A First-In-Human Study 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,[1,2] Alzheimer's disease (AD),[3] and Parkinson's disease[4]
- PGRN deficiency increases plaque deposition and impairs phagocytosis in animal models of AD, while overexpression or treatment with recombinant PGRN reduces plaque burden[5-7]
- Reduced levels of PGRN have been associated with Parkinson's disease severity[8] and neuron loss in a neurotoxic mouse model of Parkinson's disease,[9] while PGRN gene delivery protects dopaminergic neurons in the Parkinson's disease model[7]
- The Sortilin receptor, expressed on neurons and microglia, is a key regulator of PGRN levels through Sortilin-mediated degradation[10,11]
- Independent of the Sortilin-mediated lysosomal trafficking pathway, PGRN can localize to the lysosome through a pathway involving interactions with prosaposin and its receptors mannose-6-phosphate receptor and low-density lipoprotein receptor-related protein[12,13]
- AL101 is a human monoclonal immunoglobulin G1 antibody that downregulates Sortilin and increases PGRN in preclinical models, and is being developed by Alector for the treatment of neurodegenerative disorders
- Increasing PGRN levels may be an effective therapeutic approach,[14,15] potentially reducing the rate of neuron loss and clinical decline in individuals with neurodegenerative disease

Objective

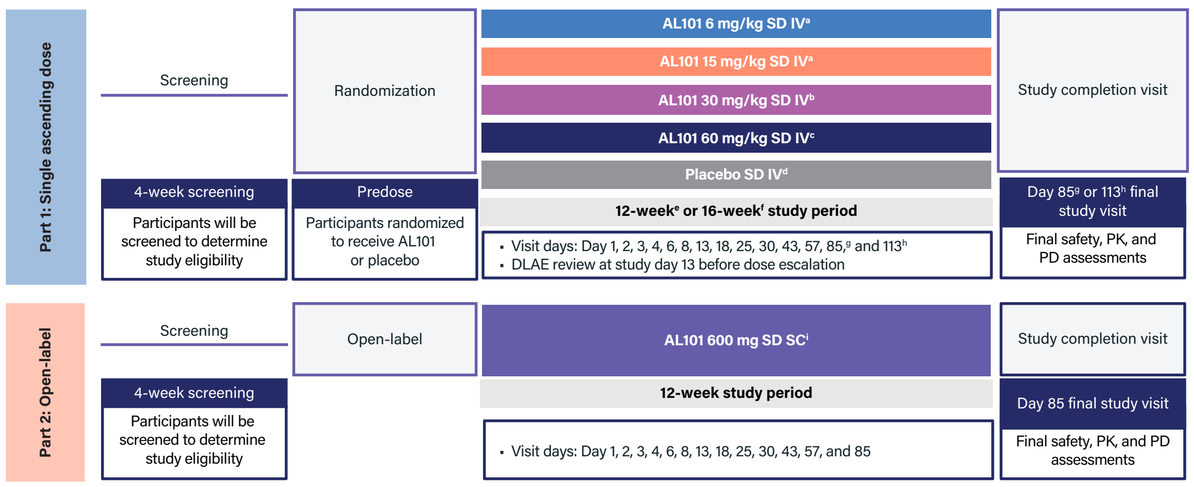
- The primary objective of this study was to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and bioavailability of AL101 in healthy volunteers when administered as a single, dose-escalating intravenous (IV) infusion, or as a single subcutaneous (SC) administration

Methods

Study design

- AL101-1 was a first-in-human, phase 1 study designed to investigate the safety, tolerability, PK, PD, and bioavailability of single doses of AL101 administered via the IV and SC routes
- As shown in **Figure 1**, AL101-1 consisted of 2 parts:
  - The first part was a randomized, double-blind, placebo-controlled, single-ascending-dose (SAD) study of AL101 vs placebo, in which participants were assigned 8:3 (AL101:placebo) to receive a single IV infusion of placebo or 6 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg AL101. The first 2 participants in each SAD IV group were sentinel-dose subjects who received study drug at least 48 hours prior to the remaining participants in that dose group. The dose-limiting adverse event (DLAE) window extends to day 13 (12 days postdose) for the SAD groups
  - The second part was an open-label study of SC administration of a single dose of 600 mg AL101 given as a slow injection over 15 minutes; this dose corresponds to a maximum dose level of 13.3 mg/kg for the lowest body weight permitted in the study (45 kg). This cohort was enrolled after the Safety Review Committee determined that the 15 mg/kg IV dose level was generally safe and tolerable

