ASPIRE-FTD: A Phase 1/2 Clinical Trial to Evaluate AVB-101 in FTD with *GRN* mutations (FTD-GRN)

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OBJECTIVE

To describe the design of ASPIRE-FTD, a Phase 1/2, open-label, ascending dose trial to evaluate safety and preliminary efficacy of AVB-101 in FTD-GRN.

BACKGROUND

- Frontotemporal dementia (FTD) is characterized by a heterogeneous group of symptoms, including uncharacteristic behaviors, changes in personality, progressive decline in language and loss of executive function and cognitive abilities.[1–3]
- It is an important cause of dementia in people under the age of 65.[2,4] The average survival reported for participants with FTD is between 3–13 years from diagnosis.[5,6]
- Currently there are no disease-modifying treatments.[5–7]
- Heterozygous loss-of-function mutations in the granulin (*GRN*) gene encoding the lysosomal protein progranulin (PGRN) account for 5–10% of all FTD cases.[8]
- AVB-101 is an adeno-associated virus serotype 9 (AAV9)-based gene therapy designed to deliver a functional copy of *GRN* to cortical neurons, restoring PGRN to physiological levels and potentially preventing disease progression.[9]
- The blood-brain barrier (BBB) poses significant challenges for gene therapy delivery in central nervous system conditions, like FTD.[10] To overcome this, AVB-101 is directly delivered to the thalamus, bypassing the BBB, via minimally-invasive stereotactic neurosurgery under magnetic resonance imaging (MRI)-guidance (**Figure 1**).[9]
- The thalamus has extensive connections to other brain regions, enabling widespread cortical distribution of AVB-101, including to the frontal and temporal lobes, which are critically affected in FTD (**Figure 1**).[11,12]
- Preclinical studies have shown that intrathalamically-delivered AVB-101 enables widespread cortical PGRN expression at doses lower than typically required via intrathecal delivery, and with minimal systemic exposure.[9,13]

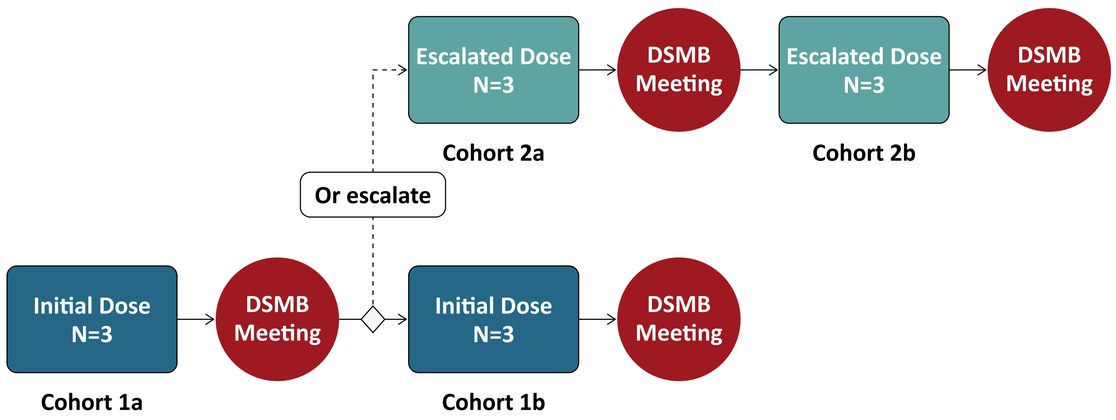
Table 1: Study population

Key inclusion criteria	Key exclusion criteria
30–75 years of age	Severe dementia, defined as CDR + NACC FTLD global score of 3.0
Carrier of a pathogenic *GRN* mutation	Any concurrent disease that may cause cognitive impairment unrelated to mutations in the *GRN* gene
FTD as evidenced by CDR + NACC FTLD global score of 0.5, 1.0, or 2.0	Clinically significant abnormality on MRI considered to be a contraindication to intrathalamic infusion
Presence of ≥1 of the criteria for diagnosis of possible bvFTD or PPA	Surgically significant pattern of brain atrophy on MRI that interferes with planned neurosurgical trajectory
Meets protocol-defined minimum thalamic volume on each side on Screening MRI	Previous treatment with any gene or cell therapy

