ASPIRE-FTD Study Update: A Phase 1/2 Clinical Study to Evaluate AVB-101 in FTD with *GRN* Mutations

AVIADOBIO

Tuesday-0018

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OBJECTIVE

To report interim data from Cohorts 1–3 of the ongoing ASPIRE-FTD clinical study (NCT06064890) of intrathalamic AVB-101 in participants with frontotemporal dementia with mutations in the granulin gene (FTD-*GRN*).

BACKGROUND

- FTD is an important type of dementia in people under the age of 65 years.[1,2] It manifests with progressively declining behavioral/language symptoms and loss of executive function and cognitive abilities.[1,3–5]
- Currently there are no disease-modifying treatments and the average survival of patients with FTD is 3–13 years from diagnosis.[6–8]
- FTD with mutations in the *GRN* gene encoding progranulin (PGRN) accounts for 5–10% of all FTD cases.[9]
- AVB-101 is an adeno-associated virus serotype 9 (AAV9)-based gene therapy designed to deliver a functional copy of *GRN* to cortical neurons to restore PGRN levels and potentially prevent disease progression.[10]
- There are challenges associated with the delivery of gene therapy to the central nervous system due to the blood brain barrier (BBB).[11] AVB-101 is delivered directly to the thalamus, bypassing the BBB, via minimally-invasive stereotactic neurosurgery guided by magnetic resonance imaging (MRI).[10]
- The thalamus has extensive connections to other brain regions, enabling widespread cortical distribution of AVB-101, including areas critically affected in FTD.[12,13]
- Preclinical studies have shown that intrathalamically-delivered AVB-101 enables widespread cortical PGRN expression at relatively low doses, with minimal systemic exposure.[10,14]

METHODS

Clinical trial design

- ASPIRE-FTD is a first-in-human, Phase 1/2, open-label, ascending dose trial evaluating the safety and preliminary efficacy of AVB-101 in participants with FTD-*GRN* over 5 years (**Figure 1**).
- 12 participants have been dosed across three ascending dose cohorts, with up to 24 months follow up.
- A single, bilateral, convection-enhanced, MRI-guided intrathalamic administration of AVB-101 is designed to transduce thalamic neurons to drive PGRN expression and enable secreted PGRN to distribute broadly to cortical regions implicated in FTD.
- The primary objective is to evaluate the safety and tolerability of AVB-101 by assessing adverse events (AEs), serious AEs (SAEs), change from baseline in regional brain volume and clinical/laboratory assessments.

Neurological administration of AVB-101

- AVB-101 is administered as two sets of bilateral infusions to the thalamus. The neurological administration and first-in-human surgical experience have been previously described.[15,16]
- The trajectories are designed to target infusion into the thalami by means of two transfrontal trajectories per hemisphere, targeting the thalamic regions that project to the frontal and temporal lobes (**Figure 2**).
- Each infusion is followed in real-time via serial MRI scans, with adjustments of flow rate and cannula depth as required to optimize target coverage (**Figure 3**).
- Real-time imaging also showed a direct correlation between distribution volume (Vd) and infusion volume (Vi), with the Vd:Vi ratio remaining consistent across individual infusions (**Figure 4**).

RESULTS

Preliminary safety results from Cohorts 1–3 (up to 24 months)

- Baseline characteristics of the 12 participants who received a one-time AVB-101 dose are shown in **Table 1**.
- AVB-101 was well-tolerated with no clinically significant safety trends observed at up to 24 months follow-up.
- Intrathalamic delivery was highly consistent across participants and centers, its safety was consistent with prior intraparenchymal experience, and serial MRI demonstrated no clinically significant hemorrhage, edema or inflammation. No prophylactic or reactive immunosuppression was required for any participant.
- There were three SAEs in two participants that were unrelated to study drug (**Table 2**).
- As expected, an early transient peak in serum neurofilament light chain (NfL) without dose-dependency was observed after intrathalamic administration, with serum NfL trending to/below baseline beyond 12 months (**Figure 5**). These preliminary data thus suggest potential for disease modification.
- Cerebrospinal fluid (CSF) PGRN showed dose-dependent increase but remained unchanged in serum, consistent with the neuronal-specific promoter used in AVB-101 (**Figure 6**).