Figure 1. Study Design



CSF, cerebrospinal fluid; DLAE, dose-limiting adverse event; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; SD, single dose.
[a]Postdose CSF sampling occurred at 2 time points on days 25, 43, or 57.
[b]Postdose CSF sampling occurred at 2 time points on days 25, 43, 57, or 85.
[c]Postdose CSF sampling occurred at 2 time points on days 43, 57, or 85.
[d]Postdose CSF sampling occurred at 2 time points on days 25, 43, 57, or 85.
[e]Participants in the 6 mg/kg, 15 mg/kg, and 30 mg/kg dose groups were followed for 12 weeks.
[f]Participants in the 60 mg/kg dose group were followed for 16 weeks.
[g]Final study visit for participants in the 6 mg/kg, 15 mg/kg, and 30 mg/kg dose groups.
[h]Final study visit for participants in the 60 mg/kg dose group.
[i]Postdose CSF sampling occurred at 2 time points on days 8, 13, 18, 25, or 43.

Study endpoints

- Safety endpoints included the incidence, nature, and severity of adverse events (AEs); the incidence of dose-limiting AEs; the incidence of treatment discontinuation due to AEs; and the emergence of abnormal values or changes from baseline in clinical laboratory tests, echocardiogram assessments, blood pressure and heart rate, and vital sign measurements
- PK endpoints included serum and cerebrospinal fluid (CSF) concentrations of AL101 at specified time points and the bioavailability of AL101 administered SC
- PD endpoints included changes in levels of PGRN in plasma and CSF after dosing relative to baseline concentration

Eligibility criteria

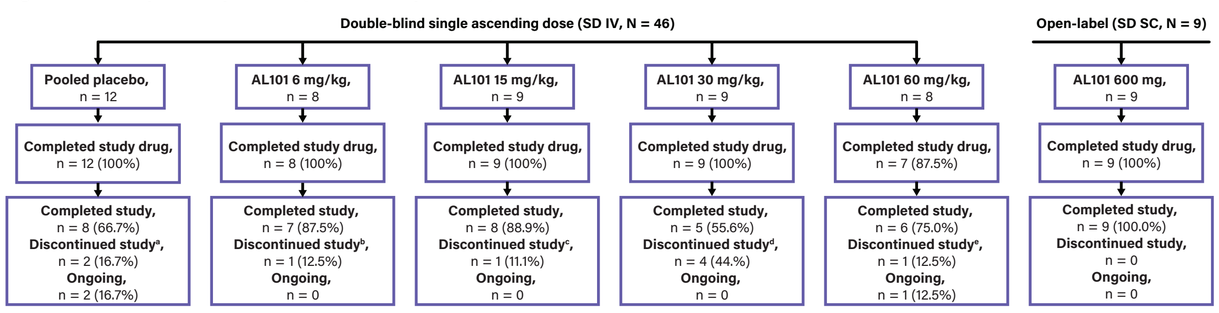
- Participants were included in the study if they were non- or light-smoking males or nonpregnant females who were 18 to 65 years of age, in good physical health, able to provide written informed consent, and had stopped taking over-the-counter and prescribed medications (with several exceptions) at least 14 and 30 days prior to the study, respectively
- Participants were excluded from the study if they met any of the following key criteria, among others: known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins; positive drug or alcohol test at screening and prior to first dose; history of alcohol or substance abuse, seizures, major depression, schizophrenia, schizoaffective disorder, bipolar disorder, or cancer (except if the cancer was considered cured, was not being actively treated, and had a low probability of recurrence); significant and/or acute illness within 5 days of dosing; surgery or hospitalization within 28 days of screening; and any serious medical condition or abnormality in clinical laboratory tests

