Design of INFRONT-3: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AL001 in FTD-*GRN*

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Background

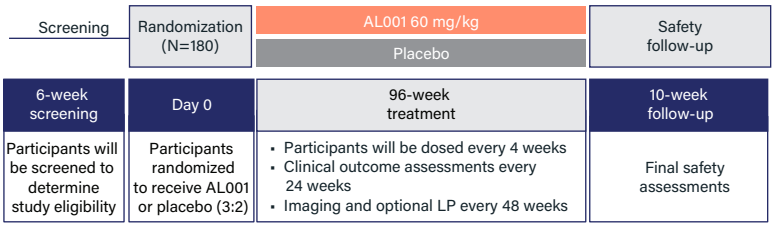
- Frontotemporal dementia (FTD) is a clinically and pathologically heterogeneous group of early-onset neurodegenerative disorders that imposes a severe social and economic burden on patients and caregivers[1,2]
- No disease-modifying treatments for FTD are currently approved by any regulatory authority
- Heterozygous loss-of-function (LOF) mutations in the progranulin gene (*GRN*), which result in progranulin (PGRN) haploinsufficiency, are a common cause of familial FTD[3-5]
- PGRN has neurotrophic and neuroimmunomodulatory effects, and growing evidence suggests it has an important role in lysosomal homeostasis[6-9]
- Sortilin is a receptor that binds PGRN and targets it for endocytosis and lysosomal degradation, reducing extracellular PGRN levels[10,11]; PGRN can enter cells and localize to the lysosome in a sortilin-independent manner via its interaction with prosaposin and its receptors mannose 6-phosphate receptor (M6PR) and the low density lipoprotein receptor-related protein 1 (LRP1)[12]
- Restoring PGRN levels by interfering with the sortilin–PGRN interaction may be an effective therapeutic strategy to treat FTD-*GRN*[13]
  - AL001 is a humanized monoclonal immunoglobulin G1 antibody that downregulates sortilin and blocks its interaction with PGRN
  - AL001 treatment slowed clinical progression compared with a matched control cohort of participants from the Genetic FTD Initiative (GENFI2) using the Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains Sum of Boxes (CDR® plus NACC FTLD-SB) scale in the INFRONT-2 phase 2 study of 12 patients with FTD-*GRN*[14]
  - Multiple disease-relevant biomarkers of lysosomal function, complement activation, and neuronal health trended toward normalization or remained stable[14]
  - AL001 was generally safe and well tolerated in FTD-*GRN* participants
- Here, we describe the design of the pivotal phase 3 trial to evaluate the efficacy and safety of AL001 compared with placebo in carriers of *GRN* mutations causative of FTD

Methods

Study design

- INFRONT-3 (NCT04374136) is a 96-week, global, multicenter, randomized, double-blind, placebo-controlled phase 3 trial to assess the efficacy and safety of AL001 60 mg/kg every 4 weeks (q4w) compared with placebo in participants who have heterozygous *GRN* mutations causative of FTD
- The primary objective is to evaluate the efficacy of AL001 in slowing disease progression as measured by change in the CDR® plus NACC FTLD-SB
- Approximately 180 participants in North America, Australia, and Europe will be randomized to receive 60 mg/kg AL001 or placebo in a 3:2 ratio (**Figure 1**)
- Randomization will be stratified into 4 groups: CDR® plus NACC FTLD-SB score ≤0.5, Global CDR® plus NACC FTLD score 0.5 (with a CDR® plus NACC FTLD-SB >0.5), Global CDR® plus NACC FTLD score 1, Global CDR® plus NACC FTLD score 2
- Participants who complete the 96-week blinded phase of the study will be invited to complete an optional 96-week, open-label extension to evaluate the long-term safety and tolerability of open-label AL001 60 mg/kg, q4w
- All participants will be asked to return for a safety follow-up visit 10 weeks after their last dose of study treatment

Figure 1. AL001-3 Study Design



LP, lumbar puncture.

