Baseline Characteristics for INFRONT-3: A Phase 3, Double-Blind, Placebo-Controlled, 96-Week Study Evaluating Latozinemab in FTD-*GRN*

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Background

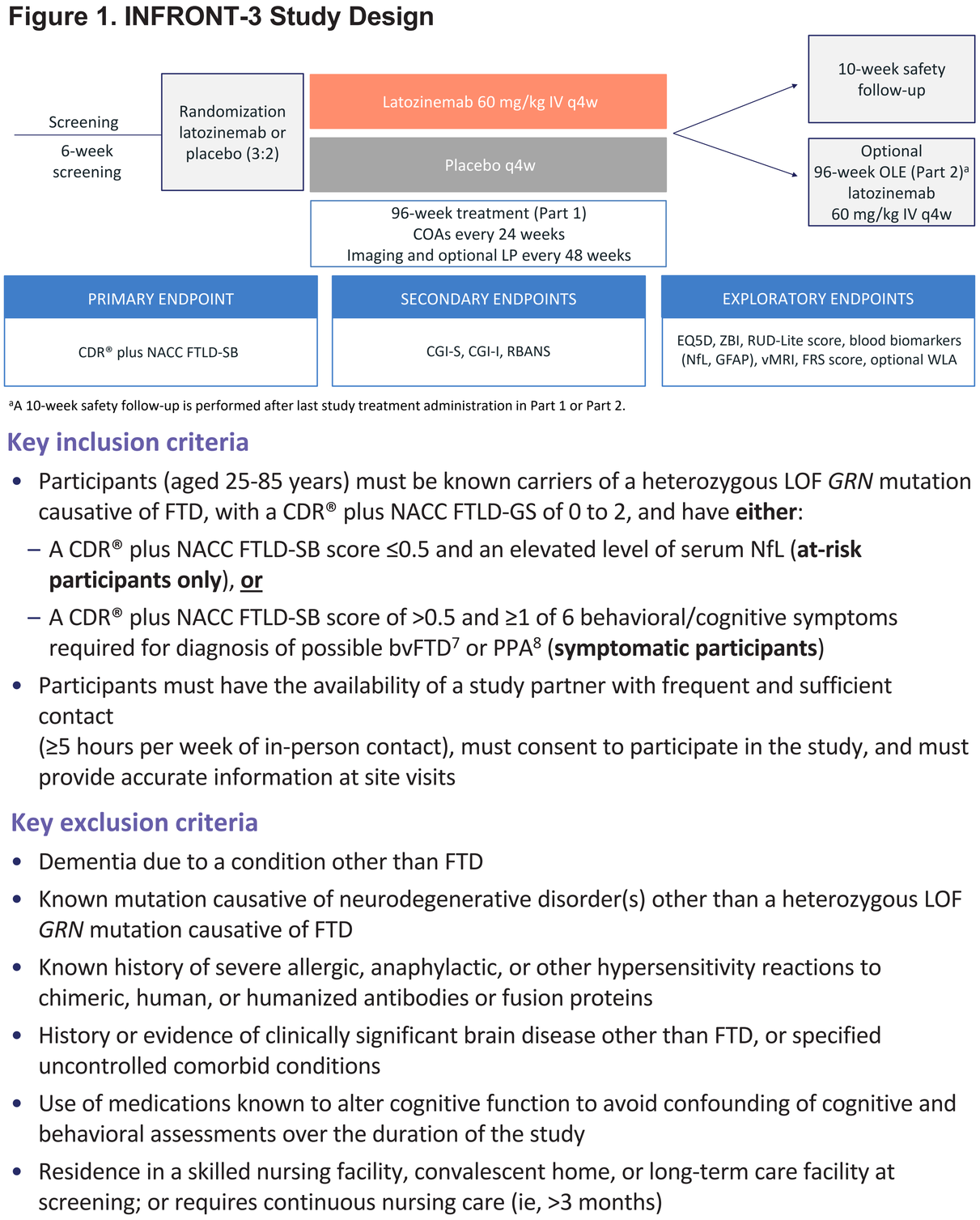
- Heterozygous loss-of-function (LOF) mutations in the granulin gene (*GRN*) cause FTD due to progranulin (PGRN) haploinsufficiency[1,2]
- Sortilin has been identified as a receptor for PGRN endocytosis/subsequent degradation,[3] and latozinemab binds sortilin with high affinity, blocking the sortilin-PGRN interaction in vitro[4]
- In a phase 1 trial, latozinemab treatment reduced sortilin levels in white blood cells and increased plasma and CSF PGRN levels in healthy volunteers, at-risk *GRN* carriers, and participants with symptomatic FTD with a heterozygous *GRN* mutation (FTD-*GRN*)[4,5]
- Interim results from a phase 2, open-label study in participants with symptomatic FTD-*GRN* showed that latozinemab treatment (up to 12 months) increased plasma and CSF PGRN levels 2- to 3-fold relative to age-matched procured controls, and slowed clinical progression in comparison to external controls[6]
- INFRONT-3 is a pivotal phase 3 trial evaluating the efficacy and safety of latozinemab in individuals who either have or are at risk for FTD due to a heterozygous LOF *GRN* mutation
- Here, we describe the baseline characteristics of participants in the INFRONT-3 trial, which achieved target enrollment in October 2023

