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RESEARCH ARTICLE

Phase 1 study of latozinemab in progranulin-associated frontotemporal dementia

Michael Ward | **Lawrence P. Carter** | **Julie Y. Huang** | **Daniel Maslyar** | **Balasubrahmanyam Budda** | **Robert Paul** | **Arnon Rosenthal**

Alector Inc., South San Francisco, California, USA

Correspondence:
Lawrence P. Carter, Alector Inc., 131 Oyster Point Blvd. #600, South San Francisco, CA 94080, USA.
Email: Lawrence.carter@alector.com

Present address
Robert Paul, Nine Square Therapeutics, Inc., South San Francisco, California 94080, USA

Abstract

INTRODUCTION: Heterozygous mutations in the *GRN* gene lead to reduced progranulin (PGRN) levels in plasma and cerebrospinal fluid (CSF) and are causative of frontotemporal dementia (FTD) with > 90% penetrance. Latozinemab is a human monoclonal immunoglobulin G1 antibody that is being developed to increase PGRN levels in individuals with FTD caused by heterozygous loss-of-function *GRN* mutations.

METHODS: A first-in-human phase 1 study was conducted to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple-dose intravenous administration of latozinemab in eight symptomatic participants with FTD caused by a heterozygous loss-of-function *GRN* mutation (FTD-*GRN*).

RESULTS: Latozinemab demonstrated favorable safety and PK/PD profiles. Multiple-dose administration of latozinemab increased plasma and CSF PGRN levels in participants with FTD-*GRN* to levels that approximated those seen in healthy volunteers.

DISCUSSION: Data from the first-in-human phase 1 study support further development of latozinemab for the treatment of FTD-*GRN*.

KEYWORDS
disease-modifying therapy, frontotemporal dementia, loss-of-function *GRN* mutation, latozinemab, phase 1 clinical trial, progranulin, sortilin

Highlights

- *GRN* mutations decrease progranulin (PGRN) and cause frontotemporal dementia (FTD).
- Latozinemab is being developed as a PGRN-elevating therapy.
- Latozinemab demonstrated a favorable safety profile in a phase 1 clinical trial.
- Latozinemab increased PGRN levels in the CNS of symptomatic FTD-*GRN* participants.

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1 | INTRODUCTION

Frontotemporal dementia (FTD) is a rare, progressive, early-onset form of dementia. The reported age of symptom onset has ranged from about 20 to 90 years, with a mean onset of ≈ 59 years that may vary among different genetic FTD groups.[1,2] FTD often progresses rapidly, with the mean survival after symptom onset ranging from 6.4 to 9.3 years across the major genetic mutations, but the duration of the illness can vary widely depending on the underlying pathology.[2,3] FTD encompasses clinical syndromes that can include changes in behavior, language, cognition, executive function, and often, motor deficits,[4,5] all of which can make obtaining an accurate diagnosis challenging.

Approximately 20% to 40% of FTD cases have a family history of dementia, and ≈ 10% are inherited in an autosomal dominant fashion.[6,7] Most of this genetic component is accounted for by mutations in three genes:[2,8] *GRN*,[9,10] microtubule-associated protein tau (*MAPT*),[11] and *C9orf72*.[12,13] Variants in *GRN* consistent with autosomal dominant FTD have been identified in ≈ 25% of persons with a family history of FTD, and in 3% to 5% of apparently sporadic FTD cases.[14] More than 100 *GRN*-heterozygous, loss-of-function mutations have been identified,[15] and these mutations lead to a ≥ 50% reduction in progranulin (PGRN) protein levels in plasma and cerebrospinal fluid (CSF).[16–18] Thus, PGRN-elevating therapies may provide a successful therapeutic approach for treating FTD caused by a heterozygous *GRN* loss-of-function mutation (FTD-*GRN*).[18,19]

