Pre-Clinical Development of AVB-101, an AAV Gene Therapy Treatment for Frontotemporal Dementia with Progranulin Mutations

AVIADOBIO

P332

Y.B. Lee,[1,2] C.J. Miranda,[1] J. Allison,[2] A. Kaliszewska,[2] Y. Bekele,[1] P. Hosseini,[1] R. Joubert,[1] Z. Walker,[1] J. Furtado,[1] M. Gumus,[2] A. Fernandes,[1] O. Brock,[2] P. Bouchard,[3] A. Bloom,[1] D.Y. Lee,[1,2] and C.E. Shaw[1,2]

[1]AviadoBio Ltd, London, UK; [2]UK Dementia Research Institute, Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [3]Rising Tide Advisors, LLC, Andover, MA, USA

OBJECTIVE

To report the pre-clinical development of AVB-101, a recombinant adeno-associated viral (AAV) vector-based gene therapy that encodes human progranulin (PGRN), designed to treat patients with frontotemporal dementia (FTD) caused by loss-of-function mutations in the granulin (*GRN*) gene (FTD-GRN).

BACKGROUND

- PGRN reduction in patients with FTD-GRN leads to lysosomal dysfunction and is associated with pathogenic accumulation of neuronal transactive response DNA-binding protein 43 (TDP-43) and exaggerated microglial reactivity, which accelerates neurodegeneration.[1–4]
- FTD-GRN accounts for 5–10% of all FTD cases and represents a serious condition with significant unmet needs as there are currently no disease-modifying therapies available.[5]
- AVB-101 is an AAV serotype 9-based gene therapy that encodes human PGRN (hPGRN) and is being developed as a one-time treatment for FTD-GRN administered bilaterally into the thalamus by convection-enhanced delivery using a stereotaxic neurosurgical procedure.

METHODS

- AVB-101 was designed to minimize vector dose and to restrict PGRN expression to neurons (**Figure 1**).
- *In vitro* experimental testing of the construct was initially conducted in neuronal cultures.
- AVB-101 was administered intrathalamically to *GRN* knockout mice in efficacy studies to assess impact on FTD-GRN disease pathology.
- AVB-101 was then administered intrathalamically to sheep via convection-enhanced delivery under stereotactic guidance.
- Finally, AVB-101 was administered to non-human primates (NHPs) by single bilateral intrathalamic injection using convection-enhanced delivery in biodistribution studies to assess the safety and tolerability of AVB-101.

RESULTS

AVB-101 induces robust levels of PGRN expression *in vitro*

- AVB-101 induces high levels of hPGRN expression and secretion into culture medium upon AVB-101 transduction of neurons *in vitro* (**Figure 2**).

AVB-101 substantially reduces pathology in *GRN* knockout mice

- Intrathalamic delivery of AVB-101 in young adult *GRN* knockout mice (6 weeks) restored wild-type levels of neuronal lipofuscinosis, a disease hallmark observed in the brains of patients with FTD, across all doses (**Figure 3**).

AVB-101 administration drives widespread PGRN expression in the CNS of sheep and NHPs

- Intrathalamic delivery of AVB-101 resulted in human-equivalent normal to supraphysiological levels of hPGRN protein in brain areas affected by FTD-GRN in sheep (**Figure 4A**)[†] and NHPs (**Figure 4B**)[‡].
- AVB-101 led to elevation of hPGRN in cerebrospinal fluid (CSF) with no changes in serum hPGRN levels in sheep (**Figure 5A**) and NHPs (**Figure 5B**), suggesting expression was restricted to the central nervous system (CNS).

AVB-101 administration is well tolerated in NHPs

- AVB-101 was well tolerated in NHPs, with no mortality or clinically evident adverse effects during the 6-month study period.
- There were no meaningful effects on hematology, coagulation, urinalysis or CSF clinical pathology, and no changes in functional observational battery, electrocardiography or ophthalmology.
- Neurofilament light chain (NfL) biomarker increased following intrathalamic administration of AVB-101, but returned to baseline in serum (**Figure 6A**) and approached baseline in CSF at 6 months (**Figure 6B**), suggesting tissue repair post-procedure.