Key inclusion criteria

- Participants (aged 25-85 years) must be a known carrier of a heterozygous LOF *GRN* mutation causative of FTD, with a global CDR® plus NACC FTLD score of 0 to 2, and have:
  - A CDR® plus NACC FTLD-SB score ≤0.5 and an elevated level of NfL (at-risk participants), or
  - A CDR® plus NACC FTLD-SB score of >0.5 and ≥1 of the 6 behavioral/cognitive symptoms required for a diagnosis of possible bvFTD[15] or a diagnosis of PPA[16] (symptomatic participants)
- Females must be nonpregnant and nonlactating, and either not a woman of childbearing potential (eg, surgically sterile, postmenopausal for ≥12 months), using a highly effective contraceptive method from screening through the follow-up period, or abstinent from heterosexual intercourse
- Men must agree to use acceptable contraception and not donate sperm from screening through the follow-up period
- Participants must have the availability of a study partner who has frequent contact (ie, ≥5 hours per week of in-person contact) with them, consents to study participation, and agrees to provide information at site visits
- All participants must provide written informed consent or assent

Key exclusion criteria

- Dementia due to a condition other than FTD
- Known mutation causative of neurodegenerative disorder(s) other than heterozygous LOF *GRN* mutations causative of FTD
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins
- Current uncontrolled hypertension, diabetes mellitus, or thyroid disease; clinically significant heart disease, liver disease, or kidney disease; history of cancer within the last 5 years except for basal cell/squamous cell carcinoma; history or evidence of clinically significant brain disease other than FTD
- Contraindication to magnetic resonance imaging (MRI) or inability to tolerate MRI
- Any experimental vaccine or gene therapy (SARS-CoV-2 vaccinations are allowed)
- Use of specific medications, including cannabinoids, benzodiazepines, tricyclic antidepressants, stimulants, passive immunotherapy, atypical or typical antipsychotics, anticoagulants, long-term opioids, or long-term barbiturates or hypnotics during predefined periods prior to first study treatment
- Use or anticipated use of systemic immunosuppressive therapy during the study; prednisone use (≤10 mg/day) or an equivalent corticosteroid is allowed under prespecified conditions
- Residence in a skilled nursing facility, convalescent home, or long-term care facility at screening; or requires continuous nursing care

Endpoints

Outcome assessments

- Clinical outcome assessments will be measured at baseline (screening), and every 24 weeks (ie, weeks 24, 48, 72, 96)
- Imaging assessments and optional lumbar puncture for cerebrospinal fluid (CSF) collection will be performed at baseline, week 48, and week 96
- All adverse events (AEs) and serious AEs will be recorded and reported throughout the study period, and a safety follow-up visit will occur 10 weeks after the last treatment visit
- Pharmacokinetic (PK), pharmacodynamic (PD), and anti-drug antibody (ADA) measurements will be made from blood samples (all participants) and PK/PD measurements from optional CSF samples

Primary endpoint

- CDR® plus NACC FTLD-SB

Secondary endpoints

- Clinical Global Impression (CGI)-Severity
- CGI-Improvement
- Repeatable Battery for the Assessment of Neuropsychological Status

Exploratory endpoints

- Frontotemporal Dementia Rating Scale
- European Quality of Life-5 Dimensions
- Zarit Burden Interview
- Resource Utilization in Dementia-Lite Version
- Winterlight Labs Speech Assessment (participants who agree to participate in the optional assessments only)

Safety endpoints

- Ongoing safety and tolerability assessments include AEs, physical and neurological examination, vital signs, electrocardiograms, clinical laboratory assessments, Sheehan-Suicidality Tracking Scale, and ADAs
- An independent Data Monitoring Committee will review the progress of the study and perform safety reviews

PD endpoints

- Volumetric MRI
- PGRN concentrations in plasma and optional CSF
- NfL concentrations in serum and optional CSF

PK endpoints

- Serum concentrations of AL001 and relevant PK parameters
- CSF concentrations of AL001 (when available)

Conclusions

- No treatment for FTD has been approved; AL001 has the potential to provide a disease-modifying treatment option for at-risk or symptomatic FTD-*GRN*
- AL001 has received orphan drug designation for the treatment of FTD in the United States
- INFRONT-3 is a pivotal phase 3 study designed to provide confirmatory evidence of the efficacy and safety of AL001, a novel, first-in-class immuno-neurological approach for treating FTD-*GRN*
- Enrollment is ongoing

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