



# 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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# Disclosures

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- RRL: Employee of The Ohio State University Wexner Medical Center, consultant to AviadoBio
- MR: Employee of ClearPoint Neuro
- MZ: Interventional Neurotherapy Center, Site Neurosurgical Investigator
- JBE: Employee of The Ohio State University Wexner Medical Center, Site Neurosurgical Investigator
- **DLC: Employee of AviadoBio**

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# Objective

To define the properties of magnetic resonance imaging (MRI) guided **intrathalamic (ITM)** convection enhanced delivery (CED) of gene therapy 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).<sup>1</sup>

<sup>1</sup>ClinicalTrials.gov. ASPIRE-FTD. Available at: <https://clinicaltrials.gov/study/NCT06064890> [Accessed May 2025].

# Background

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- For neurodegenerative and neurodevelopmental disorders, indirect gene therapy delivery methods are limited by the **blood brain barrier**, **lack of target specificity**, and/or **immune response/exposure**<sup>1,2</sup>
- **Intraparenchymal CED** overcomes these obstacles, and the use of **real-time MRI imaging** allows for the **precise monitoring of vector distribution** during target infusions<sup>3</sup>
- **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<sup>4,5</sup>
- This study uses intrathalamic convective delivery of **AVB-101**, a recombinant **AAV9 vector** expressing the human gene coding for **progranulin** as **gene replacement** therapy to treat patients with FTD-GRN
- Large animal studies in 58 sheep and non-human primates demonstrated ITM administration was well-tolerated and effective

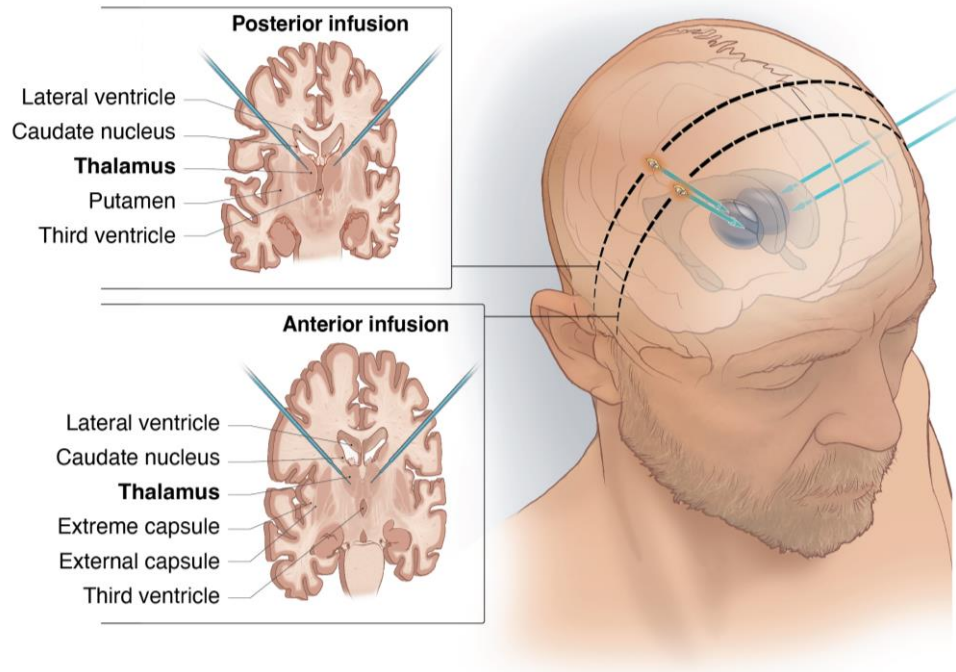
**This investigation reports the first surgical, imaging, and clinical findings associated with MR-guided convective intrathalamic gene therapy delivery in patients with FTD-GRN**

