Direct Image-Guided Convective Perfusion of the Bilateral Thalami Offers a Consistent Approach to CNS Dosing: First-in-Human Experience with Gene Therapy for Frontotemporal Dementia

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OBJECTIVE

To define the properties of magnetic resonance (MR)-guided intrathalamic convective gene therapy delivery by analyzing findings in patients with frontotemporal dementia (FTD) with mutations in the gene coding for progranulin (*GRN*), who underwent gene therapy administration in the ongoing ASPIRE-FTD Phase 1/2 study (NCT06064890).[1]

BACKGROUND

- For neurodegenerative and neurodevelopmental disorders, indirect gene therapy delivery methods, including via cerebrospinal fluid or systemic administration, are limited by the blood brain barrier, lack of target specificity, and/or immune response/exposure.[2,3]
- Intraparenchymal convection-enhanced delivery (CED) overcomes these obstacles, and the use of real-time MR-imaging allows for the precise monitoring of vector distribution during target infusions.[4]
- FTD with *GRN* mutations (FTD-*GRN*) accounts for 5–10% of all FTD cases, through loss-of-function mechanisms that result in insufficient brain progranulin levels and asymmetric frontotemporal atrophy.[5,6]
- This study uses CED to intrathalamically deliver AVB-101, a recombinant adeno-associated virus serotype 9 (AAV9) expressing the human gene coding for progranulin as gene replacement therapy to treat patients with FTD-*GRN*.
- Large animal studies in sheep and non-human primates have demonstrated the well-tolerated and effective intrathalamic administration of AVB-101;[7] this investigation reports the first surgical, imaging, and clinical findings associated with MR-guided convective intrathalamic gene therapy delivering in patients with FTD-*GRN*.

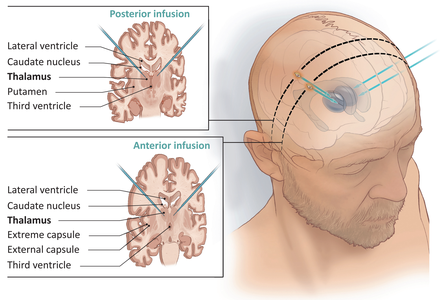
METHODS

- Three consecutive adult FTD-*GRN* patients were enrolled into the ASPIRE-FTD, Phase 1/2 open-label, multi-center study.
- AVB-101 was stereotactically administered using the ClearPoint Navigation System via ~3–4 mm twist drill holes as two pairs of equally divided, simultaneously delivered bilateral infusions to the anterior and posterior thalami (four infusions per patient; **Figure 1**) using ClearPoint SmartFlow™ Neuroventricular Cannulae (stepped, 1.65 mm maximum outer diameter).[8,9]
- Each infusion was followed in real-time via repeated T1-weighted MR-imaging sequences to monitor infusate distribution and shape infusions.
- Infusate shaping was performed by modulating infusion rates.
- Post-infusion MR-images provided an indication of target coverage achieved. Volumetric analysis was performed by subtracting pre-operative "baseline" scans from intraoperative imaging acquired during or after infusion.
- Distribution volume (Vd), the percentage of thalamus covered, and percentage of distribution within the thalamus were quantified using automated threshold-based segmentation with the Otsu method.[10]

RESULTS

- Three consecutive patients (mean age 53.0 ± 18.2 years) underwent a total of 12 thalamic infusions with 6–12 months follow-up (mean 9.0 ± 3.0 months) to date (**Table 1**).
- Despite the expected variability in segmented thalamic volume (4.8–8.3 cm^3), mean thalamic coverage was 39.1% (range: 28.7–47.6%; **Table 1**).
- The ratio of volume of distribution to volume of infusion (Vd:Vi) was consistent across all thalamic infusions for all three patients (range: 2.2–2.5; **Table 1**).
- Successful infusate shaping was performed by modulating infusion rates to conform to narrowing thalamic anatomy (spherical at lower rates, cylindrical at higher rates; **Figure 2**).
- Imaging demonstrated progressive filling of the thalamus with increasing infusate volume (**Figures 2** and **3**) with 78.6–95.1% of the perfused area contained within the thalamus (**Table 1**; **Figure 4**). Perivascular leakage and backflow along the cannulae was not seen during infusions.
- Real-time MR-imaging (**Figure 3**) demonstrated a direct correlation between increasing infusion and distribution volume during an individual infusion (R^2=0.97) consistent with the overall Vd:Vi ratio (**Figure 5**).
- There was no evidence of complication on imaging or clinical safety assessments, and no serious procedure or product-related adverse events were reported during the follow-up period.

