Repeat IV and SC Dosing of the Anti-Sortilin Antibody AL101

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Background

- Variants in *GRN*, the coding gene for progranulin (PGRN), have been implicated in a number of neurodegenerative disorders, including frontotemporal dementia (FTD),[1,2] Alzheimer's disease (AD),[3] and Parkinson's disease (PD)[4]
- Sortilin, expressed on neurons and microglia, is a key regulator of PGRN levels through sortilin-mediated degradation[5,6]
- Increasing PGRN levels may be an effective therapeutic approach, potentially reducing the rate of neuronal loss and clinical decline in individuals with neurodegenerative diseases[7,8]
- AL101 is a human immunoglobulin (Ig) G1 monoclonal antibody that blocks and decreases sortilin levels and increases PGRN levels in preclinical models. AL101 is being developed by Alector for the treatment of neurodegenerative disorders, including AD and PD
- Previous data presented on single-dose administration of AL101 (CTAD 2021) demonstrated that AL101 was well tolerated and increased PGRN levels in plasma and CSF in a dose-dependent manner[9]

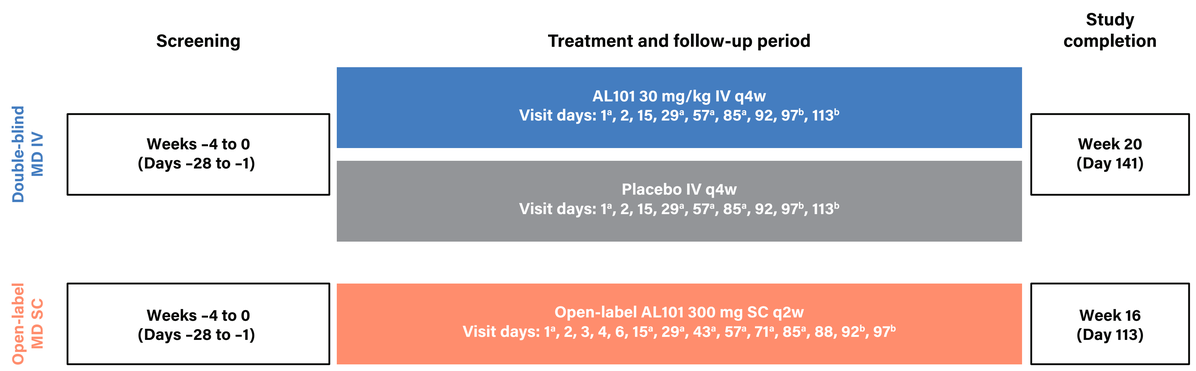
Objective

- The primary objective of this study was to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and bioavailability of AL101 when administered in single or multiple doses intravenously (IV) or subcutaneously (SC) in healthy volunteers. The data presented here summarize results from the multiple-dose (MD) cohorts of this phase 1 study

Methods

- Healthy volunteers received multiple doses of AL101 in 2 cohorts (**Figure 1**):
  - 30 mg/kg of AL101 in a double-blind, randomized, placebo-controlled fashion (8:2, AL101:placebo) administered IV using an infusion pump over ~60 minutes every 4 weeks (q4w) for a total of 4 doses
  - Open-label AL101 at 300 mg as slow SC injections over 15 minutes every 2 weeks (q2w) for a total of 7 doses
- Safety data and samples for serum and plasma levels of AL101 and PGRN, respectively, were collected during all visits from day 1 through study completion
- CSF was sampled at baseline and at specified timepoints after the last administered dose (**Figure 1**)
- Safety follow-up was conducted for up to 20 weeks in the IV cohort and up to 16 weeks in the SC cohort (**Figure 1**)

Figure 1. Study Design for Multiple-Dose AL101 Administration



IV, intravenous; MD, multiple-dose; q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous.
[a]Treatment day.
[b]Post-treatment CSF samples were collected.