<sup>1</sup>Puhl DL et al. Brain Res Bull 2019;150:216–30; <sup>2</sup>Salegio EA et al. Front Mol Neurosci 2023; doi:10.3389/fnmol.2023.1248271; <sup>3</sup>Richardson RM et al. J Neurol Neurosurg Psychiatry 2020;91:1210–8; <sup>4</sup>Greaves CV and Rohrer JD. J Neurol 2019;266:2075–86; <sup>5</sup>Sevigny J et al. Nature medicine 2024;30:1406–15

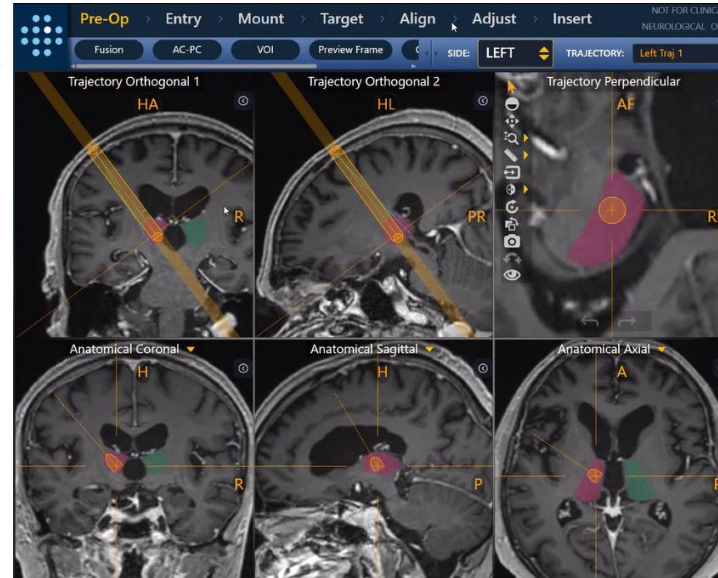


# Methods

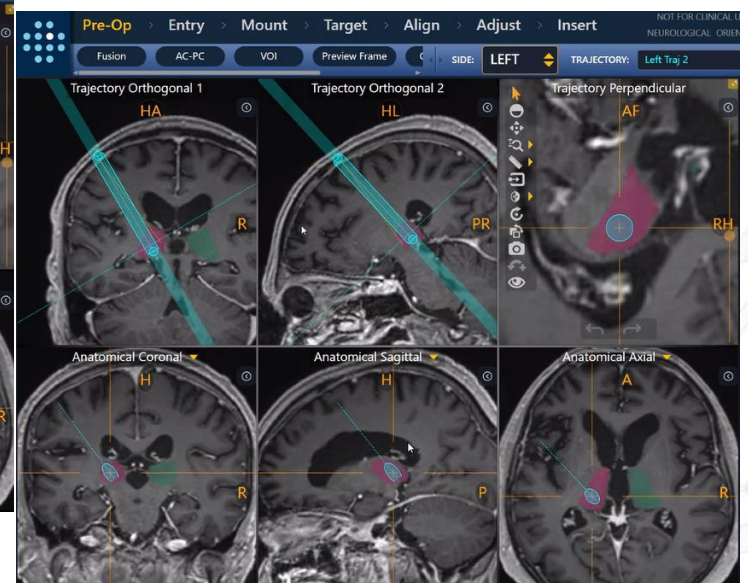
- Adult **FTD-GRN** patients were enrolled into the multi-center ASPIRE-FTD study
- **Surgical feasibility and planned trajectories** were assessed by the operating neurosurgeon in conjunction with an expert neurosurgical committee
- The planned **frontal approach to the thalamus** shown in the schematic on the left aligns with **preoperative plans** on the right