Methods

Study design

- INFRONT-3 (NCT04374136) is a global, multicenter, randomized, double-blind, placebo-controlled study in symptomatic participants and at-risk participants with FTD due to a heterozygous LOF *GRN* mutation
- The primary objective is to evaluate the efficacy of latozinemab compared with placebo in symptomatic participants as measured by the CDR® plus NACC FTLD-SB score
- Participants were randomized to receive IV infusions of latozinemab 60 mg/kg or placebo in a 3:2 ratio (latozinemab:placebo) q4w for 96 weeks (**Figure 1**)
- Eligible participants were stratified by CDR® plus NACC FTLD-SB score ≤0.5, CDR® plus NACC FTLD-GS 0.5 (with a CDR® plus NACC FTLD-SB score >0.5), CDR® plus NACC FTLD-GS 1, and CDR® plus NACC FTLD-GS 2
- Participants who completed the 96-week treatment period (Part 1) could enroll in the 96-week OLE (Part 2) assessing the long-term safety and tolerability of latozinemab as they continued to receive latozinemab 60 mg/kg q4w for up to 25 doses over a 96-week dosing period, for a total exposure of up to 196 weeks
- A safety follow-up was performed 10 weeks after the last study treatment administration, whether in Part 1 or Part 2

Figure 1. INFRONT-3 Study Design



[a]A 10-week safety follow-up is performed after last study treatment administration in Part 1 or Part 2.

Key inclusion criteria

- Participants (aged 25-85 years) must be known carriers of a heterozygous LOF *GRN* mutation causative of FTD, with a CDR® plus NACC FTLD-GS of 0 to 2, and have **either**:
  - A CDR® plus NACC FTLD-SB score ≤0.5 and an elevated level of serum NfL (**at-risk participants only**), **or**
  - A CDR® plus NACC FTLD-SB score of >0.5 and ≥1 of 6 behavioral/cognitive symptoms required for diagnosis of possible bvFTD[7] or PPA[8] (**symptomatic participants**)
- Participants must have the availability of a study partner with frequent and sufficient contact
  (≥5 hours per week of in-person contact), must consent to participate in the study, and must provide accurate information at site visits

Key exclusion criteria

- Dementia due to a condition other than FTD
- Known mutation causative of neurodegenerative disorder(s) other than a heterozygous LOF *GRN* mutation causative of FTD
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins
- History or evidence of clinically significant brain disease other than FTD, or specified uncontrolled comorbid conditions
- Use of medications known to alter cognitive function to avoid confounding of cognitive and behavioral assessments over the duration of the study
- Residence in a skilled nursing facility, convalescent home, or long-term care facility at screening; or requires continuous nursing care (ie, >3 months)

Results

- A total of 119 participants (103 symptomatic) were enrolled, with a mean age of 62.1 years (**Table 1**)
- The majority of participants were White (84.9%) and approximately half were female (51.3%)
- The at-risk cohort had a mean CDR® plus NACC FTLD-SB score of 0.0 and a median serum NfL of 14.4 pg/mL at baseline (**Table 2**)
- The symptomatic cohort had a mean CDR® plus NACC FTLD-SB score of 6.9 and a mean serum NfL of 73.0 pg/mL at baseline

Table 1. Baseline Demographic and Disease Characteristics[a]