Results

Participants

- A total of 55 participants enrolled in the study (**Figure 2**)
- 54 participants (98.2%) completed drug treatment and 43 participants (78.2%) completed the study
- Baseline demographics and characteristics were similar across groups (**Table 1**)
  - On average, participants were in their early forties
  - Across all groups, most participants were either White or Black and the majority were not Hispanic or Latino

Figure 2. Participant Disposition (Enrolled Population)



IV, intravenous; SC, subcutaneous; SD, single dose.
[a]Withdrawal by the subject (n = 2).
[b]Withdrawal by the subject.
[c]Physician decision.
[d]Physician decision (n = 1) and withdrawal by the subject (n = 3).
[e]Adverse event.

Table 1. Baseline Demographics and Characteristics (Safety Population)

	Double-blind single ascending dose IV					Open-label SC
	Pooled placebo (N = 12)	AL101 6 mg/kg (N = 8)	AL101 15 mg/kg (N = 9)	AL101 30 mg/kg (N = 9)	AL101 60 mg/kg (N = 8)	AL101 600 mg (N = 9)
Age (years), mean (SD)	43.7 (10.9)	39.0 (14.8)	41.9 (13.1)	40.0 (12.3)	39.0 (14.0)	44.4 (11.4)
Sex, n (%)						
Female	6 (50.0)	2 (25.0)	5 (55.6)	3 (33.3)	5 (62.5)	3 (33.3)
Male	6 (50.0)	6 (75.0)	4 (44.4)	6 (66.7)	3 (37.5)	6 (66.7)
Race, n (%)						
White	8 (66.7)	6 (75.0)	1 (11.1)	5 (55.6)	7 (87.5)	3 (33.3)
Black or African American	4 (33.3)	2 (25.0)	5 (55.6)	4 (44.4)	1 (12.5)	5 (55.6)
Asian	0	0	0	0	0	1 (11.1)
American Indian or Alaska Native	0	0	1 (11.1)	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0
Multiracial	0	0	1 (11.1)	0	0	0
Not reported	0	0	1 (11.1)	0	0	0
Ethnicity, n (%)						
Hispanic or Latino	4 (33.3)	1 (12.5)	3 (33.3)	3 (33.3)	4 (50.0)	4 (44.5)
Not Hispanic or Latino	8 (66.7)	7 (87.5)	6 (66.7)	6 (66.7)	4 (50.0)	5 (55.6)
Screening height (cm), mean (SD)	174.1 (11.5)	172.6 (8.9)	169.3 (6.8)	174.3 (10.7)	167.4 (8.3)	169.0 (9.8)
Screening weight (kg), mean (SD)	86.5 (13.4)	75.8 (13.8)	75.6 (11.5)	80.0 (15.5)	79.3 (16.4)	78.4 (12.9)
Predose weight (kg), mean (SD)	86.1 (13.4)	75.3 (13.6)	75.4 (11.7)	79.8 (15.0)	78.3 (16.5)	78.4 (12.9)
Screening BMI (kg/m^2), mean (SD)	28.6 (3.5)	25.3 (3.1)	26.3 (2.9)	26.1 (2.7)	28.1 (3.6)	27.4 (3.3)

BMI, body mass index; IV, intravenous; SC, subcutaneous; SD, standard deviation.

Safety

- Most AEs were considered mild to moderate in severity, with the most frequent AEs being headache (25.6%), anemia (9.3%), and procedural pain (9.3%) (**Table 2**)
- There was 1 serious and severe event of infusion reaction (60 mg/kg IV group) considered related to study treatment; this participant discontinued study drug shortly after infusion and recovered the same day
- There was 1 serious and severe adverse event of Influenza A (placebo group) considered unrelated to study treatment
- There was 1 patient (30 mg/kg group) with concurrent severe glomerular filtration rate decreased/elevated creatinine (both nonserious) considered unrelated to study treatment

Table 2. TEAEs Occurring in 2 or More Subjects Across All Groups (Safety Population)