Figure 1: Frontal approach to intrathalamic delivery



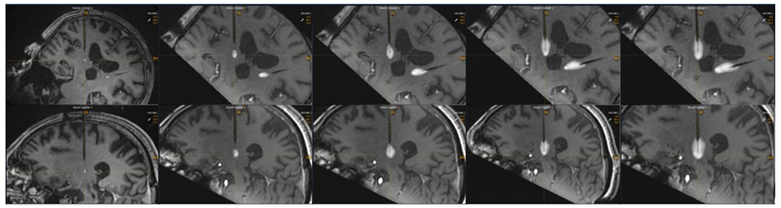
The entry point and target defining the trajectory for each infusion cannula are identified and confirmed using MR-imaging with contrast at screening, baseline and upon initiation of the administration procedure. A small skin incision is made at the cannula insertion site and a twist drill burr hole (3.4 or 4.5 mm) is created. The stepped cannula (maximal diameter: 1.65 mm) is advanced at 2–4 mm increments, starting 2–4 mm within the rostral portion of the thalamus.

Table 1: Patient characteristics and infusion/coverage parameters

Patient number	Follow-up (months)	Age (years)	Sex	Maximal infusion rate*	Right thalamus					Left thalamus				
					Thalamic volume (cm^3)	Vd (cm^3)	Vd:Vi ratio**	Thalamic coverage (%)[§]	Distribution within thalamus (%)[§§]	Thalamic volume (cm^3)	Vd (cm^3)	Vd:Vi ratio**	Thalamic coverage (%)[§]	Distribution within thalamus (%)[§§]
1	12	65	M	10	5.4	3.2	2.5	43.2	78.6	4.8	3.0	2.3	47.6	85.0
2	9	62	F	15	5.5	2.7	2.2	42.8	88.0	6.2	2.9	2.4	41.3	88.1
3	6	32	M	15	8.1	2.4	2.2	28.7	88.2	8.3	2.7	2.3	31.1	95.1
Mean (±SD)	9.0±3.0	53.0±18.2	N.A	13.3±2.9	6.3±1.5	2.8±0.6	2.3±0.2	38.2±8.0	84.9±6.0	6.4±1.7	2.9±0.2	2.3±0.1	40.0±8.0	89.4±5.0

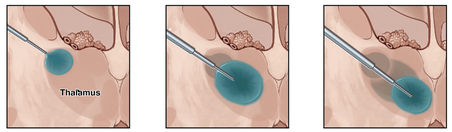
*Infusion rate in microliters per minute; **Mean Vd to Vi ratio of anterior and posterior infusions from corresponding thalamus; §Percent of the total volume of thalamus perfused (including anterior and posterior infusions); §§Percent of the total perfusion contained with thalamus.

Figure 3: Real-time T1-weighted MR-imaging during infusion



MR-imaging to monitor the infusion is accomplished using diluted gadolinium (Prohance®, 1mM) tracer mixed into the investigational product; prior, non-clinical studies have established gadolinium visualization correlates with AAV biodistribution. Shown here are selected serial MR images orthogonal in two 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 near-coronal plane shown in the top row.