PGRN is a glycoprotein that is localized within the lysosome, where it is cleaved into smaller peptides called granulins, some having known complementary biological activities.[8,20,21] PGRN is expressed in myeloid cells and in a subset of neurons in the central nervous system (CNS), as well as in myeloid, epithelial, and activated fibroblasts and endothelial cells in the periphery.[20] PGRN is involved in cell proliferation and survival, axonal growth, wound healing, tumorigenesis, and immune function.[8,20,21] Identified receptors for PGRN include sortilin, which has been identified as a major regulator of PGRN levels in plasma and the CNS;[22,23] mannose 6-phosphate receptor;[24] ephrin type-A receptor 2;[25] low-density lipoprotein receptor-related protein 1;[24] and Notch.[26] Recent approaches suggest that the sortilin–PGRN axis is a viable target for PGRN-based therapy, particularly in individuals with FTD-*GRN*.[19] Restoring PGRN levels in a mouse model of FTD-*GRN* has been shown to reverse behavioral deficits.[27]

Latozinemab (AL001) is a human monoclonal immunoglobulin G G1m17,1 kappa antibody generated against the human sortilin receptor. The pharmacology, pharmacokinetics (PK), pharmacodynamics (PD), and toxicology of latozinemab have been comprehensively assessed in non-clinical and clinical studies.[28] In vitro, latozinemab effectively binds sortilin with high affinity, decreases cell surface sortilin levels in a dose-dependent manner, and blocks the sortilin–PGRN interaction. In vivo, blocking sortilin with a single administration of latozinemab has been shown to increase PGRN levels in plasma and CSF in non-human primates, healthy volunteers (HVs), and asymptomatic carriers of a heterozygous *GRN* mutation.[28] Here, we demonstrated for the first time that multiple-dose administration of latozinemab could produce sustained elevations in PGRN levels in participants with symptomatic FTD-*GRN* to levels comparable to those of healthy controls.

RESEARCH IN CONTEXT

1. **Systematic review**: Plasma and cerebrospinal fluid (CSF) concentrations of progranulin (PGRN) are reduced in individuals with frontotemporal dementia (FTD) caused by heterozygous loss-of-function *GRN* mutations (FTD-*GRN*). Increasing PGRN levels may be an effective therapeutic approach in individuals with FTD-*GRN*. In preclinical models, latozinemab blocked and decreased sortilin, a major regulator of PGRN, thereby increasing plasma and CSF PGRN levels.
2. **Interpretation**: Multiple-dose intravenous administration of latozinemab in individuals with symptomatic FTD-*GRN* was well tolerated and increased PGRN levels in plasma and CSF to those seen in healthy volunteers, demonstrating proof of mechanism in this patient population.
3. **Future directions**: These findings support the further development of latozinemab for the treatment of dementia caused by FTD-*GRN* loss-of-function mutations.

2 | METHODS

2.1 | Study design

In the first part of the Phase 1 study, HVs received single intravenous (IV) doses of latozinemab ranging from 2 to 60 mg/kg (or placebo) to identify the maximum tolerable dose and to explore PK and PD (sortilin and PGRN concentrations) in plasma and CSF.[28] The second part of the study was conducted in two participant cohorts: the first cohort consisted of asymptomatic carriers of a loss-of-function *GRN* mutation causative of FTD;[28] the second cohort, which is the focus of this publication, consisted of participants with symptomatic FTD-*GRN*. A total of eight participants with FTD-*GRN* were enrolled. Participants with FTD-*GRN* were administered multiple IV doses of open-label latozinemab at a dose level of 30 mg/kg once every 2 weeks, for a total of three doses over a 4-week period. This dose was selected because it was half of the maximum dose tested in the first part of the study and was deemed to have an acceptable safety and tolerability profile. Minimal or no drug accumulation was anticipated with the reported half-life of ≈ 5 days and the planned dosing interval of 14 days.[28]

All participants provided informed consent and underwent screening procedures up to 42 days prior to Day 1 to determine eligibility. The first participant received latozinemab ≈ 48 hours before the remaining participants. If no dose-limiting adverse event (AE) was observed within 48 hours after the infusion of the first dose, the remaining par-

ticipants received latozinemab. All participants were monitored for 16 weeks after their last dose for evaluation of safety, PK, and PD.