Figure 1: AVB-101 key components

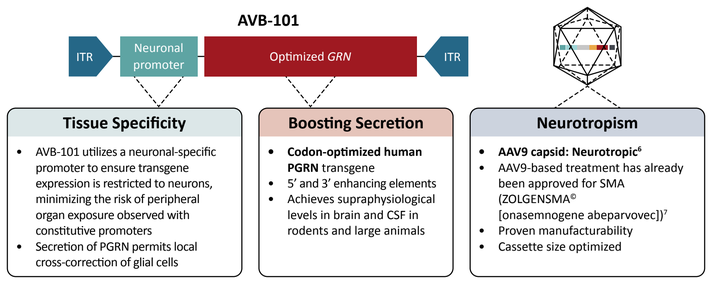
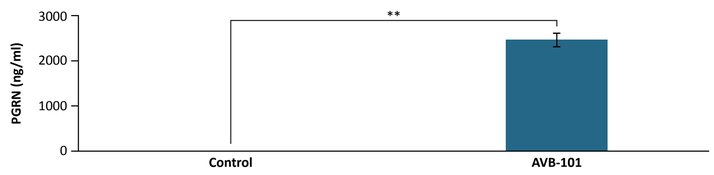
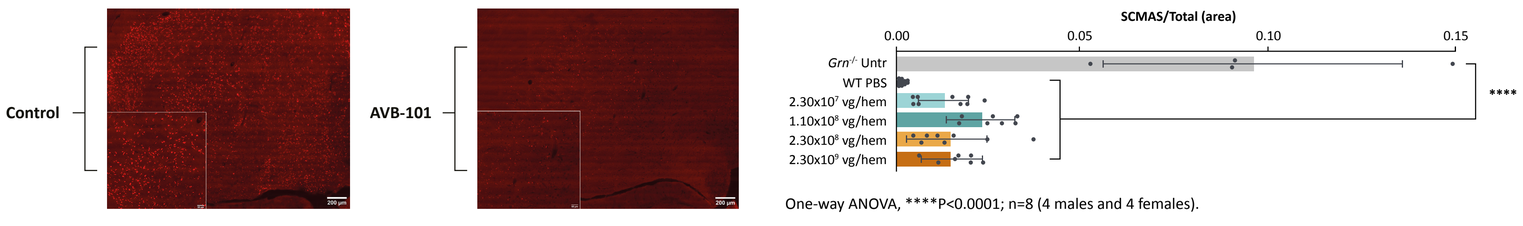


Figure 2: AVB-101 drives PGRN expression in cortical neurons



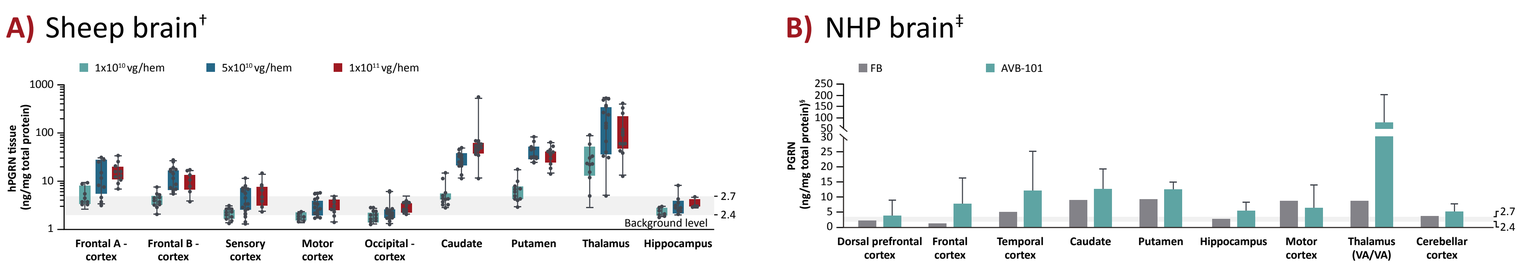
The AAV9 transduction of rat primary cortical neuron occurred on Day 7 with the MOI of $1.0x10^6$ virus particles/cell. Culture medium was collected 5 days after AAV transduction. PGRN protein levels in the cultured medium were measured by ELISA (T-test, **p<0.01). Error bars indicate standard deviation (n=3).