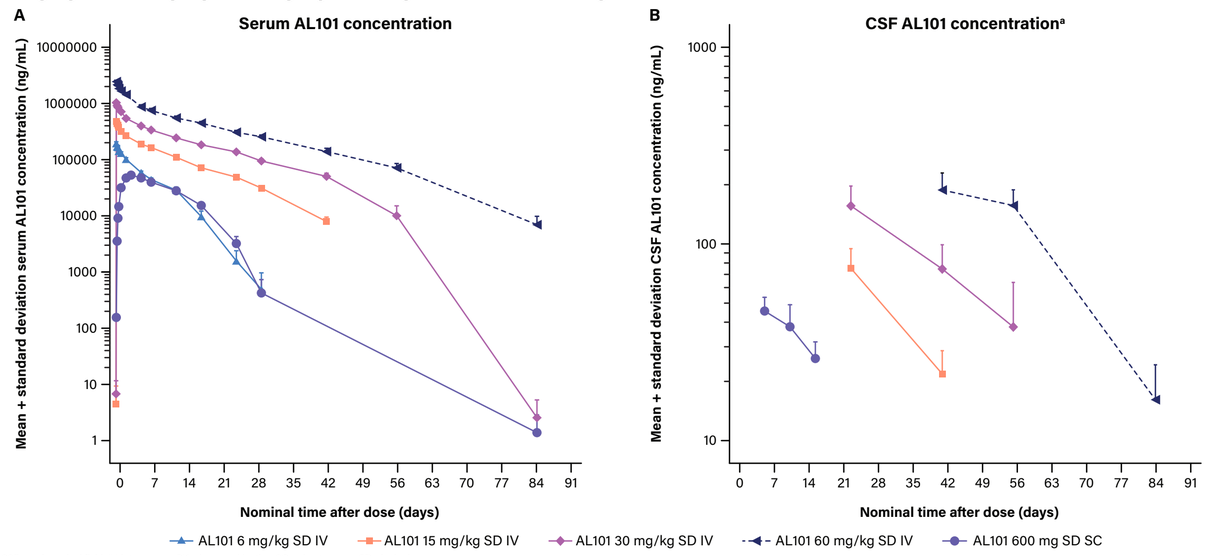
		Double-blind single ascending dose IV				Open-label SC	
n (%) [E]	Pooled placebo (N = 12)	AL101 6 mg/kg (N = 8)	AL101 15 mg/kg (N = 9)	AL101 30 mg/kg (N = 9)	AL101 60 mg/kg (N = 8)	AL101 600 mg (N = 9)	All Active AL101 (N=43)
Any TEAE	7 (58.3) [11]	4 (50.0) [9]	7 (77.8) [9]	7 (77.8) [15]	5 (62.5) [12]	6 (66.7) [14]	29 (67.4) [59]
Headache	0	3 (37.5) [5]	1 (11.1) [1]	3 (33.3) [4]	3 (37.5) [4]	1 (11.1) [1]	11 (25.6) [15]
Anemia	0	1 (12.5) [1]	2 (22.3) [3]	1 (11.1) [1]	0	0	4 (9.3) [5]
Procedural pain	0	3 (37.5) [3]	0	0	0	1 (11.1) [1]	4 (9.3) [4]
Back pain	0	0	0	1 (11.1) [1]	2 (25.0) [2]	0	3 (7.0) [3]
Injection-site erythema	0	0	0	0	0	3 (33.3) [3]	3 (7.0) [3]
Injection-site induration	0	0	0	0	0	3 (33.3) [3]	3 (7.0) [3]
Alanine aminotransferase increased	1 (8.3) [1]	0	1 (11.2) [1]	1 (11.1) [1]	0	0	2 (4.7) [2]
Post–lumbar puncture syndrome	1 (8.3) [1]	0	2 (22.2) [2]	0	0	0	2 (4.7) [2]

E, number of events; IV, intravenous; SC, subcutaneous; TEAE, treatment-emergent adverse event.