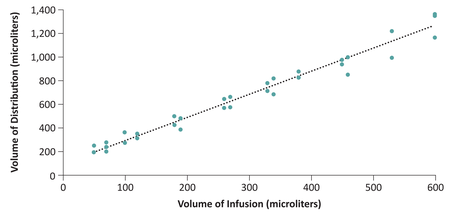
Figure 2: Shaping the AVB-101 infusion



Initial position	Cannulae advanced	Final position
Lower infusion rate	**Moderate** infusion rate	**Higher** infusion rate
Spherical perfusion pattern	**Cylindrical** perfusion pattern	**Cylindrical** perfusion pattern

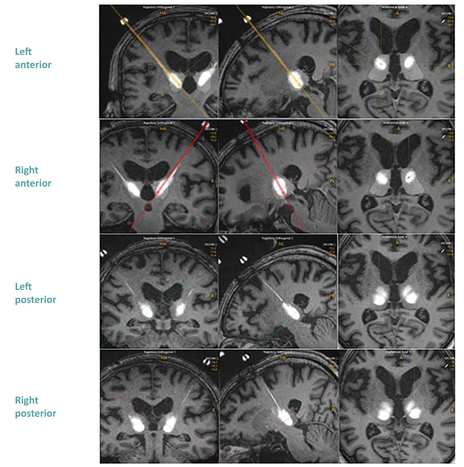
Infusion shaping is performed by modulating infusion rates and cannulae depth within the target. Lower infusion rates create more spherical perfusion while higher rates create more cylindrical perfusion.

Figure 5: Consistency of Vd:Vi during individual infusion



High correlation (R^2=0.97) reflects consistent ratio of infused volume to intrathalamic distribution during an infusion as reflected by the black dotted line. The consistency of Vd:Vi throughout in adults permits modeling of different volumes to match desired thalamic coverage.

Figure 4: Imaging after anterior/posterior infusions



Whole brain T1-weighted MR-images obtained at the end of each infusion shown here in two trajectory orthogonal images (left two columns, near coronal and sagittal) and perpendicular to trajectory along cannulae (right column, near axial).

CONCLUSIONS

- **The first-in-human data from the ongoing ASPIRE-FTD study demonstrated successful and highly consistent intrathalamic CED of AVB-101 in FTD-*GRN* patients with no significant leakback along the cannulae or perivascular loss.**
- **MR-guided convective delivery with real-time monitoring allows shaping of vector distribution to maximize coverage of key targeted thalamic nuclei by varying cannulae position and infusion rate.**
- **Predictability of Vd:Vi throughout infusions allows for potential scaling of infused volume to achieve desired coverage.**
- **No procedure or treatment-related adverse events were reported during the follow-up period.**

REFERENCES: [1]ClinicalTrials.gov. ASPIRE-FTD. Available at: https://clinicaltrials.gov/study/NCT06064890 [Accessed April 2025]; [2]Puhl DL et al. Brain Res Bull 2019;150:216–30; [3]Salegio EA et al. Front Mol Neurosci 2023; doi:10.3389/fnmol.2023.1248271; [4]Richardson RM et al. J Neurol Neurosurg Psychiatry 2020;91:1210–8; [5]Greaves CV and Rohrer JD. J Neurol 2019;266:2075–86; [6]Sevigny J et al. Nature medicine 2024;30:1406–15; [7]Lee YB et al. Presented at AAIC 2024; Sunday–224; [8]Larson PS et al. Neurosurgery 2012;70:95–103; [9]Richardson RM et al. Stereotact Funct Neurosurg 2011;89:141–51; [10]Otsu N. IEEE Trans Syst Man Cybern. 1979;9:62–66.

ABBREVIATIONS: **AAV9:** adeno-associated virus 9; **CED:** convection-enhanced delivery; **Cm^3:** cubic centimeters; **F:** female; **FTD:** frontotemporal dementia; **FTD-*GRN*:** frontotemporal dementia with progranulin deficiency; **GRN:** gene encoding progranulin; **M:** male; **MR:** magnetic resonance; **N.A:** not applicable; **SD:** standard deviation; **Vd:** volume of distribution; **Vi:** volume of infusion.

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