# A Phase 1/2 Open-Label, Ascending Dose, Multicenter Study to Evaluate the Safety and Preliminary Efficacy of AVB-101 Administered by Bilateral Intrathalamic Infusion in Subjects With Frontotemporal Dementia With Progranulin Mutations (FTD-GRN)

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Primary Objectiveo evaluate the safety and tolerability of a one-time, intrathalamic administration of AVB-101 in subjects with FTD-GRN.Secondary Objectiveo To evaluate the preliminary clinical and biomarker measures of efficacy of a one-time,…

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|---|---|
| **Ethical review** | Not approved |
| **Status** | Will not start |
| **Health condition type** | Congenital and hereditary disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON53802

**Source**
ToetsingOnline

**Brief title**
AVB-PGRN-001

### Condition

- Congenital and hereditary disorders NEC
- Structural brain disorders

- Dementia and amnestic conditions

**Synonym**
dementia, frontotemporal dementia

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** AviadoBio Ltd
**Source(s) of monetary or material Support:** Aviado Bio Ltd.

## Intervention

**Keyword:** Dementia, Frontotemporal Dementia, Progranulin Mutation

## Outcome measures

### Primary outcome

Over a 26-week initial and 5-year total follow-up period:

o Number and incidence of AEs, SAEs, and clinically meaningful laboratory test abnormalities;

o Change from baseline in vital signs, ECG parameters, and physical and neurological examinations;

o Change from baseline in the MMSE;

o Change from baseline in biochemistry and hematology safety laboratory tests;

o Time to achieve clearance of vector genomes in plasma and semen (males only);

o Incidence of treatment-emergent suicidal ideation or behavior as measured on the C-SSRS; and

o Change from baseline in MRI results including edema, inflammation, pre-symptomatic/symptomatic hemorrhage, and other structural changes.

### Secondary outcome

Secondary Endpoints

Over a 26-week initial and 5-year total follow-up period:

o Change from baseline in PGRN protein levels in CSF and blood.

Over a 52-week initial and 5-year total follow-up period:

o Change from baseline in NfL levels in CSF and blood.

Over a 5-year follow-up period:

o Change from baseline in CDR+NACC FTLD-SB score; and

o Change in CGI-C, PGI-C, and CaGI-C.

Exploratory Endpoints

Over a 5-year follow-up period:

o Change from baseline in GFAP levels in CSF and blood;

o Change from baseline in GENFI-Cog composite score;

o Change from baseline in brain volumes including whole brain,

white matter, grey matter, ventricles, thalamus, and hippocampus; cortical

thickness; and WM integrity (T1/T2/FLAIR MRI);

o Change from baseline in inflammatory and lysosomal markers in CSF; and

o Change in the Winterlight Speech Assessment score.

o Change from baseline in AAV9 immunogenicity in blood (AAV9 ELISPOT and

anti-AAV9 antibody) and CSF (anti-AAV9 antibody); and

o Change from baseline in PGRN immunogenicity in blood (hPGRN ELISPOT and

anti-hPGRN antibody) and CSF (anti-PGRN antibody).

## Study description

## Background summary

AVB-101 is a recombinant adeno-associated virus serotype 9 (AAV9) vector containing DNA encoding the human granulin (GRN) gene, leading to expression of progranulin (PGRN) under control of a neuronal specific promoter (human synapsin), designed to restore physiological levels of PGRN in haplo-insufficient individuals. A comprehensive review of AVB-101 is contained in the Investigator*s Brochure (IB).

The available nonclinical data suggest that AVB-101 has an acceptable safety profile and has the potential to improve symptoms
and prolong survival in subjects with frontotemporal dementia (FTD) with GRN mutations, and in pre-symptomatic carriers of GRN mutation at high risk of phenoconversion.
AVB-101 has demonstrated efficacy in an established disease model (PGRN-deficient knock out mice). Biodistribution studies in large animals (sheep and non-human primates [NHPs]) show that AVB-101 administered as a one-time, stereotactic, convection enhanced delivery (CED) to the thalamus results in robust, dose-dependent expression of PGRN protein to cerebrospinal fluid
(CSF), and broad distribution to brain tissue including relevant cortical regions affected in FTD pathology. In the Good Laboratory Practice (GLP) toxicology study, administration of both high- and low-dose AVB-101 was shown to be tolerated and without overt adverse effects in Cynomolgus monkeys for up to 3 months. The results of the nonclinical program to date are detailed in the IB.

## Study objective

Primary Objective
o evaluate the safety and tolerability of a one-time, intrathalamic administration of AVB-101 in subjects with FTD-GRN.

Secondary Objective
o To evaluate the preliminary clinical and biomarker measures of efficacy of a one-time, bilateral, intrathalamic administration of AVB-101 in subjects with FTD-GRN.