	At-Risk (n=16)	Symptomatic (n=103)	Total (N=119)
Age, mean (min, max), years	59.2 (37, 79)	62.5 (48, 85)	62.1 (37, 85)
Female, n (%)	8 (50.0)	53 (51.5)	61 (51.3)
Race, n (%)			
White	15 (93.8)	86 (83.5)	101 (84.9)
Asian	0	2 (1.9)	2 (1.7)
Not reported/missing	1 (6.3)	15 (14.6)	16 (13.4)
Ethnicity, n (%)			
Hispanic/Latino	1 (6.3)	7 (6.8)	8 (6.7)
Not Hispanic/Latino	14 (87.5)	83 (80.6)	97 (81.5)
Not reported/missing	1 (6.3)	13 (12.7)	14 (11.8)
Diagnosis, n (%)			
bvFTD		64 (62.1)	64 (62.1)
PPA		28 (27.2)	28 (27.2)
Both bvFTD and PPA		7 (6.8)	7 (6.8)
Missing		4 (3.9)	4 (3.9)
Approximate age at diagnosis, mean (SD), years		61.7 (6.7)	61.7 (6.7)

[a]As of July 2024.

Table 2. Baseline Clinical Characteristics[a]

	At-Risk (n=16)	Symptomatic (n=103)	Total (N=119)
CDR® plus NACC FTLD-GS, n (%)			
0	15 (93.8)	0	15 (12.6)
0.5	1 (6.3)	23 (22.3)	24 (20.2)
1	0	49 (47.6)	49 (41.2)
2	0	31 (30.1)	31 (26.1)
CDR® plus NACC FTLD-SB, n	16	103	119
Mean (SD)	0.0 (0.1)	6.9 (4.1)	6.0 (4.4)
NfL concentration (pg/mL), n	12	87	99
Mean (SD)	16.0 (9.7)	73.0 (41.5)	66.1 (43.3)
Median (min, max)	14.4 (7.8, 42.9)	66.9 (6.5, 190.0)	61.7 (6.5, 190.0)

[a]As of July 2024.

Conclusions

- INFRONT-3, the first pivotal trial in genetic FTD, is designed to provide evidence of efficacy and safety of latozinemab, a first-in-class potential immuno-neurological approach to treating FTD-*GRN*
- Compared against available registry data,[9] the baseline characteristics of INFRONT-3 participants, including age, CDR® plus NACC FTLD-SB score, and NfL levels, were representative of an FTD-*GRN* population
- In a combined cohort of registry participants, symptomatic FTD-*GRN* carriers (n=84) had a mean age of 63.7 years, mean CDR® plus NACC FTLD-SB score of 9.19 (SD: 6.53), and mean plasma NfL (natural log) of 4.04 (geometric mean: 56.8 pg/mL) at baseline (GENFI and ALLFTD studies)[9]

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Abbreviations

ALLFTD, ARTFL/LEFFTDS Longitudinal Frontotemporal Lobar Degeneration; ARTFL, Advancing Research and Treatment for Frontotemporal Lobar Degeneration; bvFTD, behavioral variant frontotemporal dementia; CDR® plus NACC FTLD-GS, Clinical Dementia Rating scale plus National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Global Score; CDR® plus NACC FTLD-SB, Clinical Dementia Rating scale plus National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Sum of Boxes; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; COA, clinical outcome assessment; CSF, cerebrospinal fluid; EQ5D, European Quality of Life-5 Dimensions; FRS, Frontotemporal Dementia Rating Scale; FTD, frontotemporal dementia; FTD-*GRN*, frontotemporal dementia with heterozygous progranulin gene mutation; GENFI, Genetic Frontotemporal Initiative; GFAP, glial fibrillary acidic protein; *GRN*, progranulin gene; IV, LEFFTDS, Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects; intravenous; LOF, loss-of-function; LP, lumbar puncture; NfL, neurofilament light chain; OLE, open-label extension; PGRN, progranulin; PPA, primary progressive aphasia; q4w, every 4 weeks; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RUD-Lite, Resource Utilization in Dementia-Lite Version; SD, standard deviation; vMRI, volumetric magnetic resonance imaging; WLA, Winterlight Labs Speech Assessment; ZBI, Zarit Burden Interview.

Disclosures

GR, GS, JYH, LPC, MJS, and TWC are employees of Alector, LLC, and may have an equity interest in Alector, Inc. LG is a consultant and has no financial disclosures. BB, BFB, CM, and ILB were investigators for INFRONT-3. ALB is a scientific advisor to and has an equity interest in Alector, Inc.

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