Intrathalamic Delivery of AVB-101 Rescues Pathology in Grn Null Mice and Achieves Widespread Cortical Expression in a Large Animal Model

Speaker: Youn Bok Lee (Co-founder & Head of Discovery)

Lee YB\textsuperscript{1,2}, Lee DY\textsuperscript{1,2}, Allison J\textsuperscript{1}, Kaliszewska A\textsuperscript{1}, Arias Del Castillo N\textsuperscript{1}, Zhang K\textsuperscript{1}, Bekele Y\textsuperscript{1,2}, Hosseini P\textsuperscript{1,2}, Joubert R\textsuperscript{1,2}, Walker Z\textsuperscript{1,2}, Furtado J\textsuperscript{1,2}, Gumus M\textsuperscript{1}, Fernandes A\textsuperscript{1,2}, Brock O\textsuperscript{1}, Shaw CE\textsuperscript{1,2}

\textsuperscript{1} United Kingdom Dementia Research Institute, Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 5 Cutcombe Road, London SE5 9RT, UK
\textsuperscript{2} AviadoBio Ltd, 86 Hatton Garden, Floor 5, London, United Kingdom, EC1N 8QQ
AviadoBio Focus: Enhanced Biodistribution From Precision Dosing

History: Formed on pioneering research by King’s College London and the UK Dementia Research Institute

Mission: Develop transformative gene therapies for neurodegenerative diseases

Method: Combining next-generation vector design with neuroanatomy-led delivery

Delivery: Precise dosing with extensive biodistribution in the brain and spinal cord

Platforms: Optimised for gene supplement and miRNA knockdown

Our lead programme uses AAV to deliver a progranulin transgene (AVB-101) to patients with frontotemporal dementia due to loss-of-function mutations in the GRN gene encoding progranulin (FTD-GRN)

Phase I/II trial to be initiated late 2022

AVV, adeno-associated virus; FTD, frontotemporal dementia; miRNA, microRNA.
Biodistribution is the Key Challenge for CNS Gene Therapies

Intrathalamic AAV delivery exploits afferent and efferent connections between the thalamus and cortex

Minimal amount of intrathalamic AAV achieves broad brain distribution

AAV, adeno-associated virus; CNS, central nervous system; MRI, magnetic resonance imaging.
FTD-GRN: A Clear Target for Gene Therapy

Significant Unmet Need

- ~30,000 patients in US and ~76,000 patients in Europe*
- Experience progressive decline in behaviour, personality, executive function and/or language, and death 6–12 years after initial symptoms of FTD1–7
- Burden is significant and costly with no disease-modifying therapies available8

Established Disease Biology

- Loss-of-function mutations in GRN gene are causative for FTD-GRN3
- Deficiency in PGRN increases microglial reactivity, accelerates neurodegeneration and TDP-43 accumulation9–12
- PGRN supplementation corrects pathological phenotype in rodent models13

Tractable Clinical Development

- Established natural history cohorts and registries14,15
- Rate of atrophy progression is measurable by MRI14
- NFL is a blood biomarker for neurodegeneration risk16
- Clinical endpoints available to support regulatory approval14,15,17

*US data is an estimate of cognitive syndromes of frontotemporal lobar degeneration. European data is an estimate of behavioural variant FTD in the EU27 of 2013, Norway, Iceland and Lichtenstein.

AVB-101: Gene Supplementation Therapy for FTD-GRN

AVB-101

**Tissue Specificity**
- AVB-101 utilises a neuronal-specific promoter to ensure transgene expression is restricted to neurones, minimising the risk of peripheral organ exposure observed with constitutive promoters (e.g., CB7, CMV).
- Secretion of PGRN permits local cross-correction of glial cells.

**Boosting Secretion**
- Codon-optimised human PGRN transgene.
- 5’ and 3’ enhancing elements that optimises splicing.
- Achieves supraphysiological levels in brain and CSF in rodents and large animals.

**Neurotropism**
- AAV9 serotype: neurotropic
- AAV9-based treatment has already been approved for SMA (ZOLGENSMA®).
- Proven manufacturability.
- Cassette size optimised.

**Designed with efficacy and safety in mind**

AAV9, adeno-associated virus serotype 9; CB7, chicken β-actin 7; CMV, cytomegalovirus; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; ITR, inverted terminal repeat; hPGRN, human progranulin; SMA, spinal muscular atrophy.

