AVB-101 Six-month Preclinical Safety and Biodistribution Data Following Intrathalamic Delivery to Cynomolgus Monkeys Demonstrates Good Tolerability and Widespread Progranulin Expression in Brain Tissues

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Poster #30

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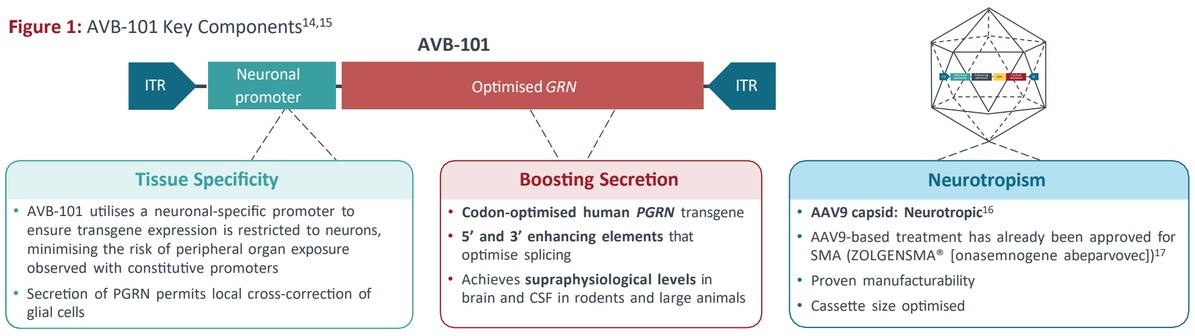
Introduction

- Frontotemporal dementia (FTD) affects ~30,000 patients in the United States of America and ~76,000 patients in Europe* causing a progressive decline in behaviour, personality, executive function and/or language, with death 6–12 years after initial symptom onset[1-7]
- The burden associated with FTD is significant and costly, and currently, no disease-modifying therapies are available[8]
- FTD caused by loss-of-function mutations in the granulin (*GRN*) gene (FTD-*GRN*) leads to deficient progranulin (PGRN) production that increases microglial activity, accelerates neurodegeneration, and leads to pathogenic transactive response DNA-binding protein 43 (TDP-43) accumulation[9-12]
- PGRN supplementation has been demonstrated to correct the pathological phenotype in rodent models of FTD-*GRN*, suggesting that it is a valid therapeutic target for patients with FTD-*GRN*[13]
- AVB-101 is an adeno-associated virus serotype 9-based gene therapy that encodes human PGRN, and is in development to treat patients with FTD-*GRN*[14,15]
- When administered into the thalamus, low doses of AVB-101 can rescue pathology in the *Grn* knock-out mouse model and result in widespread cortical and subcortical biodistribution that reaches normal to supraphysiological levels of human PGRN in an ovine model[14,15]
- AVB-101 has been designed with efficacy and safety in mind (**Figure 1**), and here we present preclinical data from toxicology and biodistribution studies performed in cynomolgus monkeys, a widely used non-human primate (NHP) model

Figure 1: AVB-101 Key Components[14,15]



AAV9, adeno-associated virus serotype 9; CSF, cerebrospinal fluid; GRN, granulin gene; ITR, inverted terminal repeat; PGRN, progranulin; SMA, spinal muscular atrophy.

Study Design

Table 1: Study Details for the Distribution and Toxicology Studies Conducted in Cynomolgus Monkeys[18]

Dose (VG/hem)	Toxicology		Biodistribution	
	3 months	6 months	8 weeks with Gd	8 weeks no Gd
0 (vehicle)	2M; 2F	2M; 2F	-	1M; 1F
8.3×10^{9}	-	-	-	1M; 1F
2.5×10^{10}	3M; 3F	3M; 3F	-	1M; 1F
7.5×10^{10}	-	-	1M; 1F	1M; 1F
2.5×10^{11}	3M; 3F	3M; 3F	-	-