CLINICAL TRIAL DESIGN

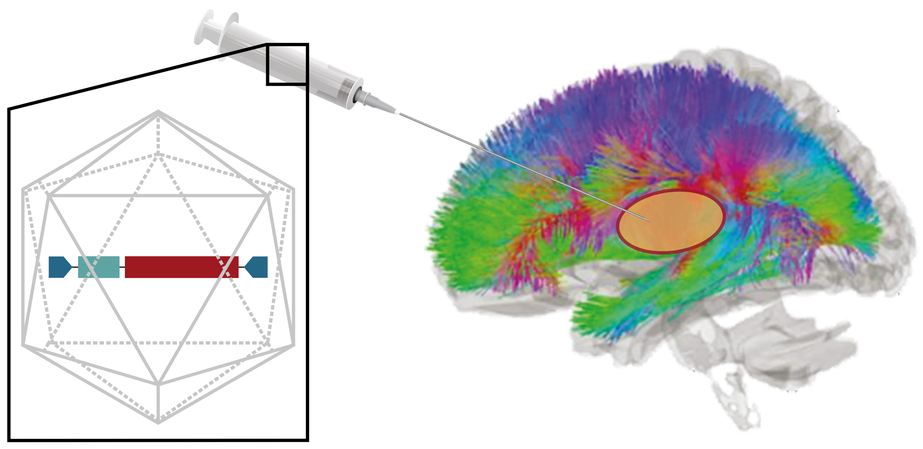
- ASPIRE-FTD is a first-in-human, Phase 1/2, open-label, ascending dose trial to evaluate the safety and preliminary efficacy of AVB-101 in participants with early stage, symptomatic FTD-GRN over 5 years.
- The study population includes participants with FTD with a pathogenic *GRN* mutation. Key study inclusion/exclusion criteria are detailed in **Table 1**.
- The study comprises a Screening and Baseline period of up to 12 weeks, a surgery visit for one-time dosing of AVB-101, and a total Follow-up period of up to 5 years (**Figure 2**).
- Screening/Baseline and Follow-up visits take place at neurology sites, while the surgery visit takes place at designated neurosurgical centers with expertise in stereotaxic neurosurgical delivery of gene therapies.
- 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.
- Six to nine participants will be dosed. The initial dose, intended to be therapeutic, will be administered in Cohort 1a. The escalated dose is planned and will be administered based upon the accumulated review of data with the Data Safety and Monitoring Board (DSMB; **Figure 3**).
- Study objectives and endpoints are detailed in **Table 2**.

Figure 3: ASPIRE-FTD: an open-label Phase 1/2 trial to explore the safety and efficacy of AVB-101 in participants with FTD-GRN