Left Anterior

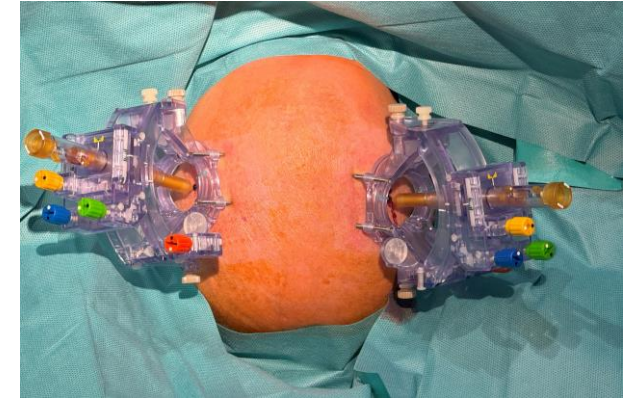


Left Posterior

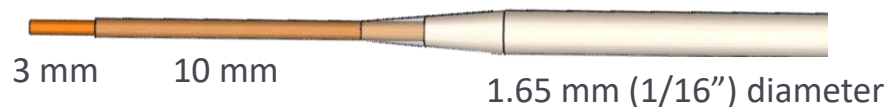


# Methods

- Patients underwent **AVB-101 administration** under general anesthesia in an MRI-OR facility
- AVB-101 was stereotactically administered using the ClearPoint Navigation System as **two pairs of simultaneously delivered bilateral infusions**
- Following **percutaneous frame** placement and alignment to planned trajectory, a small skin incision and a twist drill burr hole (3.4 or 4.5 mm) is created
- The **stepped cannula** is advanced at 2–4 mm increments, starting 2–4 mm within the rostral portion of the thalamus<sup>1,2</sup>



## ClearPoint Smartflow™ Neuroventricular Cannula



<sup>1</sup>Larson PS et al. Neurosurgery 2012;70:95–103; <sup>2</sup>Richardson RM et al. Stereotact Funct Neurosurg 2011;89:141–51.

# Methods

- Each infusion was followed in **real-time** via repeated **T1-weighted MRI** sequences to **monitor infusate distribution**
- **Infusate shaping** was performed by modulating infusion rates at various cannula depths
- Analysis of **post-infusion MR-images** using the Otsu method<sup>1</sup> provided an indication of target coverage achieved
  - **Volume of distribution (Vd)**
  - **Percentage of thalamus covered**
  - **Percentage of distribution within the thalamus**



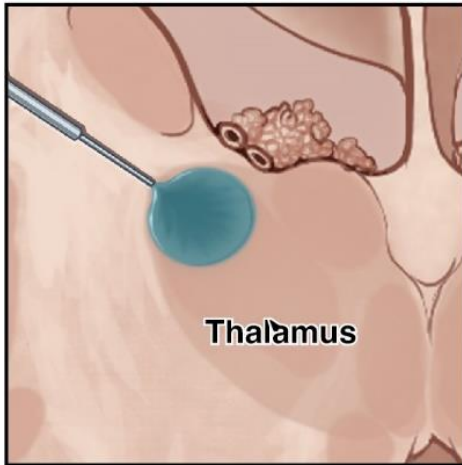
# Results: Baseline patient characteristics/infusion parameters

- **Three consecutive patients** (mean age  $53.0 \pm 18.2$  years) underwent a total of **12 thalamic infusions** with 6–12 months follow-up (mean  $9.0 \pm 3.0$  months) to date
- **Maximal infusion rate** was **10  $\mu\text{L}/\text{min}$**  in the 1<sup>st</sup> patient and **15  $\mu\text{L}/\text{min}$**  in the next two patients
- Baseline **segmented thalamic volumes**\* ranged from 4.8 to 8.3  $\text{cm}^3$