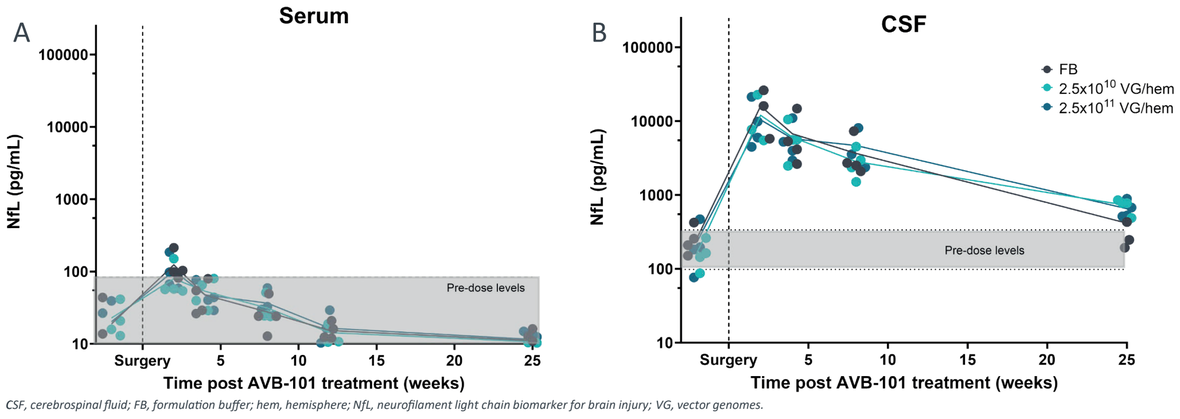
F, female; Gd, contrast agent gadolinium; hem, hemisphere; M, male; VG, vector genomes.

Results

Preclinical Safety of AVB-101 up to 6 Months[18]

- There were no observable adverse events (AEs), with all animals surviving the entire duration of both the biodistribution and the toxicology study
- There were no meaningful effects on haematology, coagulation, urinalysis or cerebrospinal fluid (CSF) clinical pathology, and no changes in functional observational battery, electrocardiography or ophthalmology
- No significant increase from baseline in alanine transaminase and aspartate transaminase at all timepoints
- Neurofilament light chain (NfL) biomarker below baseline in serum (**Figure 2A**) and approaching baseline in CSF at 6 months (**Figure 2B**), suggesting repair of the procedure-related tissue injury

Figure 2: NfL Levels in the Serum (A) and Cerebral Spinal Fluid (B) Following Intrathalamic Delivery of AVB-101[18]



CSF, cerebrospinal fluid; FB, formulation buffer; hem, hemisphere; NfL, neurofilament light chain biomarker for brain injury; VG, vector genomes.

Histopathology Summary[18]

- No test article-related organ weight changes, macroscopic observations or microscopic findings in non-nervous tissues at 3- and 6-month timepoints
- No test article-related microscopic findings in spinal cord and dorsal root ganglia at both timepoints
- Histological analysis in brain tissue indicated gradual regression/repair of the mild infusion procedure-related findings (**Table 2**) across all groups (including control animals, formulation buffer [FB]) associated with transient magnetic resonance imaging findings
- Adverse histological findings in nervous system tissues ranging from minimal to moderate were present in both low- and high-dose animals at both timepoints, and these increased in incidence and severity by 6 months (**Table 2**)
- In the low-dose group, findings were restricted. They included minimal neuronal necrosis or single-cell necrosis in the thalamus in one animal and minimal neuronophagia and neuronal degeneration in a second animal (**Table 2**)
- A no observed adverse effect level of 2.5×10^{10} vector genomes (VG)/hemisphere was established in the cynomolgus monkey

Table 2: Incidence and Grade(s) Observed for Major Test-Article-Related Findings in the Brain at 3- and 6-Months Post-Intrathalamic Administration of AVB-101[18]