AL101 Pharmacokinetics

- Mean serum (**Figure 3A**) and CSF (**Figure 3B**) concentrations of AL101 increased in a dose-dependent manner after a single ascending IV dose of AL101
- AL101 exhibited dose-proportional serum PK with IV dosing, with some increase in clearance at the lowest IV dose (**Table 3**)
- Serum (**Figure 3A**) and CSF (**Figure 3B**) concentrations of AL101 were detected for up to 30 and 17 days, respectively, after a single SC dose of 600 mg AL101, and for up to 84 days after a single IV dose of 60 mg/kg
- The mean CSF to serum partition coefficient ranged from 0.11% to 0.68% (**Table 3**)

Figure 3. (A) Serum and (B) CSF Concentrations of AL101 Plotted as a Function of Time After Receiving a Single IV Dose of AL101 Ranging From 6 mg/kg to 60 mg/kg or a Single SC Dose of 600 mg AL101



CSF, cerebrospinal fluid; IV, intravenous; PK, pharmacokinetics; SC, subcutaneous; SD, single dose.
[a]CSF concentrations of AL101 were below the limit of quantification (<15.6 ng/mL) for the 6 mg/kg IV dose group at day 25 and beyond.

Table 3. Summary of Mean (Standard Deviation) Serum PK Parameters of AL101

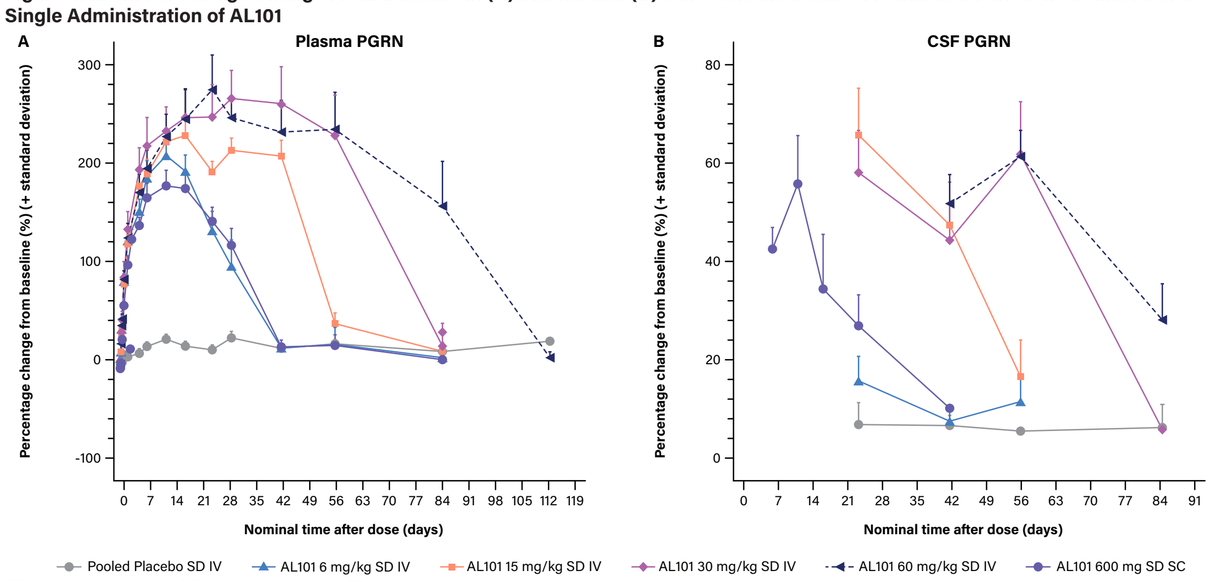
	AUC_{inf} (h*ug/mL)	CL (mL/h)	C_{max} (ug/mL)	t_{max} (h)	$t_{1/2}$ (h)	PC day 13	PC day 25	PC day 43	PC day 57
AL101 6 mg/kg IV	18700 (4010)	24.8 (5.15)	155 (32.3)	1.35 (0.02)	83.2 (16.5)	NE[a]	NE[b]	NE[b]	NE[b]
AL101 15 mg/kg IV	74400 (9830)	14.9 (1.23)	372 (49.7)	1.29 (0.04)	196 (44.0)	NE[a]	0.00183 (0.0008)	0.00347 (0.003)	NE[a]
AL101 30 mg/kg IV	178000 (20600)	13.6 (3.65)	753 (87.3)	2.61 (2.73)	261 (75.2)	NE[a]	0.00146 (0.0007)	0.00114 (0.0009)	0.00683 (0.0047)
AL101 60 mg/kg IV	438000 (85100)	NE	1740 (270)	1.81 (1.44)	294 (68.1)	NE[a]	NE[a]	0.0021 (0.0008)	0.00194 (0.0005)
AL101 600 mg SC	13500 (3280)	47.5 (15.0)	48.0 (9.86)	82.26 (27.38)	95.8 (58.8)	0.00178 (0.0009)	NE[a]	NE[a]	NE[a]

