AIMS scores over the entire observational period at baseline and 2-, 4-, and 6-weeks post BGT-PD treatment (n=15/group/timepoint; mean ± SEM). Mixed-effects analysis followed by Bonferroni's multiple comparisons test (**p<0.01, ***p<0.001).

RESULTS

BGT-PD shows a potential effect on reducing anxiety-like behaviours at 6 weeks post-treatment.

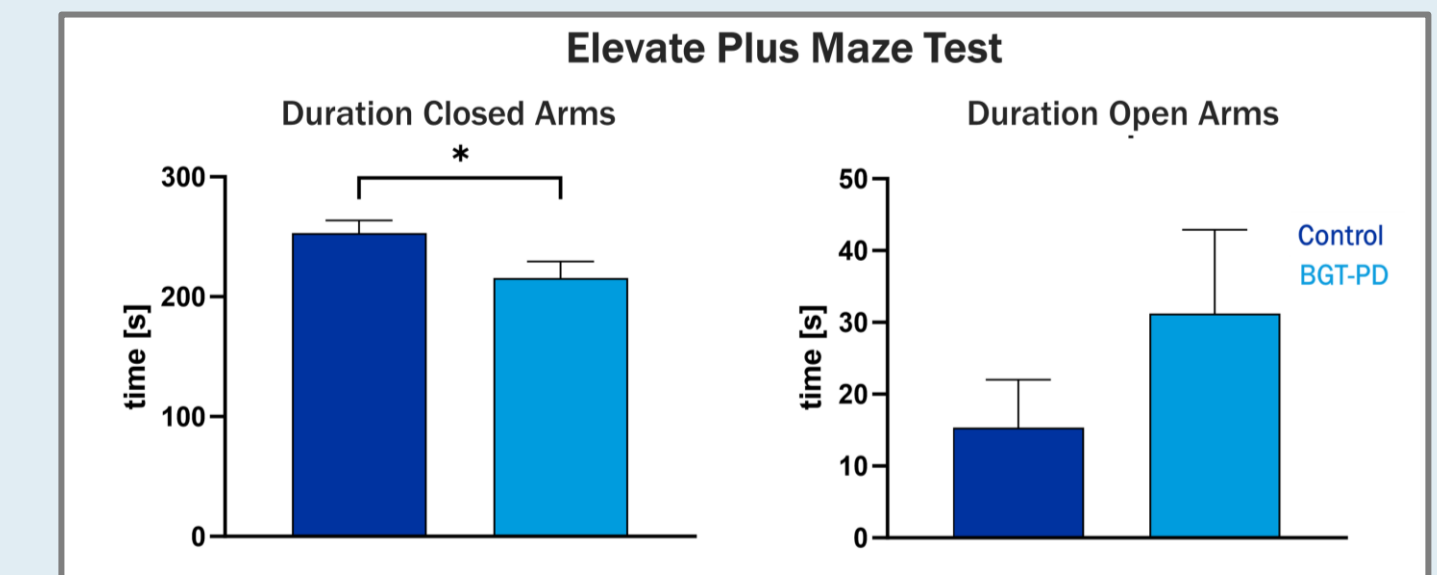


Figure 5: Elevated Plus Maze (EPM) test. Absolute duration in closed or open arms (n=15/group; mean ± SEM). BGT-PD treated animals spent significantly less time in the closed arms and showed a slight tendency for increased time in open arms compared to control animals, though non-significant. Mann-Whitney test (*p<0.05).

CONCLUSIONS & FUTURE WORK

- The data presented indicate a profound and sustained anti-dyskinetic effect of BGT-PD, with complete suppression of LID observed at 6 weeks post-treatment.
- Non-motor assessments suggest a potential effect of the treatment on anxiety-like behaviours.
- BGT-PD was well tolerated, with 100% animal survival and no overt negative side effects observed. Supportive brain histopathology data will be the subject of a future publication.
- BGT-PD has also successfully completed preclinical pharmacology studies in a mouse model for dopamine transporter deficiency syndrome, a rare form of childhood parkinsonism (BGT-DTDS program).
- In conclusion, this study provides first proof-of-concept evidence on the therapeutic potential of this novel gene therapy to completely reverse LID by reinstating DAT activity, with potential for benefits beyond motor function.
- Future investigations have been planned to confirm the long-term efficacy and safety of BGT-PD and its preservation of L-DOPA's therapeutic benefit.