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

AVIADOBIO

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OBJECTIVE

To report interim data from the initial cohort (Cohort 1) of the ongoing ASPIRE-FTD clinical study (NCT06064890) of intrathalamic AVB-101 in participants with frontotemporal dementia with progranulin mutations (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 between 3–13 years from diagnosis.[6–8]
- FTD with mutations in the granulin gene (*GRN*) 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 blood-brain barrier (BBB) and the delivery of gene therapy to the central nervous system.[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 (**Figure 1**).[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 early stage, symptomatic FTD-*GRN* over 5 years.
- Three participants were dosed at the initial dose level in Cohort 1, with 3–9 months of follow-up data available.
- 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: safety measures include adverse events (AEs) and serious AEs, and change from baseline in MRI results and clinical/laboratory assessments.
- The study overview is outlined in **Figure 2**.

Neurological administration of AVB-101

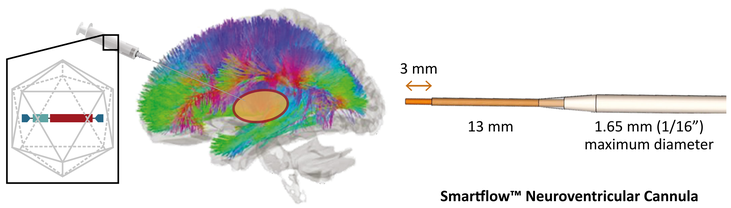
- AVB-101 is administered as two sets of bilateral infusions to the thalamus.
- The trajectories are designed to target infusion into the thalami by means of two transfrontal trajectories per hemisphere, targeting the thalamic regions that project to the frontal and temporal lobes. Infusions are initiated with the cannulae tips positioned within the target structure (**Figure 3**).
- 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 4**).
- Post-infusion images provide an indication of target coverage achieved (**Figure 5**).

RESULTS

Preliminary safety results from cohort 1 (3–9 months)

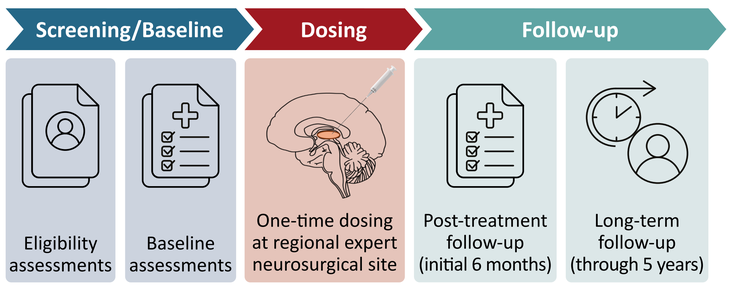
- Baseline characteristics of the three participants who received a one-time AVB-101 dose are presented in **Table 1**.
- AVB-101 was well-tolerated in all three participants at the dose tested in this initial cohort, with no clinically significant safety findings observed during the 3–9 month follow-up period.
- No serious or severe AEs were reported, and all treatment-related AEs were mild to moderate in severity. (**Table 2**).
- No prophylactic or reactive immunosuppression was required for any participant.

Figure 1: Exploiting thalamocortical neural networks for targeted delivery



Schematic illustrating intrathalamic delivery of AVB-101, superimposed upon a human brain structural connectome derived from diffusion MRI data.[14] Delivery of AVB-101 to the thalamus (represented by orange oval), a key hub for connectivity in the brain, via a stepped catheter (Smartflow™ cannula) with a very small tip diameter, aims to maximize cortical biodistribution of PGRN by exploiting highly-connected neuronal networks.

