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

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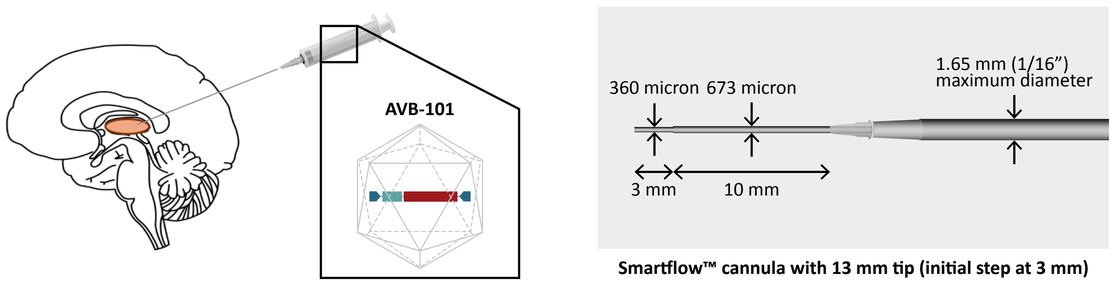
OBJECTIVE

To report early experiences and safety data from the ongoing ASPIRE-FTD clinical study of intrathalamic AVB-101 in participants with frontotemporal dementia with progranulin mutations (FTD-GRN).

BACKGROUND

- The development of the methods relating to modern gene therapy infusion to the brain has been influenced by experience gained over past decades, including in neurodegenerative diseases, notably Parkinson's Disease.[1]
- State-of-the-art intraparenchymal gene therapy uses stepped catheters to infuse the gene therapy directly into the brain by convection-enhanced delivery (CED), guided by real-time magnetic resonance imaging (MRI) to achieve optimal target coverage (**Figure 1**).[2]
- Adeno-associated virus (AAV)-based gene therapy is a well-established platform technology, with at least five approved products in the US and/or EU, including the intraparenchymally-delivered treatment for aromatic amino acid decarboxylase deficiency (AADC), a rare neurometabolic disorder.[3–7]
- FTD is a neurodegenerative disease that affects cortical neurons primarily in the frontal and temporal lobes.[8,9]
- In FTD-GRN, the therapeutic aim of gene supplementation is to restore progranulin (PGRN) levels in haploinsufficient individuals, ultimately stopping or slowing disease progression. The therapeutic potential of an AAV gene therapy in FTD-GRN is thus directly related to the durable expression and distribution of PGRN to the frontal and temporal lobes.[10]
- AAV vectors can cross the blood brain barrier (BBB), however, there are challenges associated with the biodistribution achievable via systemic injection including into the cisternal magna.[11]
- AVB-101 uses an AAV9 vector and intrathalamic delivery to bypass the BBB and pial membrane to enable broad distribution of PGRN to cortical areas relevant for FTD, at relatively low doses.[12–14]
- AVB-101 has been granted Fast Track Designation by the US Food and Drug Administration (FDA) and orphan designation by the FDA and European Commission (EC) as a one-time gene therapy for the treatment of FTD-GRN.[15]

Figure 1: ClearPoint Smartflow® stepped cannula used in AVB-101 administration procedure



Smartflow™ cannula with 13 mm tip (initial step at 3 mm)

NEUROSURGICAL ADMINISTRATION OF AVB-101

- In the ASPIRE-FTD study, AVB-101 is administered as two sets of bilateral infusions to the thalamus (**Figure 2**).
- 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**).
- End of infusion images provide an indication of target coverage achieved (**Figure 5**).
- Intra-operative MRI demonstrated AVB-101 coverage of thalamic regions projecting to frontal and temporal lobes.

PRELIMINARY SAFETY RESULTS

- Two participants in Cohort 1A underwent the neurosurgical administration procedure as planned. Baseline characteristics of these participants are presented in **Table 1**.
- No clinically significant safety findings have been observed through follow-up of up to 12 weeks and 8 weeks post-dosing for participants 1 and 2, respectively. To date, there have been no serious adverse events.
- Notably, post-operative MRI has not shown any significant hemorrhage, edema or inflammation.
- Neither prophylactic nor reactive immunosuppression has been required for either participant.