Results

Participants

- A total of 27 participants enrolled in these 2 multiple-dose cohorts of the study (pooled placebo MD IV, N = 3; AL101 30 mg/kg IV q4w, N = 11; AL101 300 mg SC q2w, N = 13)
- 23 participants (85.2%) completed drug treatment and 21 participants (77.8%) completed the study
- Reasons for study discontinuation included adverse event (AE; AL101 30 mg/kg MD IV, n = 1), lost to follow-up (AL101 30 mg/kg MD IV, n = 1; AL101 300 mg MD SC, n = 3), and withdrawal by the subject (pooled placebo MD IV, n = 1)
- Baseline demographics and characteristics were similar across groups
  - The majority of participants in the pooled IV and SC active groups and the placebo group were white (83.3% and 66.7%, respectively) and male (62.5% and 66.7%, respectively)
  - The median age in the active and placebo groups was 51 and 36 years, respectively

Safety

- Across the active treatment groups, most AEs were considered mild (n = 13, 54.2%) or moderate (n = 2, 8.3%) in severity (**Table 1**)
- The most frequent AEs (occurring in ≥2 participants in any group) regardless of relationship to study drug were headache, injection site erythema, back pain, SARS-CoV-2 positive test result, dizziness, injection site pruritus, injection site swelling, and neck pain
- There was 1 serious AE during the study, which was an event of myocardial infarction in a 57-year-old male with previously undiagnosed atherosclerotic heart disease in the SC 300 mg q2w cohort after receiving 6 doses. This event was assessed as severe in intensity and not related to study drug

Table 1. Summary of Adverse Events (Safety Population)

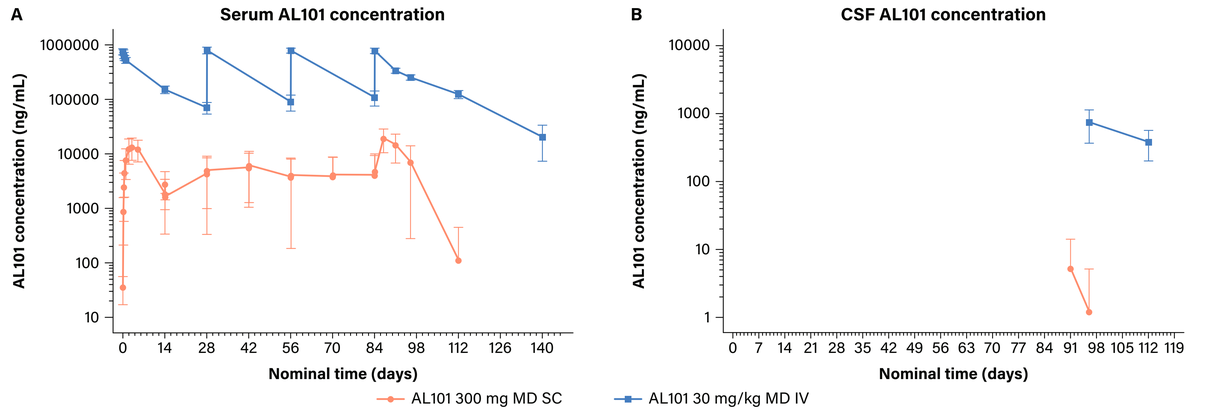
n (%) [E]	Double-blind MD IV		Open-label	All Active AL101 (N = 24)
	Pooled Placebo MD IV (N = 3)	AL101 30 mg/kg MD IV (N = 11)	AL101 300 mg MD SC (N = 13)	
All TEAEs	0	5 (45.5) [11]	11 (84.6) [47]	16 (66.7) [58]
Treatment-related TEAE	0	2 (18.2) [3]	8 (61.5) [23]	10 (41.7) [26]
All SAEs	0	0	1 (7.7) [1]	1 (4.2) [1]
Treatment-related SAE	0	0	0	0
TEAEs leading to discontinuation	0	1 (9.1) [1]	0	1 (4.2) [1]
All DLAEs	0	1 (9.1) [1]	1 (7.7) [1]	2 (8.3) [2]

DLAE, dose-limiting adverse event; E, number of events; IV, intravenous; MD, multiple-dose; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Pharmacokinetics of AL101

- Serum and CSF concentrations of AL101 after IV q4w and SC q2w multiple-dose administration are shown in **Figure 2**
  - AL101 was distributed into the central nervous system (CNS), as evidenced by CSF AL101 concentrations
- AL101 serum pharmacokinetic parameters as calculated using a non-compartmental analysis are summarized in **Table 2**

Figure 2. Mean (± SD) Pharmacokinetic Profiles of AL101 After Multiple-Dose Administration of AL101 (Pharmacokinetic Population). (A) Serum and (B) CSF concentrations of AL101 plotted as a function of time



CSF, cerebrospinal fluid; IV, intravenous; MD, multiple-dose; SC, subcutaneous.