On Days 1, 15, and 29, participants received an IV infusion of 30 mg/kg latozinemab over 1 hour. Serum PK samples and plasma PGRN samples were collected prior to dosing on Day 1 and at predesignated times post dose on Days 1, 2, 8, 15, 22, 29, 36, 57, 85, and 141. To assess target engagement, whole blood to assess sortilin levels on white blood cells (WBCs) was collected at predesignated times on Days 1, 8, 15, 22, 29, 36, 57, 85, and 141. Lumbar puncture for CSF collection was performed at baseline and on Day 57 (28 days after the last administered dose of latozinemab).

2.2 | Participants

Participants had to be symptomatic and meet diagnostic criteria for possible behavioral variant frontotemporal dementia (bvFTD) or probable bvFTD or primary progressive aphasia.[29,30] Additional inclusion criteria included being in good physical health and being a heterozygous carrier of a loss-of-function *GRN* mutation. Participants were eligible for inclusion if they were males or non-pregnant females using adequate contraception throughout the study duration. Participants were excluded from the study if they met any of the following criteria: known history of reactions to antibodies or fusion proteins; dementia or mild cognitive impairment due to a condition other than FTD; history of severe, clinically significant CNS trauma; history of alcohol or substance abuse within the past 2 years; significant and/or acute illness within 5 days prior to the first drug administration; history of seizures; serious infection requiring antibiotics within 30 days prior to screening; clinically significant systemic immunocompromised condition because of continuing effects of immune-suppressing medication; history of major depression (unless effectively treated), schizophrenia, schizoaffective disorder, or bipolar disorder; history of cancer except if it was considered cured, was not being actively treated, or was considered to have a low probability of recurrence; any serious medical condition or abnormality in clinical laboratory tests; or any other severe or unstable medical condition.

2.3 | Objectives and endpoints

The primary objective of this study was to evaluate the safety, tolerability, PK, and PD of latozinemab administered as multiple IV doses in participants with symptomatic FTD-*GRN*.

The safety endpoints of this study included the following: incidence and severity of AEs; changes from baseline over time in clinical laboratory test results, electrocardiogram (ECG) assessments, vital signs, imaging abnormalities as measured by magnetic resonance imaging (MRI), and antidrug antibodies (ADAs); physical and neurologic examination abnormalities; and scores on the Sheehan Suicidality Tracking Scale (Sheehan-STS). Serum and CSF concentrations of latozinemab were assessed at specified time points to derive PK parameters. PD endpoints included changes in sortilin expression in WBCs and changes in the levels of PGRN in plasma and CSF after dosing relative to baseline concentrations. Enzyme-linked immunosorbent assays were used for the detection of all PK and PD endpoints, including the detection of latozinemab in serum and CSF, PGRN in plasma and CSF, and sortilin in human WBCs, as previously described.[28]

2.4 | Statistical methods

All analyses were conducted using SAS software version 9.4 (SAS Institute, Inc.). No adjustments were made to the planned analyses for missing data resulting from participant dropout or other reasons. No adjustments were made to control for multiplicity or to account for covariates.

Participant disposition and demographic information was summarized for the enrolled population. All safety analyses were conducted on the safety population, which included all enrolled participants who received at least one dose of latozinemab. Mean serum and CSF concentrations of latozinemab were calculated for each time point. Individual PK parameters were derived by non-compartmental analysis using Phoenix WinNonlin Version 8 (Pharsight Corporation). PD endpoints (i.e., sortilin and PGRN concentrations) were summarized as changes from baseline per time point.

2.5 | Ethical considerations

The study was conducted in accordance with the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, International Council for Harmonisation Guideline for Good Clinical Practice, and the Declaration of Helsinki. The protocol and informed consent form were reviewed and approved by the institutional review board/independent ethics committee of each participating clinical site prior to study initiation. Participants provided written informed consent prior to participating in the study.