AUC_{inf}, area under the concentration-time curve from time 0 extrapolated to infinity; CL, total body clearance; C_{max}, maximum observed concentration; CSF, cerebrospinal fluid; IV, intravenous; NE, not evaluable; PC, partition coefficient; PK, pharmacokinetic; SC, subcutaneous; $t_{1/2}$, terminal elimination half-life; t_{max}, time of maximum observed concentration.
[a]PCs could not be calculated because CSF AL101 samples were not collected.
[b]PCs could not be calculated due to CSF samples being below the limit of quantification.

Pharmacodynamic response to AL101

- Generally a single ascending IV dose of AL101 caused an increase in PGRN levels in the periphery (**Figure 4A**) and the brain (**Figure 4B**), with a dose-dependent effect on the duration of the increase
- SC administration of 600 mg AL101 caused a robust increase in plasma PGRN that persisted up to 29 days after dosing (**Figure 4A**) and a parallel increase in CSF PGRN that persisted up to 24 days after dosing (**Figure 4B**)

Figure 4. Mean Percentage Change From Baseline in (A) Plasma and (B) CSF Concentrations of PGRN as a Function of Time After a Single Administration of AL101



CSF, cerebrospinal fluid; IV, intravenous; PGRN, progranulin; SC, subcutaneous; SD, single dose.

Conclusions

- In this first-in-human phase 1 study, AL101 was found to be generally safe and well tolerated with single-dose IV or SC administrations
- AL101 exposure increased in a dose-proportional manner. AL101 was distributed into the central nervous system, as evidenced by CSF AL101 concentrations
- AL101 is a potent modulator of PGRN levels in the CSF, with a PK/PD profile that supports development of SC AL101 in chronic conditions
- AL101 is being developed for the treatment of neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease

References

1. Baker M, et al. *Nature*. 2006;442(7105):916-919.
2. Cruts M, et al. *Nature*. 2006;442(7105):920-924.
3. Perry DC, et al. *JAMA Neurol*. 2013;70(6):774-778.
4. Nalls MA, et al. *Lancet Neurol*. 2019;18(12):1091-1102.
5. Guan Z, et al. *Front Cell Neurosci*. 2020;14:260.
6. Minami SS, et al. *Nat Med*. 2014;20(10):1157-1164.
7. Van Kampen JM & Kay DG. *PLoS One*. 2017;12(8):e0182896.
8. Yao YN, et al. *Neurosci Lett*. 2020;725:134873.
9. Martens LH, et al. *J Clin Invest*. 2012;122(11):3955-3959.
10. Carrasquillo MM, et al. *Am J Hum Genet*. 2010;87(6):890-897.
11. Hu F, et al. *Neuron*. 2010;68(4):654-667.
12. Paushter DH, et al. *Acta Neuropathol*. 2018;136(1):1-17.
13. Zhou X, et al. *J Cell Biol*. 2015;210(6):991-1002.
14. Lee WC, et al. *Hum Mol Genet*. 2014;23(6):1467-1478.
15. Meeter LH, et al. *Dement Geriatr Cogn Dis Extra*. 2016;6(2):330-340.

Disclosures

This study was funded by Alector, Inc. All authors are employees and shareholders at Alector, Inc.

Acknowledgments

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 14th Clinical Trials on Alzheimer's Disease Conference | November 9-12, 2021 | Boston, MA, USA