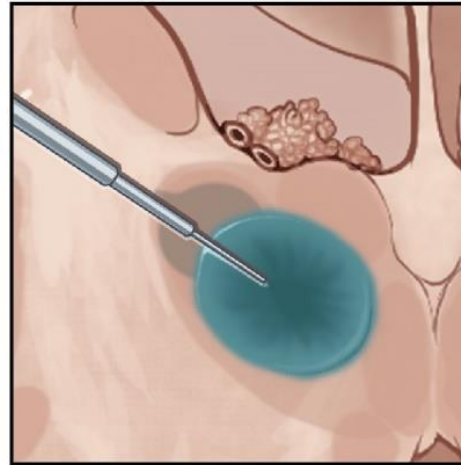
| Patient number          | Follow-up (months) | Age (years)  | Sex | Maximal infusion rate ( $\mu\text{L}/\text{min}$ ) | Right thalamic volume* ( $\text{cm}^3$ ) | Left thalamic volume* ( $\text{cm}^3$ ) |
|-------------------------|--------------------|--------------|-----|--|--|---|
| 1                       | 12                 | 65           | M   | 10   | 5.4                                      | 4.8                                     |
| 2                       | 9                  | 62           | F   | 15   | 5.5                                      | 6.2                                     |
| 3                       | 6                  | 32           | M   | 15   | 8.1                                      | 8.3                                     |
| Mean ( $\pm\text{SD}$ ) | $9.0\pm 3.0$       | $53\pm 18.2$ | N.A | $13.3\pm 2.9$                                      | $6.3\pm 1.5$                             | $6.4\pm 1.7$                            |

# Results: Shaping the AVB-101 infusion

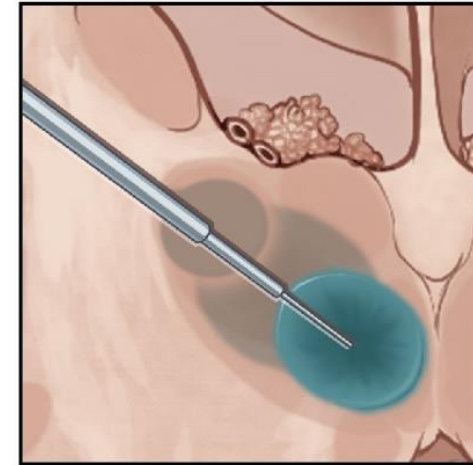
- **Successful infusate shaping** was performed by **modulating infusion rates and cannula depth** to conform to narrowing thalamic anatomy
- Lower infusion rates create more **spherical** perfusion; higher rates create more **cylindrical** perfusion



Initial position  
**Lower** infusion rate  
**Spherical** perfusion  
pattern



Cannulae advanced  
**Moderate** infusion rate  
**Cylindrical** perfusion  
pattern