CONCLUSIONS

- **12 participants have been dosed across three ascending dose cohorts in this ongoing Phase 1/2 study, with preliminary data supporting the safety and tolerability of AVB-101 and its administration procedure.**
- **MRI-guided, convection-enhanced delivery of AVB-101 into the thalamus has been highly consistent across participants and centers.**
- **Recruitment is ongoing in the US, EU, UK, and Canada. Data from this clinical trial are expected to inform further clinical development of AVB-101.**

Figure 1: ASPIRE-FTD study overview

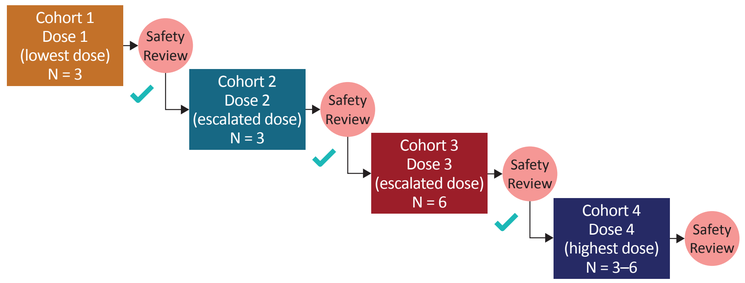
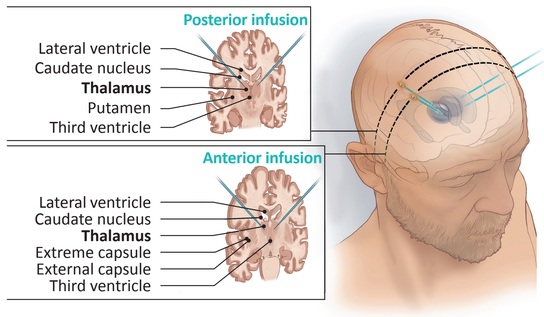
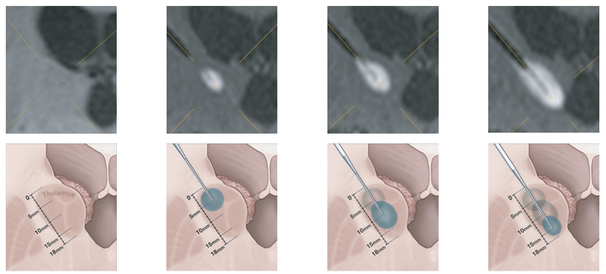


Figure 2: Bilateral transfrontal approach to intrathalamic delivery as two pairs of infusions



The participant lies supine with the head pinned in the intraoperative MRI scanner. Percutaneously mounted, MRI-compatible, frameless, stereotactic platforms set each cannula's entry point and planned trajectory (blue arrows). Following skin incision, twist drill burr hole and sharp dural opening, each cannula is introduced into the rostral thalamus along its preplanned path, then advanced rostrally to caudally during infusion to optimize thalamic distribution.

Figure 3: Shaping the AVB-101 infusion

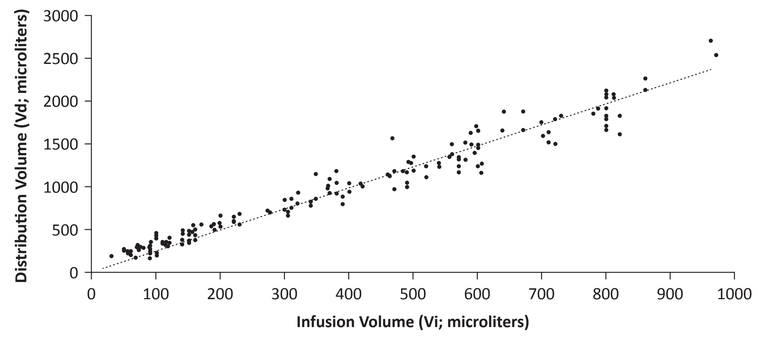


Successful infusate shaping was performed by modulating infusion rates and cannula depth to conform to narrowing thalamic anatomy. **[a]** Lower infusion rate, spherical perfusion pattern; **[b]** Moderate infusion rate, cylindrical perfusion pattern; **[c]** Higher infusion rate, cylindrical perfusion pattern.

Table 1: Baseline characteristics

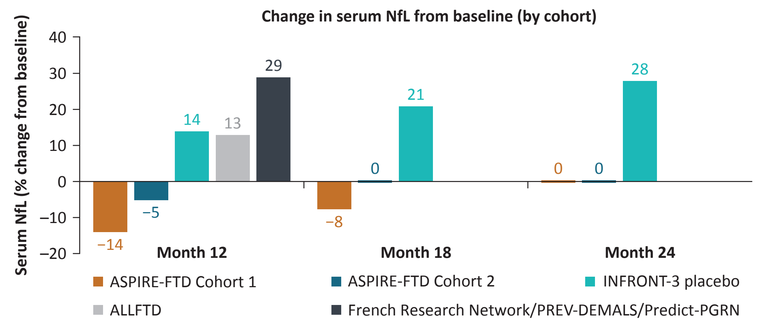
Characteristic	Cohort 1	Cohort 2	Cohort 3
n	3	3	6
Age, years, mean (SD)	53.0 (18.2)	61.3 (2.1)	60.2 (7.9)
Sex, n			
Male	2	3	6
Female	1	0	0
Primary FTD phenotype, n			
bvFTD	3	0	4
PPA	0	3	2
Disease duration, years, mean (SD)	1.9 (0.1)	1.9 (1.8)	1.6 (1.7)
CDR plus NACC FTLD, mean (SD)			
Global score	1.7 (0.6)	1.7 (0.6)	1.0 (0.5)
Sum of Boxes score	7.0 (4.4)	9.8 (2.3)	5.7 (2.9)