Exploratory Objectives
o To further explore the preliminary efficacy of a one-time, bilateral, intrathalamic administration of AVB-101 in subjects with FTD-GRN.
o To evaluate the effect on immunogenicity of a one-time, bilateral, intrathalamic administration of AVB-101 in subjects with FTD-GRN

## Study design

This is a Phase 1/2 open-label, ascending dose study to evaluate the safety and preliminary efficacy of adeno-associated virus serotype 9 delivered PGRN to FTD-GRN subjects aged 30 to 75 years. Subjects will receive a one-time, bilateral, intrathalamic administration of AVB-101 with the primary analysis occurring at 26 weeks post-treatment, interim analyses every 6 to 12 months thereafter, and final analysis after 5 years. All subjects receiving a dose of AVB-101 will be followed for 5 years following AVB-101 administration according to the current guidelines for recommended follow-up for adeno-associated virus gene therapies.
Approximately 10 to 15 symptomatic subjects and optionally up to 9 pre-symptomatic subjects will be enrolled across approximately 20 sites from the United Kingdom, Europe, and the United States. The study drug (AVB-101) will be administered at specialized neurosurgery sites with expertise in stereotaxic neurosurgical delivery of gene therapies under the coordination of a central Neurosurgical Committee. When possible, subjects will be dosed in their country of domicile; where transfer to a regional center of excellence is required, subjects will be accompanied by translators as necessary. When this is not possible, subjects will be transferred to a neurosurgical site within another country. This will be communicated to the neurology sites and subjects during consent and will be managed with the support of a subject concierge specialist service including translation services, as appropriate.
The maximum duration of the study is approximately 63 months per subject. This comprises of ~12 weeks of a screening period, treatment period, and then 60 months of follow-up period. A minimum of 2 dose levels of AVB-101 are planned for evaluation over 2 cohorts of symptomatic subjects in this study. If required, an additional cohort may be added to further explore the optimal dose. The starting dose will be 8 x 10^11 vg/brain (4 x 10^11 vg/thalamus), which is anticipated to be a potentially efficacious dose based on nonclinical data. Actual doses at subsequent dose levels will be based on review of cumulative safety data and a Data and Safety Monitoring Board (DSMB) recommendation, against the planned 3-fold escalation step between dose levels. Dose levels tested in this study will not exceed the maximum planned dose level of 7.2 x 10^12 vg/brain, which is the highest tested dose in the non-human primate Good Laboratory Practice toxicology study at which no clinical findings were observed.

**Intervention**

Eligible subjects will be administered a one-time dose of AVB-101 at ambient temperature by bilateral, intrathalamic infusion on Study Day 0 (Treatment Visit). AVB-101 will be mixed with a gadolinium-based contrast agent during pharmacy preparation to facilitate direct visualization of the delivery on intraoperative MRI. The targeting for the thalamic infusion will be overseen by a Neurosurgical Committee and use standardized stereotactic techniques for MRI-compatible catheter placement specified in the Neurosurgery Manual. A target volume of 2500 ±50 µL per hemisphere will be administered under real-time MRI guidance at a planned maximum flow rate up to maximum of 15

µl/min via convection enhanced delivery in accordance with the procedure set out in the Neurosurgical Administration Manual. It will be up to the neurosurgeon to determine if discontinuation of the administration prior to reaching target dose is suggested based upon the intraoperative situation (eg, complete filling of the target structure, excessive perivascular loss). The total procedure time under general anesthesia is estimated to be 8 to 10 hours.

**Study burden and risks**

The potential risks of AVB-101 treatment are based on nonclinical data with AVB-101 and/or known potential risks of other AAV9 gene therapies. The IB contains detailed information on the potential risks that may be associated with AVB-101 and its administation procedure. Based on the existing nonclinical AVB-101 data and other human clinical studies using an AAV9 vector, the risks associated with AVB-101 for intrathalamic infusion are considered minimal.
This is a first-in-human study of AVB-101, which is designed to generate data that will inform further development of AVB-101 as a therapy to slow or stop the progression of FTD in subjects with GRN mutations as well as potentially prevent phenoconversion in pre-symptomatic carriers at high risk of developing clinical FTD. The study population includes subjects with symptomatic disease, as well as an optional cohort of pre-symptomatic subjects at risk of phenoconversion based on elevated risk biomarker, NfL. This is reflective of both the likely optimal anticipated benefit:risk for the given therapeutic approach, as well as practicalities and motivation for study participation as expressed by subjects/carers. Subjects with advanced dementia are excluded because it is not expected that such advanced pathology can be rescued and therefore the benefit:risk is questionable, and additionally it would be impossible from a practical perspective for such subjects to comply with study requirements.
As AVB-101 is an investigational medicine, it is possible that unforeseen or unanticipated drug reactions and toxicities may occur. The current nonclinical data available for AVB-101 does not yet permit comprehensive assessment of the benefit:risk profile. However, this protocol is designed to mitigate risks to subjects through a detailed plan for careful safety monitoring, systematic review of adverse events (AEs) and serious AEs (SAEs), and active pharmacovigilance review to assess for safety signals or trends. The identified risks are therefore justified by the anticipated benefits that may be afforded to study subjects.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Subjects will be eligible to be included in the study if all of the following criteria apply:
1. Are male or female, 30 to 75 years of age, inclusive, at Screening;
2. Are carriers of a pathogenic GRN mutation as confirmed by a Sponsor approved genetic test;
3. Have EITHER symptomatic FTD OR pre-symptomatic carrier of a pathogenic GRN mutation at risk of conversion based on plasma NfL >20 pg/mL;
4. If symptomatic, presence of 1 or more of the criteria for diagnosis of possible behavioral variant FTD or PPA;
5. Have an identified, informed study partner able to support the subject for the duration of the study;
6. For women of childbearing potential, must have a negative serum pregnancy test at Screening, a negative urine dipstick, and not be breastfeeding within 2 weeks prior to treatment;
7. For sexually active subjects, must agree to use a highly effective barrier method of contraception until at least 3 consecutive negative blood (or semen for male subjects, where possible) vector shedding samples are collected at least 1 week apart;

