Introduction

Parkinson's disease (PD) is caused by the progressive degeneration of dopaminergic neurons. The primary standard of care for PD is oral dopaminergic based therapies; these are highly efficacious but their long term use is complicated by motor fluctuations from intermittent stimulation of dopamine receptors and off-target effects. Therefore, a therapy that provides a more continuous and local supply of dopamine offers the potential for reduced motor fluctuations and off-target effects for these patients.

ProSavin® is a gene therapy product that utilises a lentiviral vector to transfer three genes that are critical for de novo dopamine biosynthesis from endogenous tyrosine in the striatum, the area of the brain that is depleted of dopamine in PD. Fifteen advanced PD patients have received ProSavin® in three dose cohorts. ProSavin® has been demonstrated to be safe and well tolerated at all doses evaluated to date. No serious adverse events related to the study drug or surgical procedures were observed. ProSavin® continued to be safe and well tolerated in patients with PD. Improvements in motor behaviour over baseline continued to be reported in the majority of patients who could still be evaluated up to 6 years of follow up.

To increase the potency further we have developed AXO-Lenti-PD, an improved version of ProSavin®, that expresses the same enzymes but with an increased dopamine production per genetically modified cell. AXO-Lenti-PD has been tested in primary human neurons and non human primates.

A potentially pivotal clinical trial of AXO-Lenti-PD for patients with PD is planned to commence in the UK and France before the end of 2018. The project has been supported by the UK Technology Strategy Board (Innovate UK).

Conclusions

• In vivo studies indicate AXO-Lenti-PD is at least 5-10 times more potent than ProSavin®
• Increased potency of AXO-Lenti-PD is supported by quantification of AADC activity by FMT PET
• AXO-Lenti-PD led to significant improvements in the clinical rating scale versus placebo
• A six month GLP toxicology study of AXO-Lenti-PD in NHPs showed no dose-limiting toxicity following stereotactic administration into the putamen.
• Potentially pivotal clinical trial of AXO-Lenti-PD in the UK and France in PD patients will dose first patient in H2 2018.

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