AVB-101 Substantially Reduces Pathology in Grn Knock-Out Mice

• Grn⁻/⁻ mice develop extensive lipofuscinosis and age-dependent neuroinflammation

Lipofuscinosis (SCMAS)

Visualisation and quantification of SCMAS (lipofuscinosis) in the thalamus of control and treated young Grn⁻/⁻ mice. Infused at 8 weeks, imaged at 20 weeks

Neuroinflammation (CD68)

Visualisation and quantification of prefonsal cortex CD68⁺ve microglia in control and treated old Grn⁻/⁻ mice. Infused at 40 weeks, imaged at 52 weeks

• Intrathalamic delivery of AVB-101 in young Grn⁻/⁻ mice (6 weeks) restored wild-type levels of lipofuscinosis (SCMAS) across all doses
• Intrathalamic delivery of AVB-101 in older Grn⁻/⁻ mice (28 weeks) reduced levels of microglial activation throughout the CNS
AVB-101 Sheep Study: Overview

**Thalamus:** Chosen as **centralised hub** connected to almost all cortical and sub-cortical regions.

**AAV9:** Capsid chosen as it is **neuronotropic** and facilitates anterograde and retrograde transport.

**Sheep:** Chosen as brain size is **twice that of a macaque**.

**Administration:** Convection-enhanced delivery catheter placed in thalamus under stereotactic guidance. AVB-101 +/- gadolinium infused, and animals sacrificed after four weeks in life.

**MRI** scans are used to define anatomy and select optimal trajectory and have shown **hPGRN** expression in cortical layers I–VI.
Robust Cortical hPGRN Expression Without Microglial Reactivity

PGRN detected in 60–75% of NeuN positive neurons in the sheep prefrontal cortex

*Isolectin binds to CD68 receptors and used as a marker of activated microglia.
CD, cluster of differentiation; hem, hemisphere; hPGRN, human progranulin; IBA1, ionized calcium binding adaptor molecule 1; PGRN, progranulin; NeuN, neuronal nuclear protein; vg, vector genome.
Dose-dependent Increase of hPGRN in Brain Reflected in CSF After Intrathalamic AVB-101

Normal to supraphysiologial levels of hPGRN achieved across the brain and CSF at very low vector doses
Negligible Levels of hPGRN in Sheep Serum Demonstrates CNS-Restricted Expression

Sheep Serum hPGRN

Serum hPGRN was undetectable before and four weeks after intrathalamic infusion of AVB-101

*Single outlier result likely due to contamination
**Intrathalamic vs. Intracisternal Magna Shows Intrathalamic Superiority**

**Adult WT sheep**

- **Intrathalamic** delivery achieved extensive neuronal expression throughout the cortex and subcortex including non-neuronal cells
- **Intracisternal magna** delivery results in negligible levels of hPGRN throughout the CNS in all intracisternal magna treated animals

**Minimal amount of intrathalamic** AAV administration achieves **broad brain distribution**

- AVV1, adeno-associated virus serotype 1; AVV9, adeno-associated virus serotype 9; CB7, chicken β-actin 7; CNS, central nervous system; hPGRN, human progranulin; ICM, intracisternal magna; IF, immunofluorescence; IHC, immunohistochemistry; ITM, intrathalamic; PGRN, progranulin; RNA, ribonucleic acid; vg, vector genome; WT, wild type.
Superior Vector Distribution Using Intrathalamic vs. Intracisternal Magna Delivery

Intrathalamic
AVB-101

Intracisternal Magna
AAV1-CB7-PGRN
AAV9-CB7-PGRN
AVB-101

AAV1, adeno-associated virus serotype 1; AAV9, adeno-associated virus serotype 9; CB7, chicken β-actin 7; CT, corticothalamic; L, left; PGRN, progranulin; PT, pyramidal tract; R, right; vg, vector genome
Intrathalamic Delivery Minimises AAV Liver Exposure and Shedding vs. Intracisternal Magna

AVB-101 vector was undetectable in liver biopsies following intrathalamic delivery but was detected following intracisternal magna delivery of three different AAV constructs.

Undetectable AAV liver levels confirm minimal vector shedding from CNS following intrathalamic delivery.
Summary

- AviadoBio is developing novel gene supplementation and silencing therapies for neurodegenerative disorders
- AVB-101 is designed to normalise cortical PGRN levels in patients with FTD due to GRN mutations while restricting PGRN expression to neurons and enhancing secretion to lower vg dose

AVB-101 in *Grn/-* mice suppressed neuronal lipofuscinosis and reactive microglia

AVB-101 in sheep was well tolerated, with minimal liver exposure and widespread cortical and subcortical biodistribution

AVB-101 delivered by intrathalamic infusion constitutes a novel and promising approach to address unmet medical need in FTD-GRN

Coming soon: GLP toxicology studies in nonhuman primates are ongoing and clinical trials are due to be initiated late 2022
Acknowledgements

UK Dementia Research Institute
King’s College London
Van Geest Foundation
My Name’5 Doddie Foundation
Neurochase
University of Bristol
University of Lincoln