3 | RESULTS

3.1 | Participants

A total of eight participants with FTD-*GRN* were enrolled in the study (Figure 1). All participants completed open-label treatment with latozinemab. Three participants completed the study up to Day 141. After Day 57, one participant discontinued due to withdrawal of consent and four participants transferred to the phase 2 study (INFRONT-2; NCT03987295), as permitted per protocol. All participants were White and not Hispanic or Latino, with the majority (87.5%) being male (Table 1). The mean (standard deviation [SD]) age was 62 (8.42) years. The only comorbidity reported in more than two of the eight participants was anxiety (37.5%; data not shown). Regarding

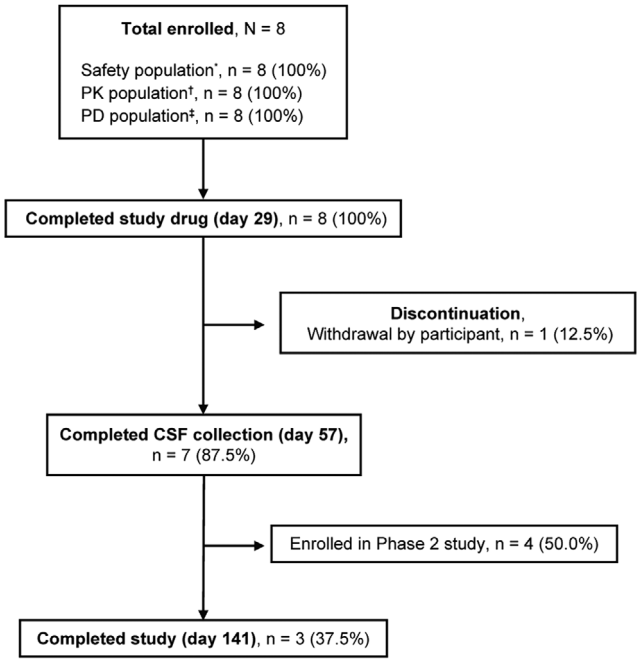

FIGURE 1 Participant disposition (enrolled population). * The safety population included all enrolled participants who received at least one dose of latozinemab. † The PK population included all participants in the safety population who had adequate assessments for determination of PK parameters. ‡ The PD population included all participants in the safety population who had both a baseline and at least one postdose PD assessment. CSF, cerebrospinal fluid; PD, pharmacodynamics; PK, pharmacokinetics

TABLE 1 Demographic and other baseline characteristics (safety population).

Variable	FTD-*GRN* 30 mg/kg × 3 doses (*N* = 8)
Age (years)	
Mean (SD)	62.0 (8.42)
Median	63.5
Min, max	47, 71
Sex, *n* (%[a])	
Female	1 (12.5)
Male	7 (87.5)
Race, *n* (%[a])	
White	8 (100.0)
Ethnicity, *n* (%[a])	
Not Hispanic or Latino	8 (100.0)
Height (cm), mean (SD)	165.96 (38.54)
Weight (kg), mean (SD)	88.05 (15.91)
BMI (kg/m^2), mean (SD)	27.15 (4.18)

Abbreviations: BMI, body mass index; FTD-*GRN*, frontotemporal dementia caused by loss-of-function *GRN* mutation; SD, standard deviation.
[a]Percentages were based on the number of participants for the safety population.

TABLE 2 Summary of TEAEs (safety population).

	FTD-*GRN* 30 mg/kg × 3 doses (*N* = 8)
Any TEAE, *n* (%) [E]	7 (87.5) [12][a]
Any treatment-related TEAE, *n* (%) [E]	1 (12.5) [1][b]
Severity of TEAEs, *n* (%) [E]	
Mild	7 (87.5) [12]
Moderate	0 (0.0) [0]
Severe	0 (0.0) [0]
Life threatening	0 (0.0) [0]
Death	0 (0.0) [0]
Severity of treatment-related TEAEs, *n* (%) [E]	
Mild	1 (12.5) [1]
Moderate	0 (0.0) [0]
Severe	0 (0.0) [0]
Life threatening	0 (0.0) [0]
Death	0 (0.0) [0]
Any SAE, *n* (%) [E]	0 (0.0) [0]
Any treatment-related SAE, *n* (%) [E]	0 (0.0) [0]
Any TEAE leading to discontinuation, *n* (%) [E]	0 (0.0) [0]

Abbreviations: E, number of events; FTD-GRN, frontotemporal dementia caused by loss-of-function GRN mutation; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Bradycardia, blepharitis, dyspepsia, fungal skin infection, nasopharyngitis, upper respiratory tract infection, Murphy's sign positive, arthralgia, musculoskeletal pain, myalgia, headache, depression.
[b]Murphy's sign positive.

metabolic comorbidities, one participant had hyperlipidemia and one participant had dyslipidemia. No one had obesity or diabetes.