Figure 4: Consistency of Vd:Vi during individual infusion



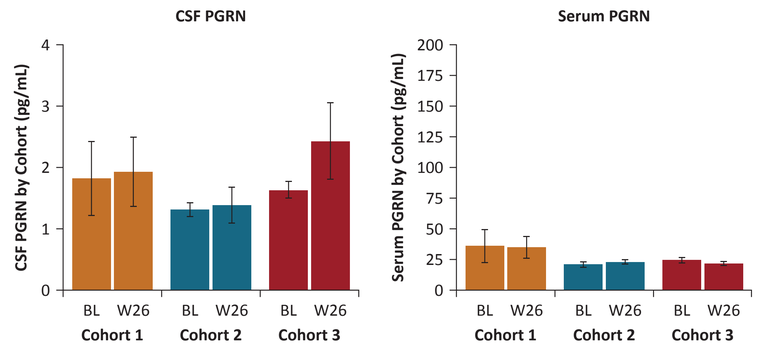
Vd versus Vi for individual infusions. The linear relationship through the origin indicates a consistent Vd:Vi ratio across the volume range.

Figure 5: Percentage change in serum NfL from baseline in ASPIRE-FTD compared with data from clinical and observational studies



At Month 12 in the ASPIRE-FTD study, reductions in serum NfL of −14% (Cohort 1; n=3) and −5% (Cohort 2; n=1) from baseline have been observed. In contrast, it has been shown in clinical and observational studies that NfL increases over time: +14% at 12 months in the INFRONT-3 placebo cohort (n=34; increased to +28% by 24 months);[17] +13% at 12 months in the ALLFTD reference cohort (n=24; data reflect an AviadoBio analysis of the ALLFTD natural history cohort); +29% at 12 months in patients with *GRN* mutations recruited from the French Research Network on FTD/ALS, and the PREV-DEMALS and Predict-PGRN studies (n=15; symptomatic FTD-*GRN* patients; mean years since diagnosis: 2.9).[18]

Figure 6: Changes from baseline to Week 26 in CSF PGRN and serum PGRN by cohort



Error bars are the standard error of the mean (SEM).

Table 2: Summary of adverse events

Category	Number of events
TEAEs	77
Perioperative TEAEs	33
SAEs	3
SAEs related to AVB-101	0
SAEs related to administration procedure	1

Data from Cohorts 1–3 as of 27 May 2026.

ABBREVIATIONS: **AAV9:** adeno-associated virus 9; **AE:** adverse event; **BBB:** blood brain barrier; **BL:** baseline; **bvFTD:** behavioral variant frontotemporal dementia; **CDR:** clinical dementia rating; **CED:** convection enhanced delivery; **CSF:** cerebrospinal fluid; **FTD:** frontotemporal dementia; **FTLD:** frontotemporal lobar degeneration; ***GRN*:** granulin; **MRI:** magnetic resonance imaging; **NACC:** National Alzheimer's Coordinating Center; **NfL:** neurofilament light chain; **PGRN:** progranulin; **PPA:** primary progressive aphasia; **SAE:** serious AE; **SD:** standard deviation; **SEM:** standard error of the mean; **TEAE:** treatment-emergent adverse event; **Vd:** distribution volume; **Vi:** infusion volume; **W:** week.

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ACKNOWLEDGMENTS & DISCLOSURES: This study was funded by AviadoBio Ltd. **JDR:** Provided consultancy for Alector, Asceneuron, Astex, Astronautx, Boehringer Ingelheim, Booster Therapeutics, ClinicalInk, CumulusNeuro, Curasen, Eisai, Ferrer, Prevail, SVHealth, UCB, VesperBio, and WAVE; research grants from AstraZeneca, Eli Lilly and Company, and Janssen, unrelated to the current work; **WG:** Receives institutional funding from AviadoBio and is a consultant for LifeEdit and uniQure; **CMP, JYCC, YGH, DLC:** Employees and/or shareholders of AviadoBio Ltd; **All other authors:** None disclosed. 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 Oscar Jenkyn-Jones, MSc, and Isabel Katz, BA, of Costello Medical, UK, and design support was provided by the Costello Medical Creative team, funded by AviadoBio Ltd.