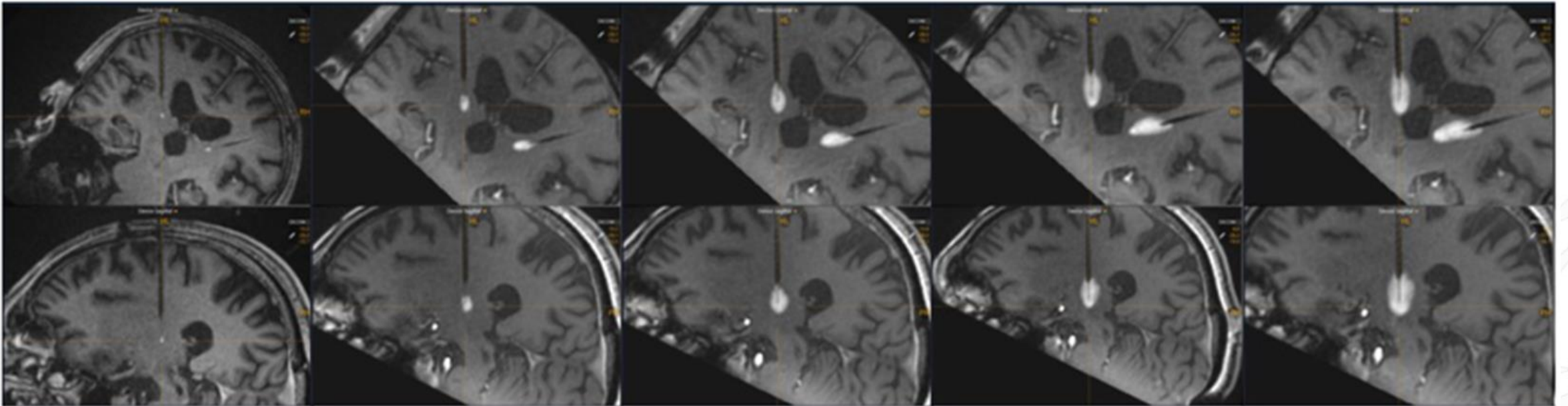


Final position  
**Higher** infusion rate  
**Cylindrical** perfusion  
pattern



# Results: Real-time T1-weighted MRI during infusion

- Infusion monitoring is accomplished using **diluted gadolinium (Prohance<sup>®</sup>, 1mM) tracer** mixed into the investigational product; prior non-clinical studies have established that gadolinium visualization correlates with AAV biodistribution
- Selected images below in two planes orthogonal to the left anterior thalamic cannula demonstrates **progressive filling of the thalamus** with increasing infusate volume



Note: The contralateral (right) infusion can also be visualized in the near-coronal plane shown in the top row.



## Results: Infusion coverage parameters

- **Mean thalamic coverage** was **39.1%** (range: 28.7–47.6%)
- The ratio of volume of distribution to volume of infusion (**Vd:Vi**) was **consistent across all thalamic infusions** for all three patients with **mean Vd:Vi ratio of 2.3**