3.2 | Safety and tolerability of multiple-dose administration of latozinemab in participants with symptomatic FTD-*GRN*

Overall, seven of eight participants with FTD-*GRN* (87.5%) reported a total of 12 treatment-emergent AEs (TEAEs; Table 2). All TEAEs were mild in severity and the majority of TEAEs were not related to the study drug; one participant experienced one treatment-related TEAE (right upper quadrant pain [Murphy's sign positive]). No participants experienced a serious AE or a TEAE leading to early discontinuation. The most frequently reported TEAEs were classified as infections and infestations ($n = 3$; including one case each of upper respiratory tract infection, fungal skin infection, and nasopharyngitis), and musculoskeletal disorders ($n = 3$; one case each of arthralgia, musculoskeletal pain, and myalgia). No individual TEAEs were reported by more than one participant.

Shifts in hematology, clinical chemistry, and urinalysis values from normal at baseline to low or high after dosing occurred sporadically

during the study. Because PGRN is known to interact with low-density lipoprotein receptor-related protein one and elevated PGRN has been associated with visceral obesity and dyslipidemia, clinical chemistry lipid parameters were of clinical interest.[24,31] Shifts in lipid parameters to the upper limit of normal (ULN) after dosing in two or more participants were as follows: cholesterol was elevated in two participants and triglycerides were elevated in three participants. Among those participants, one had cholesterol > ULN at baseline and one had triglycerides > ULN at baseline. No clinically meaningful changes from baseline were observed in more than one participant at any time point in high-density lipoprotein cholesterol or low-density lipoprotein cholesterol.

Overall, mean vital sign measurements were generally similar to those observed at baseline. One participant experienced a TEAE of bradycardia (mild, not related to study drug in the clinical judgement of the investigator). No abnormal/clinically significant ECG results were observed at any time point during the study. No participants had new abnormal MRI findings during the study. No increases from baseline were observed in Sheehan-STS scores. Four participants (50.0%) had treatment-emergent positive ADAs (TEPADAs); one participant was positive for TEPADA on Day 85, and three participants were positive for TEPADAs at study completion. There were no associated AEs suggestive of clinically significant immunogenic responses associated with the development of TEPADAs.

3.3 | PK of multiple-dose administration of latozinemab in participants with symptomatic FTD-*GRN*

After the final infusion on Day 29, the median time of maximum observed concentrations of latozinemab in the serum of participants with FTD-*GRN* was ≈ 5 hours; thereafter, serum concentrations declined with a mean half-life of 205 hours. After three infusions (Days 1, 15, and 29), latozinemab concentrations were detectable for 30 days or longer after the last infusion (Figure 2). Total observed concentration (area under the concentration-time curve from time 0 to the end of the dosing interval) was similar with each administration of 30 mg/kg at Days 15 and 29 with a minimal accumulation of ≈ 1.6 relative to first dose on Day 1 (Table 3). The maximum observed concentration of latozinemab exposure after each administration was similar on all three dosing days (Table 3).

The mean ± SD CSF concentration of latozinemab on Day 57 (28 days after last infusion) was 375 ± 179 ng/mL. The mean ± SD serum to CSF partition coefficient on Day 57 was 0.003 ± 0.001.

3.4 | Sortilin and PGRN levels after multiple-dose administration of latozinemab in participants with symptomatic FTD-*GRN*

After multiple-dose administration of latozinemab in participants with symptomatic FTD-*GRN*, a robust and sustained decrease in WBC sortilin from baseline was observed (Figure 3A). After the first dose, the median decrease in WBC sortilin from baseline was ≈ 82% and that decrease was sustained up to Day 57 after two more doses at Day 14 and Day 29 (Figure 3A).