Table 2. Mean (SD) Serum Pharmacokinetic Parameters of AL101 After IV q4w or SC q2w Multiple-Dose Administration (Pharmacokinetic Population)

Cohort	Day	AUC_{inf} (h*µg/mL)	CL[a] CL/F[b] (mL/h)	C_{max} (ug/mL)	t_{max} (h)[c]	$t_{1/2}$ (h)	PC day 97	PC day 113
AL101 30 mg/kg MD IV	1	179000 (21600)	13.3 (2.29)	754 (92.9)	1.20 (1.17, 5.13)	215 (23.3)	0.00285 (0.0013)	0.00311 (0.00167)
	85	262000 (25500)	NA	782 (89.9)	1.13 (1.02, 1.33)	296 (75.8)	NA	NA
AL101 300 mg MD SC	1	3530 (2300)	108 (70.2)	14.3 (6.17)	72.58 (48.25, 120.47)	93.8 (58.1)	0.000259 (0.000391)	0.0000481 (0.000152)
	85	10600 (6140)	NA	19.5 (9.04)	70.05 (69.35, 72.12)	79.0 (23.3)	NA	NA

AUC_{inf}, area under the concentration-time curve from time 0 extrapolated to infinity; CL and CL/F, total body clearance; C_{max}, maximum observed concentration; CSF, cerebrospinal fluid; IV, intravenous; MD, multiple-dose; NA, not available; PC, partition coefficient (CSF concentration/serum concentration); q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous; SD, standard deviation; $t_{1/2}$ terminal elimination half-life; t_{max}, time of maximum observed concentration.
[a]Applies to AL101 30 mg/kg MD IV cohort.
[b]Applies to AL101 300 mg MD SC cohort.
[c]Data are shown as median (min, max).

Pharmacodynamic response of AL101

- Multiple-dose administration of AL101 increased plasma PGRN levels, with a higher elevation observed in the AL101 30 mg/kg MD IV group than in the AL101 300 mg MD SC group (**Figure 3A**)
- Plasma PGRN levels remained ~160% to 200% (~2.6- to 3-fold) elevated above baseline levels throughout the study duration for the AL101 30 mg/kg MD IV group
- Multiple-dose IV administration of AL101 at 30 mg/kg q4w led to an increase in CSF PGRN by 85.8% (1.86-fold) and 97.7% (1.98-fold) from baseline at day 97 and day 113, respectively (**Figure 3B**)
- Multiple-dose SC administration of AL101 at 300 mg q2w led to an increase in CSF PGRN by 36.2% (1.36-fold) and 25% (1.25-fold) from baseline at day 92 and day 97, respectively

Figure 3. Pharmacodynamics of AL101 (Pharmacodynamic Population). Mean (±SD) percentage change from baseline in (A) plasma and (B) CSF concentrations of PGRN as a function of time

CSF, cerebrospinal fluid; IV, intravenous; MD, multiple-dose; PGRN, progranulin; SC, subcutaneous; SD, standard deviation.

Conclusions

- In this first-in-human phase 1 study, AL101 was found to be generally safe and well tolerated following multiple-dose IV (q4w) and SC (q2w) administrations
- Consistent with our previously presented data following single doses,[9] AL101 was measurable in the CSF following multiple IV and SC doses, indicating distribution into the CNS
- Multiple IV doses of AL101 at 30 mg/kg (q4w) increased and maintained the levels of PGRN ~160% to 200% (2.6- to 3-fold) above baseline in plasma and ~80% (1.8-fold) above baseline in the CSF of healthy volunteers
- The pharmacokinetic/pharmacodynamic profile of AL101 following single[9] and multiple IV doses supports future development with either a q4w dosing interval at 30 mg/kg or a q8w interval at a higher dose
- The pharmacokinetic/pharmacodynamic profile of AL101 following single[9] and multiple SC doses suggests that a 300 mg SC (q2w) dosing is not sufficient and further optimization of SC dose regimen is needed
- AL101 is a potent modulator of PGRN levels in the CSF, with a pharmacokinetic/pharmacodynamic profile that supports development in chronic neurological conditions, such as AD and PD

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Disclosures and Acknowledgments

This study was funded by Alector, Inc. All authors are employees and shareholders at Alector, Inc. Medical writing services were provided by SCIENT Healthcare Communications and funded by Alector, Inc. We thank the site staff, participants, and their families for participation in the clinical trial.

Presented at the 15th Clinical Trials on Alzheimer's Disease Conference | November 29-December 2, 2022 | San Francisco, CA