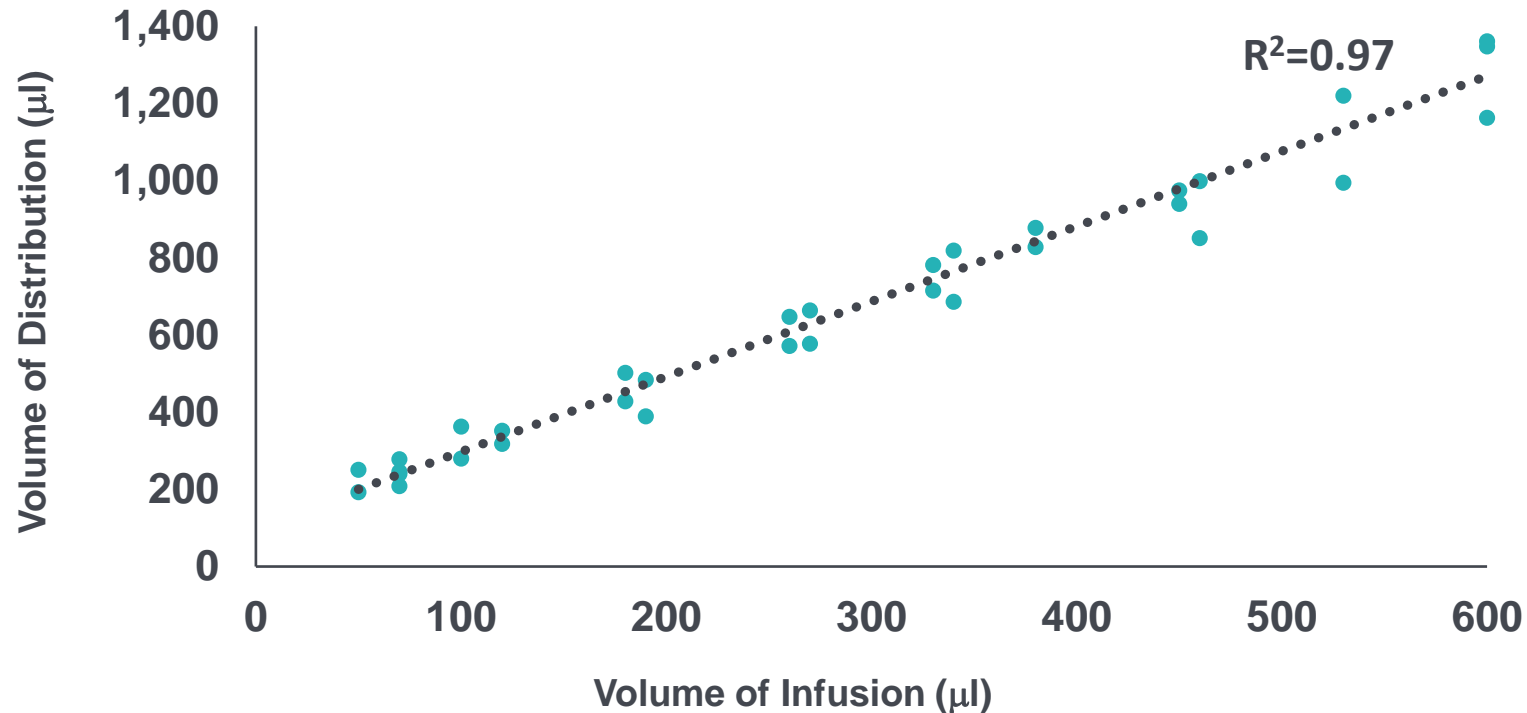
| Patient number    | Right Thalamus                            |                |                                    | Left thalamus                             |                |                                    |
|-------------------|---|----------------|------------------------------------|---|----------------|------------------------------------|
|                   | Volume of Distribution (cm <sup>3</sup> ) | Vd:Vi ratio*   | Thalamic coverage (%) <sup>§</sup> | Volume of Distribution (cm <sup>3</sup> ) | Vd:Vi ratio*   | Thalamic coverage (%) <sup>§</sup> |
| 1                 | 3.2                                       | 2.5            | 43.2                               | 3.0                                       | 2.3            | 47.6                               |
| 2                 | 2.7                                       | 2.2            | 42.8                               | 2.9                                       | 2.4            | 41.3                               |
| 3                 | 2.4                                       | 2.2            | 28.7                               | 2.7                                       | 2.3            | 31.1                               |
| <b>Mean (±SD)</b> | <b>2.8±0.6</b>                            | <b>2.3±0.2</b> | <b>38.2±8.0</b>                    | <b>2.9±0.2</b>                            | <b>2.3±0.1</b> | <b>40.0±8.0</b>                    |

\*Mean Vd to Vi ratio of anterior and posterior infusions from corresponding thalamus; <sup>§</sup>Percent of the total volume of thalamus perfused (including anterior and posterior infusions); <sup>§§</sup>Percent of the total perfusion contained with thalamus. Cm<sup>3</sup>: cubic centimeters; F:female; M: male; N.A: not applicable; SD: standard deviation; Vd: distribution volume, Vi: volume of infusion.