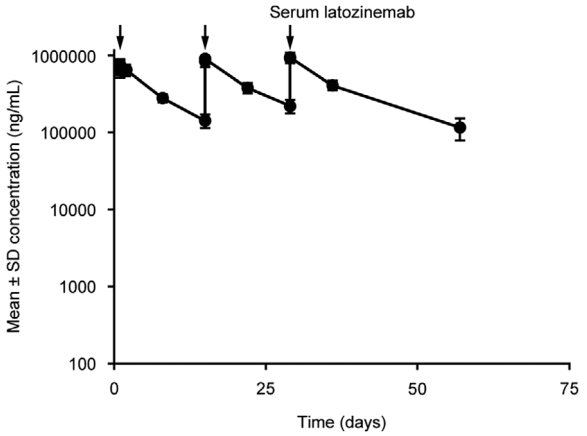

FIGURE 2 Pharmacokinetics of multiple-dose administration of latozinemab in participants with FTD-*GRN*. Mean ± SD serum concentration of latozinemab versus time. Arrows indicate the timing of latozinemab infusions. $n = 7–8$ for all time points except Day 141 for which $n = 3$. Note that serum latozinemab concentrations were zero on Days 80 and 140. FTD-*GRN*, frontotemporal dementia caused by loss-of-function *GRN* mutation; SD, standard deviation

The mean ± SD baseline plasma PGRN concentration in participants with symptomatic FTD-*GRN* was 31.7 ± 12.7 ng/mL. Multiple-dose administration of 30 mg/kg latozinemab led to a robust and sustained increase in plasma PGRN levels (Figure 3B). After the first dose, plasma PGRN levels continued to rise and reached steady state around Day 22 with a median increase of 200% relative to baseline. That increase was sustained up to Day 57 with plasma PGRN levels starting to decline after the last infusion on Day 29; they remained elevated relative to baseline for more than 100 days after the last infusion (Figure 3B). Treatment of symptomatic FTD-*GRN* participants with 30 mg/kg latozinemab increased plasma PGRN levels by ≈ 2-fold from Day 8 through Day 57.

The mean baseline CSF PGRN concentration in participants with symptomatic FTD-GRN was 1.82 ng/mL. Multiple-dose administration of 30 mg/kg latozinemab in symptomatic FTD-*GRN* participants increased CSF PGRN levels from baseline levels of 1.82 to 3.76 ng/mL (Figure 3C).

4 | DISCUSSION

Haploinsufficiency of *GRN* gene expression due to a loss-of-function mutation leads to decreased peripheral and central PGRN levels that are causative of FTD with > 90% penetrance.[32,33] Thus, an intervention that restores PGRN levels may be an effective therapeutic approach to treat or prevent FTD in carriers of a loss-of-function *GRN* mutation.

In this study, multiple-dose administration of latozinemab was generally well tolerated by participants with symptomatic FTD-*GRN*. All TEAEs were mild in severity and the majority of TEAEs were not

TABLE 3 Geometric mean (CV) serum PK parameters of latozinemab in participants with FTD-*GRN* (PK population).

Parameter	Day 1	Day 15	Day 29
AUC_{tau} (h·μg/mL)	115000 (17.5)	157000 (14.6)	180000 (13.5)
C_{max} (μg/mL)	763 (17.9)	859 (15.5)	946 (14.4)
t_{max} (h)[a]	3.13 (1.17, 13.00)	5.03 (1.00, 9.08)	4.96 (1.12, 5.42)
$t_{1/2}$ (h)[b]	139 (7.58)	191[c]	204 (13.7)[d]
AUC_{tau}/Dose ([h·μg/mL]/[mg/kg])	3840 (17.5)	5240 (14.6)	6020 (13.5)
C_{max}/Dose ([μg/mL]/[mg/kg])	25.4 (17.9)	28.6 (15.5)	31.5 (14.4)

Abbreviations: AUC_{tau}, area under the concentration-time curve from time 0 to the end of the dosing interval; $AUC_{0\text{-tlast}}$, area under the concentration time curve from time 0 to the last measurable time point; C_{max}, maximum observed concentration; CV, coefficient of variation; FTD-*GRN*, frontotemporal dementia caused by loss-of-function *GRN* mutation; PK, pharmacokinetic; t_{max}, time of maximum observed concentration; $t_{1/2}$, terminal elimination half-life.
[a]For t_{max}, the median (minimum, maximum) values are presented.
[b]For $t_{1/2}$, the mean (CV) values are presented.
[c]$n = 1$.
[d]$n = 2$.