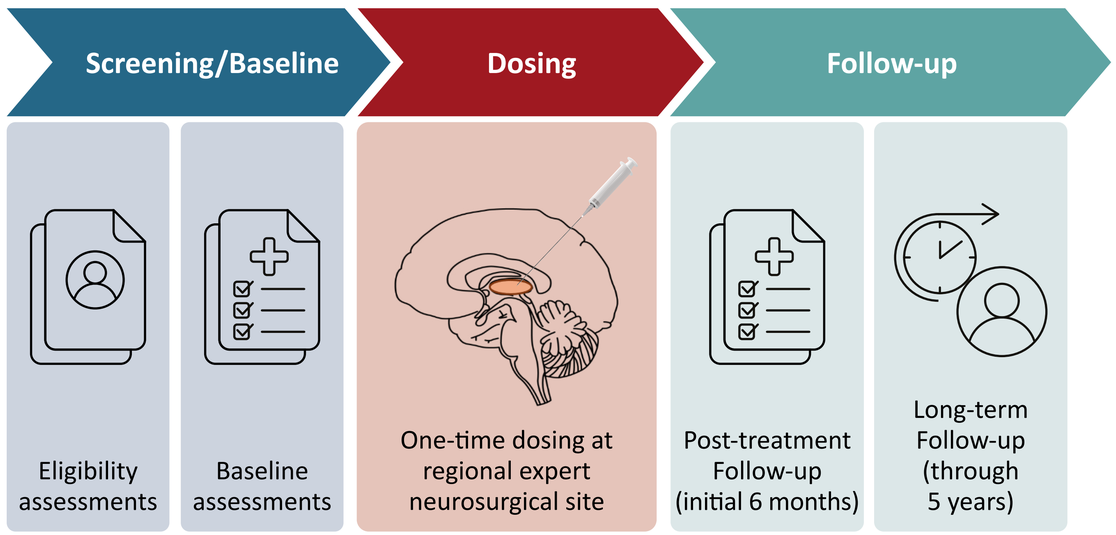
Six to nine participants will be enrolled sequentially. Each cohort will consist of 3 participants receiving a specified dose. Once the last participant in a cohort has completed ≥12 weeks of post-treatment follow-up, the DSMB (red) will decide whether to expand the cohort at the same dose (cohort 1b, dark blue) escalate or de-escalate the dose (cohort 2a, light blue), pause enrolment, or stop the study.

Figure 1: Exploiting thalamocortical neural networks for targeted cortical PGRN delivery



Schematic illustrating intrathalamic delivery of AVB-101, superimposed upon a human brain structural connectome derived from diffusion MRI data.[13] Delivery of AVB-101 to the thalamus (represented by orange oval), a key hub for connectivity in the brain, 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 will take place at an expert neurosurgical center. This will be followed by a 6-month post-treatment Follow-up period and a long-term Follow-up (through 5 years), conducted at the trial site.

Table 2: Key objectives and endpoints

Primary objective	Endpoints
Safety and tolerability	Over a 26-week initial and 5-year total Follow-up period, measure: • AEs, SAEs, laboratory tests • Vital signs, ECG, physical and neurological examinations • MMSE • MRI
Preliminary clinical and biomarker measures of efficacy	Over a 26-week initial and 5-year total Follow-up period, measure change from Baseline in: • PGRN protein and NfL levels in CSF and blood • CDR + NACC FTLD-SB score • CGI-C, PGI-C, and CaGI-C
Further exploration of efficacy	Over a 5-year Follow-up period, measure the change from Baseline in: • Exploratory biomarkers of inflammation, neurodegeneration and lysosomal function • Brain volumes on MRI • Cognitive measures

CURRENT STATUS

- ASPIRE-FTD (NCT06064890) is actively recruiting in Poland, Spain, the Netherlands and the USA, with additional countries/sites planned.
- Experience and preliminary data from the first dosed participants are discussed in Poster P049.

CONCLUSIONS

- **ASPIRE-FTD is designed to evaluate the optimal dose, safety, tolerability and preliminary efficacy of AVB-101 in participants with FTD-GRN. Results of this trial are expected to inform future clinical development.**

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ABBREVIATIONS: **AAV9:** adeno-associated virus 9; **AE:** adverse event; **BBB:** blood-brain barrier; **bvFTD:** behavioral variant frontotemporal dementia; **CaGI:** critical assessment of genome interpretation; **CDR:** clinical dementia rating; **CGI-C:** clinical global impression of change; **CSF:** cerebrospinal fluid; **DSMB:** data safety and monitoring board; **ECG:** electrocardiogram; **FTD:** frontotemporal dementia; **FTLD:** frontotemporal lobar degeneration; ***GRN*:** granulin; **MMSE:** mini mental state examination; **MRI:** magnetic resonance imaging; **NACC:** National Alzheimer's Coordinating Center; **NfL:** neurofilament light chain; **PGI-C:** patient's global impression of change; **PGRN:** progranulin; **PPA:** primary progressive aphasia; **SAE:** serious adverse event; **SB:** sum of boxes.

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