8. Able and willing to comply with all procedures and the study visit schedule as outlined in the protocol; and
9. The subject and/or legally authorized representative is able and willing to give written informed consent prior to study participation. If a subject lacks the capacity to consent in the Investigator*s opinion, the subject*s assent should be obtained, if required in accordance with local laws, regulations, and customs, plus the written informed consent of a legal representative should be obtained. In countries where local laws, regulations, and customs do not permit subjects who lack capacity to consent to participate in this study, they will not be enrolled.

## Exclusion criteria

Subjects will be excluded from the study if any of the following criteria apply:
1. Have a classification of the mutation in the GRN gene as *not pathogenic,* *likely benign variant,* or *benign variant* in the Alzheimer*s Disease and Frontotemporal Dementia Mutation Database;
2. Have severe dementia, defined as Clinical Dementia Rating (CDR)+National Alzheimer*s Coordinating Center (NACC) frontotemporal lobar degeneration (FTLD) global score of 3.0, that precludes the ability to comply with study procedures and/or poses unacceptable safety
risk to the subject;
3. Have any concurrent disease that may cause cognitive impairment unrelated to mutations in the GRN gene, such as other causes of dementia, neurosyphilis, hydrocephalus, stroke, small vessel ischemic disease, uncontrolled hypothyroidism, or vitamin B12 deficiency;
4. Have a clinically significant abnormality on MRI at Screening considered to be a contraindication to intrathalamic infusion;
5. Have a surgically significant pattern of brain atrophy on MRI at Screening that interferes with planned neurosurgical trajectory;
6. Have had previous treatment with any gene or cell therapy;
7. Have had previous treatment with any investigational medicinal product within 60 days or 5 half-lives (whichever is longer) prior to study drug treatment;
8. Have had a concomitant disease, any clinically significant laboratory abnormality, or treatment which, in the opinion of the Investigator, may pose an unacceptable safety risk to the subject or interfere with study conduct or the subject's ability to comply with study procedures;
9. Have a malignancy within 5 years of Screening, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated;
10. Have any contraindications to MRI as per local guidelines;
11. Have any contraindications to gadolinium-based contrast agents per local guidelines;
12. Have any contraindications to general anesthesia for a period of up to 10

hours and/or cardiopulmonary disorders that would result in higher American Society of Anesthesiology risk classification;
13. Have any contraindications to lumbar puncture as per local guidelines;
14. Have been hospitalized for any major medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned procedure during the study;
15. Are using anticoagulants at Screening, or will have an anticipated need during the period of treatment. Antiplatelet therapies are acceptable concomitant medication if they can be stopped at least 48 hours prior to treatment;
16. Have a history of previous serious or recent Coronavirus Disease 2019 (COVID-19) as defined by (1) any history of hospitalization for severe illness at any time, (2) any history of significant respiratory symptoms at any time, or (3) any pre-symptomatic or mildly symptomatic
COVID-19 positivity within 12 weeks prior to planned treatment;
17. Have a positive drug screen for drugs of abuse;
18. Have a history of substance abuse disorder;
19. Have the presence of an implanted deep brain stimulation device, ventriculoperitoneal or other cerebrospinal fluid shunt, or other implanted device;
20. Have evidence of suicide risk, as assessed by the Columbia-Suicide Severity Rating Scale, defined as either a suicide attempt within 6 months prior to Screening or have a significant risk of suicide as judged by the Investigator; or
21. Have a known or suspected intolerance or hypersensitivity to the study drug or any of the stated ingredients.

# Study design

## Design

**Study type:** Interventional

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Will not start |
| Enrollment: | 3 |
| Type: | Anticipated |

# Ethics review

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|---|---|
| Approved WMO Date: | 18-11-2022 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Not approved Date: | 14-06-2023 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 03-01-2024 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2022-002568-62-NL |
| CCMO | NL82614.000.22 |