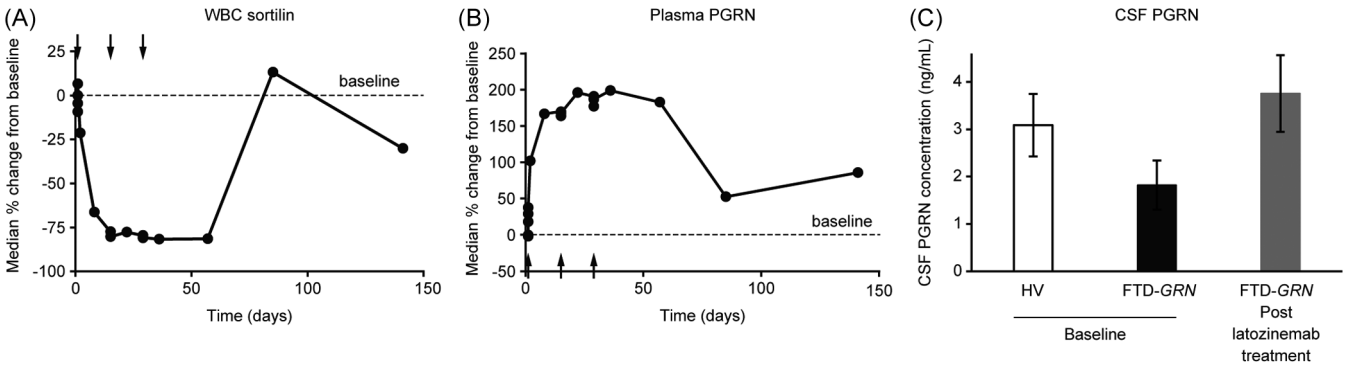

FIGURE 3 Latozinemab decreases median sortilin expression in WBCs and increases PGRN levels in the plasma and CSF of participants with FTD-*GRN* (PD population). A–B, Median percentage change from baseline in WBC sortilin (A) and plasma PGRN (B) plotted as a function of time. Arrows indicate the timing of latozinemab infusions. For WBC sortilin, $n = 8$ at all time points, except for the end of infusion and 4, 12, and 24 hours after the first dose ($n = 1$) and 7 days ($n = 7$), 56 days ($n = 5$), and 140 days ($n = 3$) after the third dose. For plasma PGRN, $n = 8$ at all time points, except for 4 hours after the second dose ($n = 7$) and 56 days ($n = 4$) and 140 days ($n = 3$) after the third dose. C, Mean ± SD CSF PGRN concentrations at baseline for HVs and FTD-*GRN* participants and for FTD-*GRN* participants on Day 57, which is 28 days after administration of three doses of 30 mg/kg latozinemab. For HVs, $n = 33$, and for FTD-*GRN* participants, $n = 7$ at baseline and $n = 8$ post-treatment. CSF, cerebrospinal fluid; FTD-*GRN*, frontotemporal dementia caused by loss-of-function *GRN* mutation; HV, healthy volunteer; PD, pharmacodynamic; PGRN, progranulin; SD, standard deviation; WBC, white blood cell

related to the study drug, as judged by the investigators. No apparent differences from baseline were observed in clinical laboratory tests, ECG assessments, physical and neurologic examinations, or vital signs. Because all TEPADAs in participants (4/8) were long after the last dose (Day 29), the impact of ADAs on longer-term exposure and pharmacodynamics remains unknown and will be assessed in longer-term studies of latozinemab.