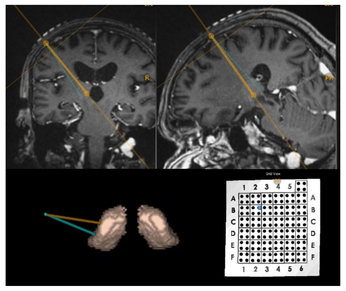
Figure 2: ASPIRE-FTD study overview



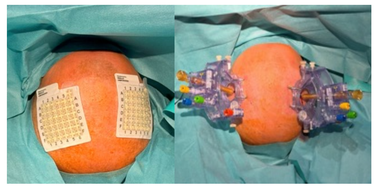
ASPIRE-FTD consists of a screening period lasting ≤12 weeks at the trial site, followed by one-time AVB-101 dosing, which takes place at an expert neurosurgical center. This is followed by a 6-month post-treatment follow-up period and a long-term follow-up (through 5 years) conducted at the trial site.

Figure 3: Pre-infusion set-up

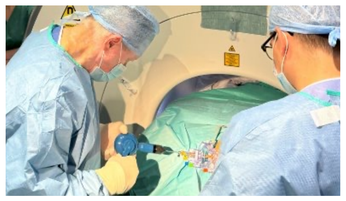
1. Grid registration scans



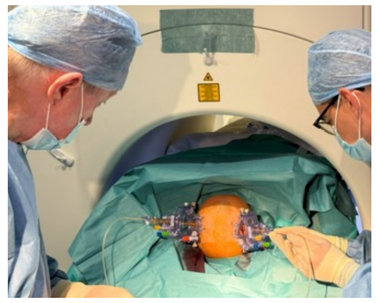
2. Percutaneously mounted stereotaxic frames



3. Stereotaxic twist drill hole

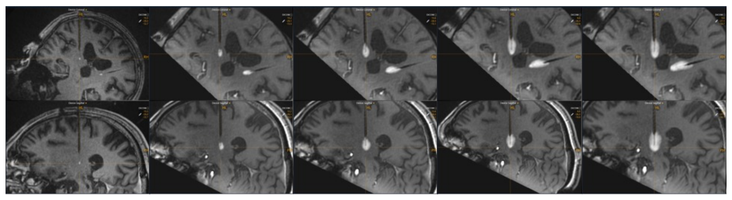


4. Catheter placement



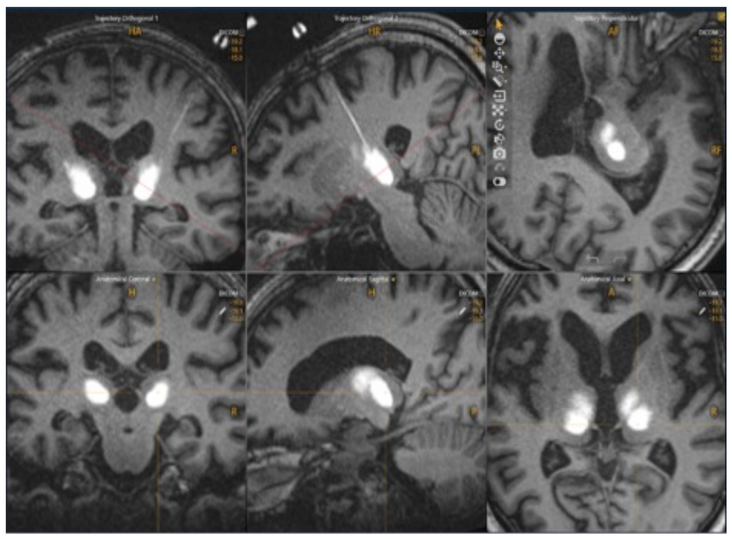
1: SmartGrid® and image analysis software are used to accurately plan catheter trajectories, to optimize coverage of the thalamus and avoid the ventricles, sulci, and blood vessels. **2–3:** The MRI-compatible aiming device (SmartFrame®) is mounted percutaneously with tiny screws and aligned stereotactically to allow a small twist drill hole. **4:** Clearpoint Smartflow® MRI Safe cannulae are inserted, and real-time, MRI-guided bilateral AVB-101 infusion takes place using CED with ramping increase in flow and progressive catheter insertion to optimize coverage, minimize reflux along the catheter and avoid perivascular loss.