Figure 3: SCMAS (lipofuscinosis) in the thalamus of control and AVB-101-treated young adult *GRN* knockout mice



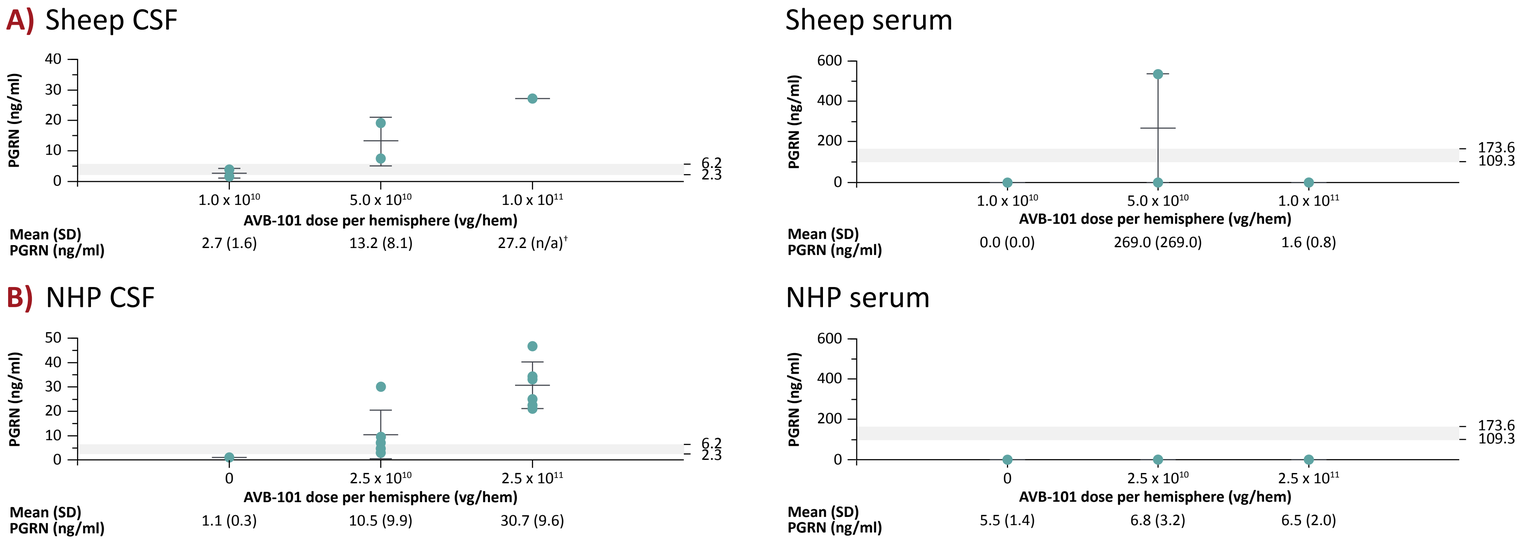
One-way ANOVA, ****P<0.0001; n=8 (4 males and 4 females).

Figure 4: hPGRN levels in the brain of sheep and NHPs following intrathalamic AVB-101 administration



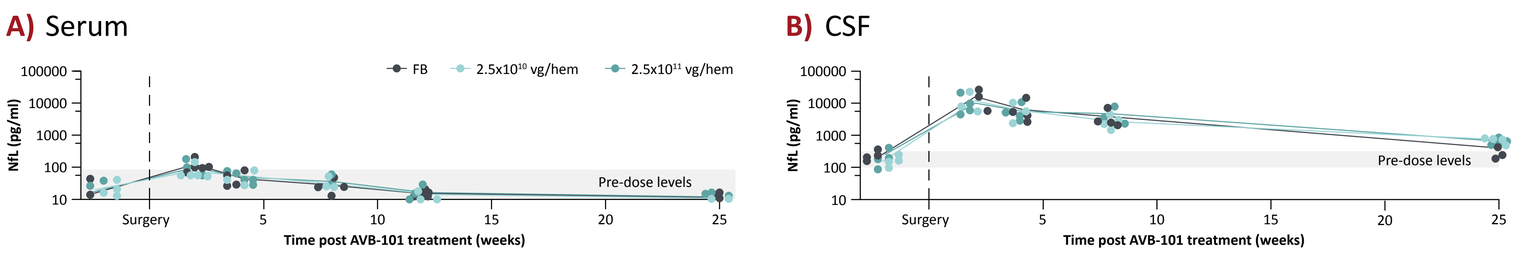
†4-weeks post-dose in sheep; ‡8-weeks post-dose in NHPs; §Minus background PGRN levels. Gray area: hPGRN levels in cortex tissue (2.4 to 2.7 ng/mg total protein). Control had no FTD-GRN.