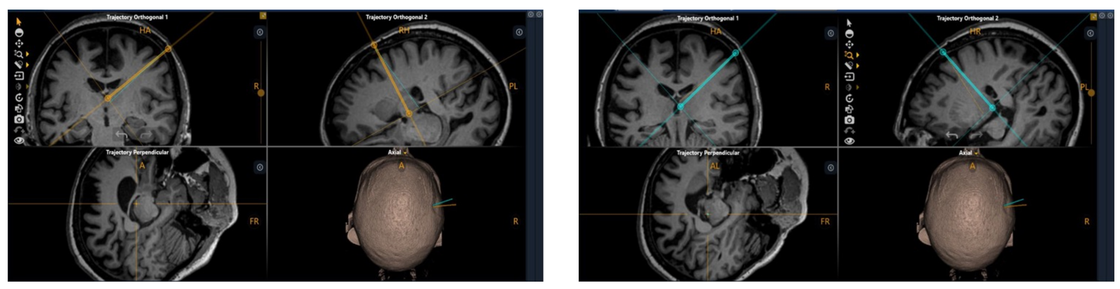
CONCLUSIONS

- **The first patients treated in this study represent the first successful intrathalamic gene therapy delivery for any adult with neurodegenerative disease.**
- **Preliminary data from the ongoing ASPIRE-FTD trial suggest acceptable safety and tolerability of AVB-101, including the administration procedure.**
- **ASPIRE-FTD (NCT06064890) is actively recruiting in Poland, Spain, the Netherlands and the USA, with additional countries/sites planned.**
- **Data from this clinical trial are expected to inform further clinical development of AVB-101.**

Figure 2: Trajectory planning using Baseline MRI scans

A) Anterior trajectory (right)

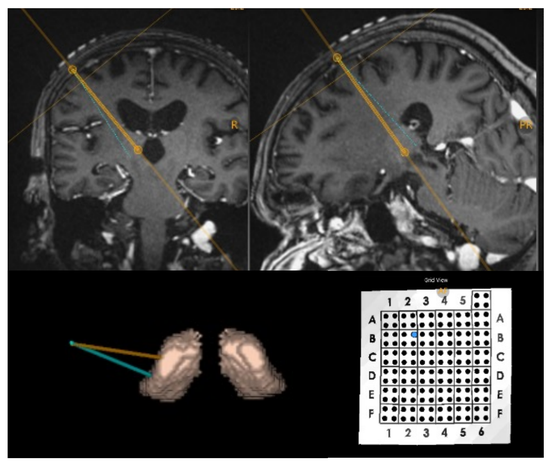
B) Posterior trajectory (left)



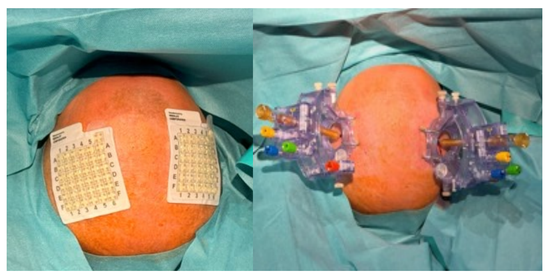
Trajectory plans are developed based upon patient-specific anatomic considerations (atrophy, gyral/sulcal pattern) and reviewed by the ASPIRE-FTD neurosurgical committee. Non-overlapping trajectories are generally planned to optimize coverage while avoiding vascular structures.