		3-month cohort						6-month cohort					
		Vehicle control (n=4)		2.5×10^10 VG/hem (n=6)		2.5×10^11 VG/hem (n=6)		Vehicle control (n=4)		2.5×10^10 VG/hem (n=4)		2.5×10^11 VG/hem (n=4)	
Finding	**Region**	INC	Grade	INC	Grade	INC	Grade	INC	Grade	INC	Grade	INC	Grade
Neuronal necrosis	Thalamus	-	-	-	-	-	-	-	-	25%	1	100%	1
	Midbrain	-	-	-	-	-	-	-	-	25%	1	-	-
Single cell necrosis	Thalamus	-	-	-	-	17%	1	-	-	25%	1	100%	1
	Midbrain	-	-	-	-	-	-	-	-	25%	1	-	-
	Cerebral cortex	-	-	-	-	-	-	-	-	-	-	50%	1
	Medulla oblongata	-	-	-	-	-	-	-	-	-	-	25%	2
Neuronal degeneration/ neuronophagia	Thalamus	-	-	-	-	17%	1	-	-	25%	1	25%	1
Microgliosis*	Thalamus	25%	1	50%	1 to 2	100%	2 to 4	25%	2	100%	2	100%	3
	Midbrain	100%	1 to 2	50%	1	67%	1 to 3	-	-	75%	1 to 2	75%	2

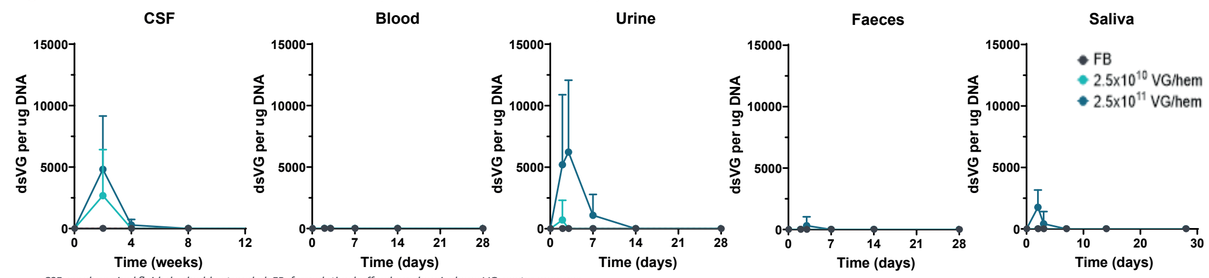
*"-" = not observed, * = this finding was observed elsewhere, but was most notable in the thalamus and midbrain.*
hem, hemisphere; INC, incidence; VG, vector genomes.

- \- = Not present
- 1 = Minimal
- 2 = Mild
- 3 = Moderate
- 4 = Marked
- 5 = Severe

Vector Biodistribution[18]

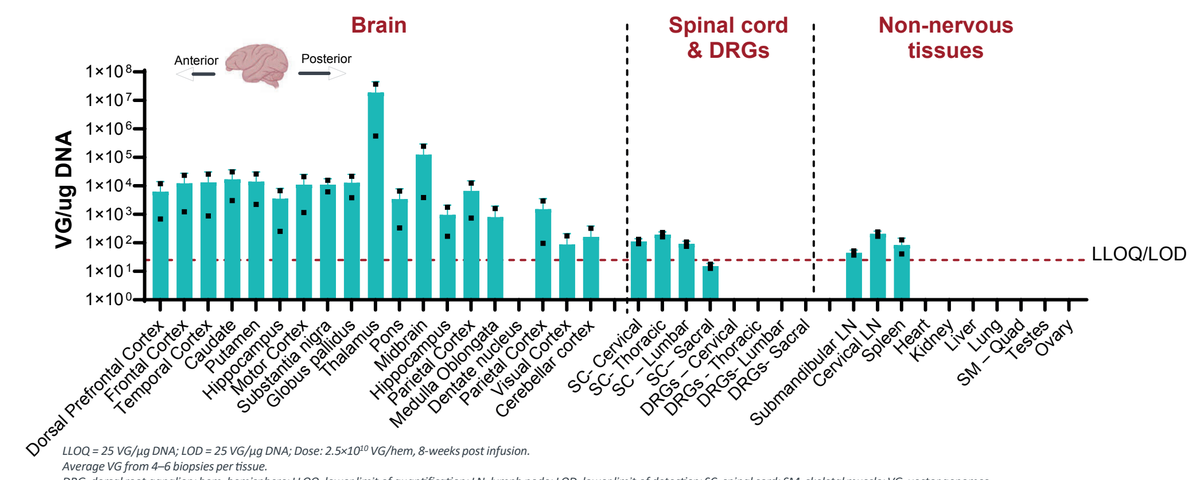
- Low and short-lived circulating VG in CSF with limited shedding outside the central nervous system (CNS; **Figure 3**)
- Broad brain distribution of VG, suggesting VG transport to brain regions receiving thalamic projections (**Figure 4**)