Figure 5: hPGRN levels in CSF and serum following AVB-101 administration in sheep (A) and NHPs (B) at 4 weeks post-infusion



Gray area: hPGRN reference values (ng/mL): CSF - PGRN (no-FTD-GRN) 4.5 ± 1.5 ng/ml (n=6, 2.3 to 6.2 ng/ml); Serum - PGRN (no-FTD-GRN) 138.6 ± 26.7 ng/ml (n=6, 109.3 to 173.6 ng/ml). **A:** n=2 per treatment group; **B:** n=4 per control group; n=6 per treatment group. †A sample from one of the animals was not possible to collect for this group at this time point.

Figure 6: NfL levels following intrathalamic delivery of AVB-101 in NHPs



CONCLUSIONS

- **Intrathalamic infusion of AVB-101 constitutes a novel and promising approach to supplement PGRN in the CNS and address the unmet medical needs of patients with FTD-GRN.**
- **These data support the clinical development of AVB-101 for FTD-GRN in ASPIRE-FTD, an ongoing phase I/II clinical study to evaluate the safety and preliminary efficacy of AVB-101 in FTD-GRN (NCT06064890).[8]**

REFERENCES: [1]Ahmed Z, *et al*. Am J Pathol 2010;177:311–24; [2]Chang MC, *et al*. J Exp Med 2017;214:2611–28; [3]Root J, *et al*. Neurobiol Dis 2021;154:105360; [4]Yin F, *et al*. J Exp Med 2010;207:117–28; [5]Greaves CV and Rohrer JD. J Neurol 2019;266:2075–86; [6]Korneyenkov MA and Zamyatnin Jr AA. Pharmaceutics. 2021;13:750; [7]Zolgensma. Prescribing information. Bannockburn, IL: Novartis Gene Therapies, Inc. February 2023; [8]ClinicalTrials.gov. NCT06064890. Available at: https://www.clinicaltrials.gov/study/NCT06064890 [Accessed August 2024].

ABBREVIATIONS: **AAV:** adeno-associated virus; **AAV9:** adeno-associated virus serotype 9; **CNS:** central nervous system; **CSF:** cerebrospinal fluid; **ELISA:** enzyme-linked immunosorbent assay; **FB:** formulation buffer; **FTD:** frontotemporal dementia; ***GRN*:** granulin; ***Grn*$^{-/-}$:** *GRN* knockout; **Hem:** hemisphere; **hPGRN:** human PGRN; **ITR:** inverted terminal repeat; **MOI:** multiplicity of infection; **n/a:** not applicable; **NfL:** neurofilament light chain; **NHP:** non-human primate; **PBS:** phosphate buffered saline; **PGRN:** progranulin; **SCMAS:** subunit C mitochondrial adenosine triphosphate synthase; **SD:** standard deviation; **SMA:** spinal muscular atrophy; **TDP-43:** transactive response DNA-binding protein 43; **Untr:** untreated; **VA:** ventral anterior nucleus; **vg:** vector genome; **WT:** wild type.

ACKNOWLEDGEMENTS & DISCLOSURES: This study was funded by AviadoBio Ltd. **YBL, CJM, YB, PH, AF, RJ, ZW, JF, DYL** and **CS** are employees and/or shareholders of AviadoBio Ltd. **JA, AK, MG** and **OB** are employees of King's College London (SRA contract sponsored by AviadoBio Ltd). The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). Medical writing and editorial support was provided by Charlotte Sutherland, MSc, of Costello Medical, UK, and funded by AviadoBio Ltd.

Presented at the 14th International Conference on Frontotemporal Dementias (ISFTD) | 19–22 September 2024 | Amsterdam, The Netherlands