# Results: Consistency of Vd:Vi during individual infusion

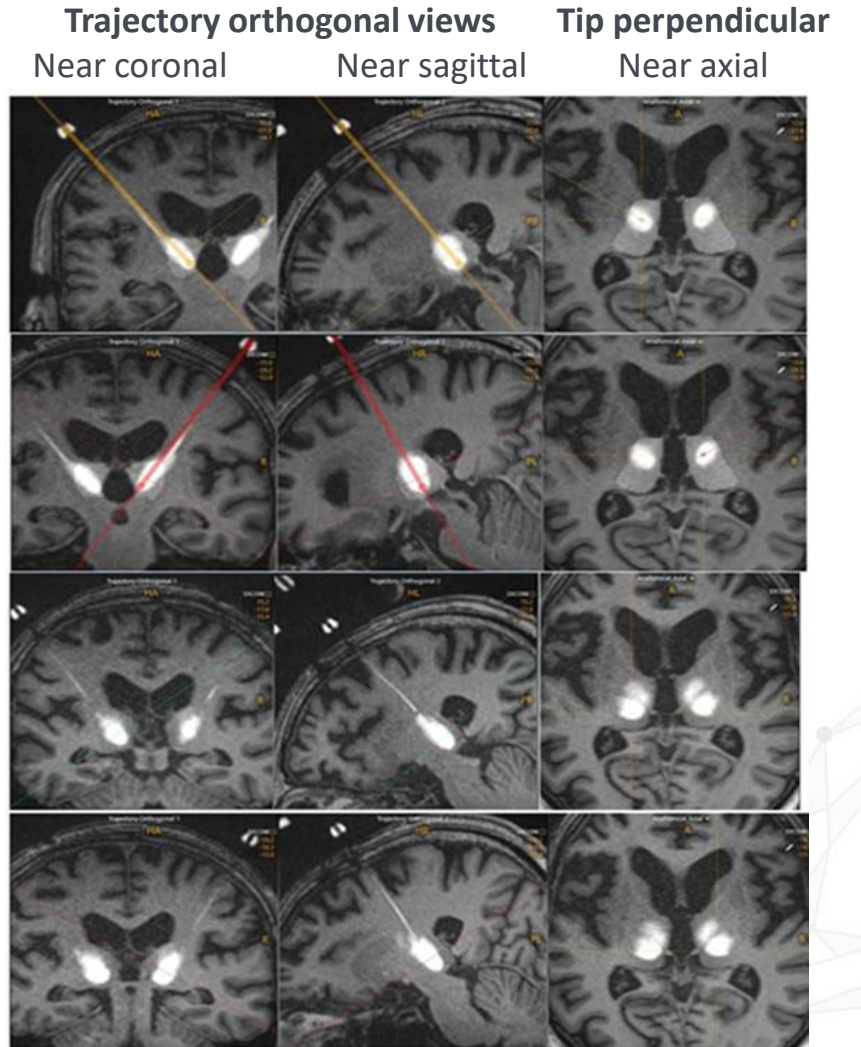
- Real-time imaging also demonstrated a **direct correlation between increasing infusion and distribution volume during** an individual infusion consistent with the overall Vd:Vi ratio
- The high correlation reflects **consistent ratio of infused volume to distribution during** each infusion
- The consistency of Vd:Vi permits **modeling** of different volumes to match desired thalamic coverage



# Results: Imaging after anterior/posterior infusions

- **Perivascular leakage and backflow** along the cannula was **not seen** during infusions.
- As a result, **78.6–95.1%** of the perfused area was contained **within the thalamus**
- 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

| Patient number    | Right thalamus                   | Left thalamus                    |
|-------------------|----------------------------------|----------------------------------|
|                   | Distribution within thalamus (%) | Distribution within thalamus (%) |
| 1                 | 78.6                             | 85.0                             |
| 2                 | 88.0                             | 88.1                             |
| 3                 | 88.2                             | 95.1                             |
| <b>Mean (±SD)</b> | <b>84.9±6.0</b>                  | <b>89.4±5.0</b>                  |



# Conclusions

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- The first-in-human data from the ongoing ASPIRE-FTD study demonstrated **successful and highly consistent intrathalamic delivery of AVB-101** in FTD-*GRN* patients with no significant perivascular loss or leakback along the cannula
- **No serious procedure or product-related adverse events were reported** during the follow-up period of 6-12 months
- MRI-guided convection enhanced delivery with real-time monitoring **allows shaping of vector distribution to maximize coverage of key targeted thalamic nuclei** by varying infusion rate and cannula position
- **Predictability of Vd:Vi throughout infusions** allows for potential scaling of infused volume to achieve desired coverage



We would like to thank the patients and their caregivers in addition to all the investigators and their teams who contributed to this study



# THANK YOU FOR YOUR TIME



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