Figure 3: VG Presence in Various Matrices Upon Intrathalamic Delivery of AVB-101[18]



CSF, cerebrospinal fluid; ds, double-stranded; FB, formulation buffer; hem, hemisphere; VG, vector genomes.

Figure 4: VG Biodistribution in Various Tissues Following Intrathalamic Delivery of AVB-101[18]

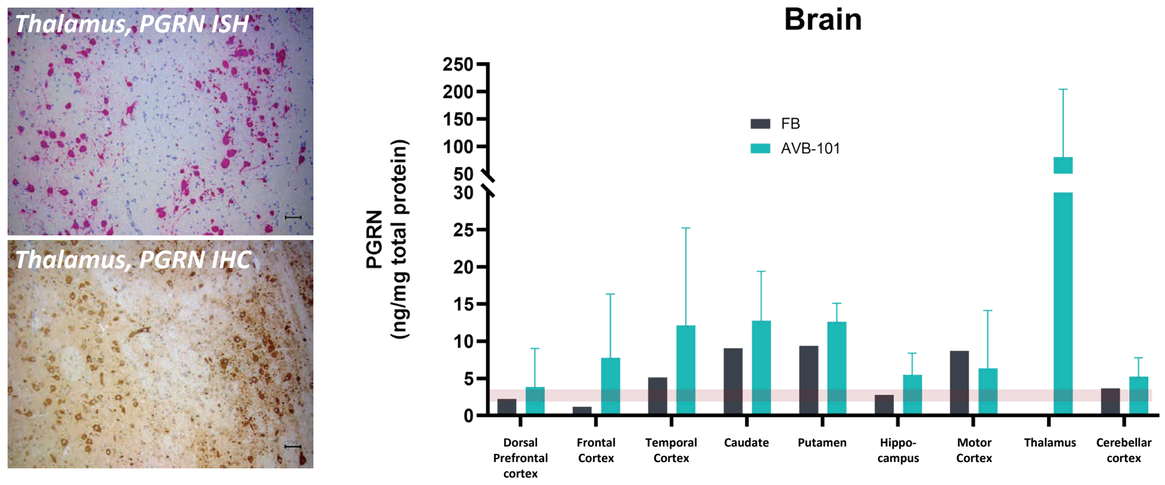


LLOQ = 25 VG/µg DNA; LOD = 25 VG/µg DNA; Dose: 2.5×10^{10} VG/hem, 8-weeks post infusion.
Average VG from 4–6 biopsies per tissue.
DRG, dorsal root ganglion; hem, hemisphere; LLOQ, lower limit of quantification; LN, lymph node; LOD, lower limit of detection; SC, spinal cord; SM, skeletal muscle; VG, vector genomes.