Figure 3: Pre-infusion set-up

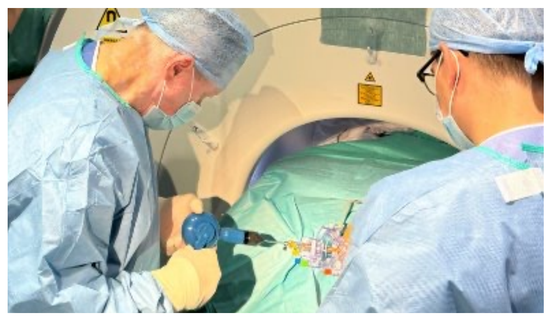
1. Grid registration scans



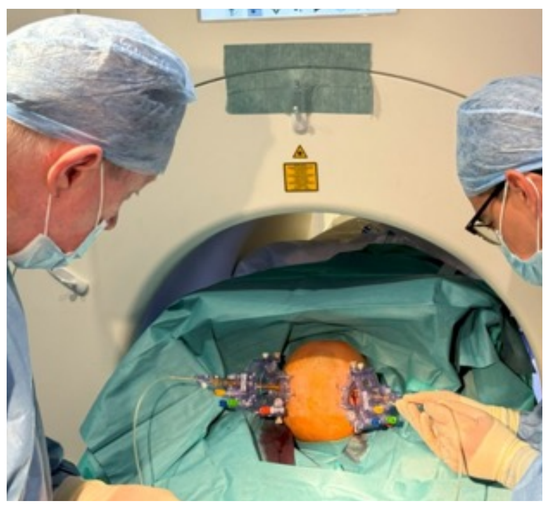
2. Percutaneously mounted stereotaxic frames



3. Stereotaxic twist drill hole

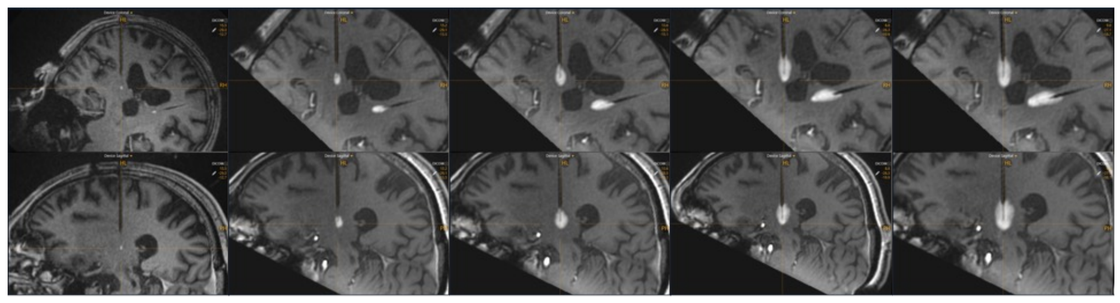


4. Catheter placement



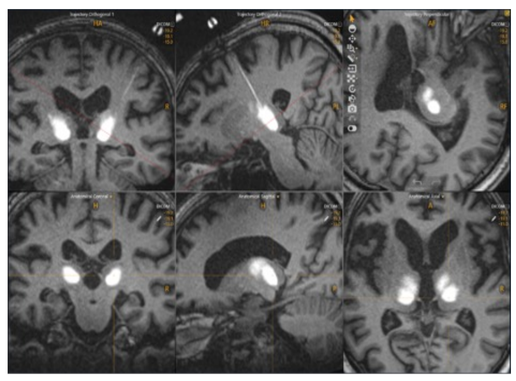
1: SmartGrid® and image analysis software are used to accurately plan catheter trajectories, to optimize coverage of the thalamus and avoid the ventricles, sulci, and blood vessels. **2–3:** The MRI-compatible aiming device (SmartFrame®) is mounted percutaneously with tiny screws and aligned stereotactically 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	Participant 1	Participant 2
Age, years	65	62
FTD phenotype	bvFTD	bvFTD
Age at diagnosis, years	63	60
CDR plus NACC FTLD score, global score	2.0	2.0
CDR plus NACC FTLD, SB score	10.5	8.5

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ABBREVIATIONS: **AADC:** aromatic amino acid decarboxylase; **AAV9:** adeno-associated virus 9; **BBB:** blood brain barrier; **bvFTD:** behavioral variant frontotemporal dementia; **CDR:** clinical dementia rating; **CED:** convection-enhanced delivery; **EC:** European Commission; **FDA:** US Food and Drug Administration; **FTD:** frontotemporal dementia; **FTLD:** frontotemporal lobar degeneration; ***GRN*:** granulin; **NACC:** National Alzheimer's Coordinating Center; **PGRN:** progranulin; **SB:** sum of boxes.

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