Serum and CSF concentrations of latozinemab after first dose in participants with FTD-*GRN* were comparable to data from HVs after single dose administration, and PK analyses suggested no differences in the disposition of latozinemab in participants with FTD-*GRN* and HVs.[28] In this study, the dosing regimen of 30 mg/kg administered every 2 weeks was selected based on single dose PK from doses ranging from 2 to 60 mg/kg that were deemed to have an acceptable safety and tolerability profile. As expected from single dose PK of latozinemab from HVs and participants with FTD-*GRN*, minimal accumulation of latozinemab, ≈ 1.6-fold relative to first dose on Day 1, was observed (Table 3). These results also provided further refinement to the dosing regimen for subsequent drug development. For example, the dose-normalized steady-state exposure from 30 mg/kg every 2 weeks dosing was similar to the dose-normalized total exposure from single dose of 60 mg/kg (6020 h•μg/mL from 30 mg/kg every 2 weeks vs. 6160 h•μg/mL from 60 mg/kg single dose[28]) indicating that the dosing regimen of 60 mg/kg every 4 weeks could be taken forward for future phases of drug development, providing a more convenient dosing frequency for participants.

Because latozinemab binds to sortilin and causes the complex to internalize, its binding was expected to reduce sortilin levels. This direct aspect of target engagement was demonstrated by reduction in WBC sortilin and further supported by reduction in CSF sortilin. In this

study, multiple-dose administration resulted in a sustained increase in PGRN levels in plasma and CSF, possibly as a direct result of sortilin binding by latozinemab. During the treatment period, plasma PGRN levels in the symptomatic FTD-*GRN* participants were increased to near-normal levels and CSF PGRN levels exceeded baseline levels in HVs. The increases in plasma and CSF PGRN levels after three doses of 30 mg/kg latozinemab administered every 2 weeks were sustained for at least 112 and 28 days (these findings are limited by the sampling time), respectively, after the final infusion.

In summary, this study demonstrates that latozinemab can increase PGRN levels in plasma and CSF, with a safety and PK/PD profile that supports further development of latozinemab for FTD-*GRN*. Latozinemab was generally well tolerated; there were no deaths, no study treatment-related serious AEs, and no AEs leading to study discontinuation. Reported AEs were predominantly mild to moderate in severity. There were some participants, including those with and without a history of hyperlipidemia or dyslipidemia, who had an elevation of cholesterol or triglyceride to > ULN; such elevations will be further evaluated in larger studies that include a placebo control. This study also demonstrated that multiple-dose administration of latozinemab was able to increase PGRN levels in the CNS of participants with symptomatic FTD-*GRN*. Limitations of this study include the relatively small sample size, and the homogeneity of a predominantly White, male population with relatively few comorbidities. Future studies will evaluate the relationships among target engagement, downstream PD effects, and clinical outcomes in a broader patient population to assess the efficacy of latozinemab in treating FTD-*GRN*.

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CONFLICT OF INTEREST STATEMENT

Michael Ward was an employee of Alector at the time of the study; has received consulting fees and travel support from Alector; is listed on patents with Alector; and has stock and stock options with Alector. Lawrence P. Carter is an employee of Alector; has received travel support from Alector; has stock and stock options with Alector; and has received honoraria as an invited speaker from the University of Michigan. Julie Y. Huang is an employee of Alector; has received travel support from Alector; is listed on provisional patents for Alector; and has received stock and stock options from Alector. Daniel Maslyar was an employee of Alector at the time of the study; has received consulting fees and travel support to conferences from Alector; and is an Alector stockholder. Balasubrahmanyam Budda is an employee of Alector; has received support for travel to conferences from Alector; and has received stock and stock options from Alector. Robert Paul was an employee of Alector at the time of the study; is listed on patents with Alector; and has received stock and stock options from Alector. Arnon Rosenthal is an employee of Alector; is listed on multiple patents for progranulin elevating drugs as a co-inventor; and has received stock and stock options from Alector. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided informed consent.

ORCID

Lawrence P. Carter https://orcid.org/0009-0008-7403-4242

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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