PGRN Biodistribution[18]

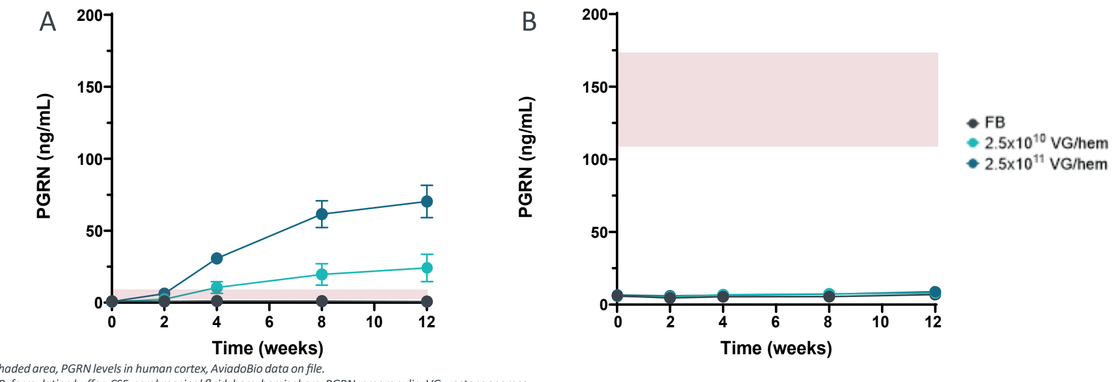
- No PGRN tissue expression outside of CNS (not shown, data on file)
- Broad biodistribution of PGRN expression in the cynomolgus monkey's brain following AVB-101 delivery reaching normal to supraphysiological levels of PGRN in human cortex tissue (**Figure 5**)
- AVB-101 leads to a specific elevation of PGRN in CSF with no changes in serum, suggesting expression restricted to the CNS and offering a potential biomarker of vector transduction and expression in the CNS (**Figure 6**)

Figure 5: PGRN Expression in Brain Tissue Following Intrathalamic Delivery of AVB-101[18]



AVB-101 dose: 2.5×10^{10} VG/hem; ISH and IHC – 12 weeks post AVB-101; PGRN ELISA – 8 weeks post AVB-101. Shaded area, PGRN levels in human cortex, AviadoBio data on file.
ELISA, enzyme-linked immunosorbent assay; FB, formulation buffer; hem, hemisphere; IHC, immunohistochemistry; ISH, in situ hybridisation; PGRN, progranulin; VG, vector genomes.

Figure 6: PGRN Levels in CSF (A) and Serum (B) Following Intrathalamic Delivery of AVB-101[18]



Shaded area, PGRN levels in human cortex, AviadoBio data on file.
FB, formulation buffer; CSF, cerebrospinal fluid; hem, hemisphere; PGRN, progranulin; VG, vector genomes.

Conclusions[18]

- AVB-101 has been engineered for specific, effective and targeted CNS expression of PGRN in patients with FTD-*GRN*
  - AVB-101 is designed to normalise cortical PGRN levels in patients with FTD due to *GRN* mutations while restricting PGRN expression to neurons and enhancing secretion efficiency to minimise the required dose of vector
- Intrathalamic delivery of AVB-101 in NHP:
  - Was well tolerated at all doses tested, with no mortality or clinically evident AEs
  - Biodistribution analysis showed that human PGRN was most abundant in the thalamus but detected throughout the brain
  - Human PGRN reached physiological levels in the temporal and frontal lobes, the cortical regions most severely affected in FTD-*GRN*
  - VG were minimal or undetectable in most visceral tissues, and human PGRN expression was restricted to the CNS
  - Levels of PGRN in the CSF showed a dose-dependent increase, offering a potential biomarker of vector transduction and expression in the CNS

AVB-101 delivered by intrathalamic infusion constitutes a novel and promising approach to address unmet medical needs in FTD-*GRN*. ASPIRE-FTD is an ongoing Phase I/II clinical study to evaluate the safety and preliminary efficacy of AVB-101 in FTD-*GRN* (NCT06064890)[19]

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Notes: *US data are an estimate of cognitive syndromes of frontotemporal lobar degeneration.[1] European data are an estimate of behavioural variant FTD in the European Union of 2013, Norway, Iceland and Lichtenstein.[2]

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