Figure 4: Intra-operative monitoring of infusion



MRI imaging to monitor the infusion is accomplished using a gadolinium (Prohance®) tracer, as non-clinical studies have established gadolinium visualization correlates with AAV biodistribution. Shown here are selected serial MRI images orthogonal in 2 planes to the left anterior thalamic infusion cannula as the infusion rate is increased and the cannula advanced. The contralateral (right) infusion can also be visualized in the coronal plane.

Figure 5: Post-infusion imaging



Following completion of the posterior infusion (right). Images orthogonal and perpendicular to the cannula (top row) and anatomic coronal, sagittal and axial (bottom row) demonstrate coverage of the 2nd infusion. The anterior (1st) infusion has faded due to the elapsed time since the infusion.

Table 1: Baseline characteristics

Characteristic	Cohort 1 (n=3)
Age, years, mean (range)	53.0 (32–65)
Sex, n (%)	
Male	2 (66.7)
Female	1 (33.3)
FTD phenotype, n (%)	
bvFTD	3 (100)
Disease duration, years, mean (range)	1.9 (1.8–2.0)
CDR plus NACC FTLD, mean	
Global score	1.7
SB score	7.0

Table 2: Summary of AEs

Category	Number of events
Total AEs	10
By severity	
Mild	7
Moderate	3
Severe	0
By relationship	
Related to AVB-101	1*
Related to procedure	0
Unrelated	9
By seriousness	
Serious	0
Non-serious	10

*Mild headache, self-limiting.

CONCLUSIONS

- **The first three participants treated in this study represent the first successful intrathalamic gene therapy delivery in any adult with neurodegenerative disease.**
- **Preliminary data from Cohort 1 of the ongoing ASPIRE-FTD trial suggest acceptable safety and tolerability of AVB-101 and its administration procedure.**
- **MRI-guided convection-enhanced delivery with real-time monitoring allowed consistent shaping of vector distribution to maximize thalamic coverage.**
- **ASPIRE-FTD has completed dosing of the second cohort and is actively recruiting with additional cohorts planned.**
- **Data from this clinical trial are expected to inform further clinical development of AVB-101.**

REFERENCES: [1]Young JJ, *et al.* Ther Adv Psychopharmacol 2018;8:33–48; [2]Hendriks S, *et al.* JAMA Neurol 2021;78:1080–90; [3]Pressman P and Miller BL. Biol Psychiatry 2014;75:574–81; [4]Hogan DB, *et al.* Can J Neurol Sci 2016;43 Suppl 1:S96–109; [5]Rohrer JD, *et al.* Lancet Neurol 2015;14:253–262; [6]Onyike CU. Neuroepidemiology 2011;37:166–7; [7]Riedl L, *et al.* Neuropsychiatr Dis Treat 2014;10:297–310; [8]Kuang L, *et al.* Hum Mol Genet 2019;29:624–34; [9]Greaves CV and Rohrer JD. J Neurol 2019;266:2075–86; [10]Lee YB, *et al.* Oral presentation at ESGCT Annual Congress 2022; [11]Kimura S and Harashima H. Pharmaceutics 2020;12:1216; [12]Perera A, *et al.* Acta Neurochir 2024;166:136; [13]Yeh FC, *et al.* Neuroimage 2018;178:57–68; [14]Miranda CJ, *et al.* Poster presented at ESGCT Annual Congress 2023.

ABBREVIATIONS: **AAV9:** adeno-associated virus 9; **AE:** adverse event; **BBB:** blood brain barrier; **bvFTD:** behavioral variant frontotemporal dementia; **CDR:** clinical dementia rating; **CED:** convection enhanced delivery; **FTD:** frontotemporal dementia; **FTLD:** frontotemporal lobar degeneration; ***GRN*:** granulin; **MRI:** magnetic resonance imaging; **NACC:** National Alzheimer's Coordinating Center; **PGRN:** progranulin; **SB:** sum of boxes.

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