A Phase 1 Study of AL003 in Healthy Volunteers and Participants With Alzheimer's Disease

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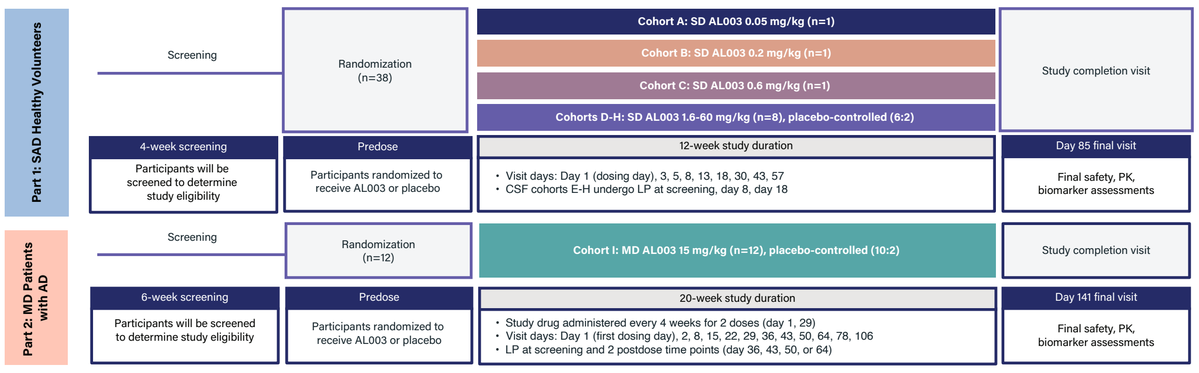
Background

- AL003 is a humanized anti–cluster of differentiation 33 (CD33) monoclonal antibody in development for the treatment of Alzheimer's disease (AD)
- AL003 targets CD33 (ie, sialic acid–binding immunoglobin-type lectin-3 [Siglec-3]), a transmembrane receptor expressed primarily on cells of myeloid lineage, including microglia[1-3]
- A growing body of evidence indicates that CD33 inhibition may be a promising therapeutic approach for treating AD
  - Large-scale genome-wide association studies (GWAS) identified CD33 as a susceptibility locus for late-onset AD (LOAD)
  - The CD33 rs3865444[A] allele variant is associated with reduced CD33 expression and confers protection against LOAD[4-6]
  - The rs3865444[C] risk allele is associated with (1) increased cell surface expression of CD33 on monocytes; (2) reduced uptake of Aβ42; (3) greater neuritic amyloid plaque burden and fibrillar amyloid on in vivo imaging; (4) increased numbers of activated human microglia in vivo[7]
  - Another single nucleotide polymorphism (SNP), rs12459419, which is in strong linkage disequilibrium (ie, coinherited) with rs3865444, appears to be the causal SNP modulating the alternative splicing of CD33 exon 2 and thus influencing susceptibility to AD[8,9]
  - Transgenic expression of human full-length CD33M in murine microglia inhibits phagocytosis[10]
- Preclinical models have shown that AL003 downregulates human CD33 expressed in microglia of transgenic mice, suggesting that AL003 may have potential clinical benefit against a pathologic process associated with AD

Methods

- INTERCEPT (NCT03822208) was a first-in-human, multicenter, randomized, placebo-controlled, double-blind phase 1 study designed to investigate the safety, tolerability, immunogenicity, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenous (IV) AL003 administered as single ascending doses (SADs) in healthy volunteers (HVs) and as multiple doses (MDs) in patients with mild-to-moderate AD
- The SAD portion of the trial (Part 1) enrolled a total of 38 HVs (29 received single-dose [SD] AL003; 9 received placebo), with doses ranging from 0.05 mg/kg to 60.0 mg/kg (**Figure 1**)
  - SAD cohorts A through C: Three HVs were sequentially enrolled into 3 single-participant cohorts and treated with AL003 0.05 mg/kg, 0.2 mg/kg, or 0.6 mg/kg
  - SAD cohorts D through H: Cohorts of 8 HVs (6 active; 2 placebo) were sequentially enrolled and treated with SDs of AL003 or placebo at dose levels ranging from 1.6 to 60 mg/kg
  - For cohorts E through H, lumbar puncture (LP) was performed at screening and on days 8 and 18 to obtain cerebrospinal fluid (CSF) samples to measure PK and exploratory biomarker levels
- In the MD portion of the trial (Part 2), 12 participants with mild-to-moderate AD were enrolled into Cohort I and received 2 doses of AL003 15 mg/kg or placebo (10 active; 2 placebo) administered 4 weeks apart (ie, q4w × 2)
  - The MD cohort had LP performed at screening and at 2 postdose time points for each patient (day 36, 43, 50, or 64)
- SAD cohorts were followed for safety for 12 weeks after SD study drug, and MD cohorts were followed for 16 weeks after the last dose of study drug

Figure 1. AL003-1 Study Design and Enrollment



AD, Alzheimer's disease; CSF, cerebrospinal fluid; LP, lumbar puncture; MD, multiple-dose; PK, pharmacokinetics; SAD, single ascending dose; SD, single-dose.

Key inclusion criteria

General

- Participants with body weight from 50 kg to 120 kg with clinical laboratory evaluations within the reference range for the test laboratory, unless deemed not clinically significant by the investigator
- Females must be nonpregnant and nonlactating, and either surgically sterile, using a highly effective contraceptive method from screening through the follow-up period, abstinent from heterosexual intercourse, or postmenopausal for ≥12 months
- Men must be surgically sterile, abstinent from heterosexual intercourse, or use acceptable contraception and must not donate sperm from screening through the follow-up period
- Negative test for selected drugs of abuse at screening (does not include alcohol) and at admission (includes alcohol breath test)

In addition, for SAD cohorts (HVs):

- Aged 18 to 65 years and in good health, determined by no clinically significant findings from medical history, physical examination, 12-lead electrocardiogram (ECG), laboratory tests, and vital signs

In addition, for MD cohorts (patients with AD):

- Aged 50 to 85 years, with a diagnosis of probable AD dementia based on National Institute on Aging Alzheimer's Association criteria
- Mini-Mental State Examination (MMSE) score of 16–28 points
- Screening Clinical Dementia Rating-Global Score (CDR-GS) of 0.5, 1.0, or 2.0
- A positive amyloid positron emission tomography scan based on qualitative read
- If taking cholinesterase inhibitor and/or memantine therapy for AD, on a stable dosing regimen for 4 weeks prior to screening

Key exclusion criteria

General

- Carriers of two copies of the rs12459419[T] allele, which may be protective against AD through reduced CD33 expression
- Contraindication for LP

In addition, for SAD cohorts (HVs):

- QT interval corrected using Fridericia's formula (QTcF) >450 ms, demonstrated by ≥2 ECGs >30 minutes apart

In addition, for MD cohorts (patients with AD):

- Dementia due to a condition other than AD
- History or presence of stroke within the past 2 years; history or presence of vascular disease that has the potential to affect cognitive function; history of severe, clinically significant central nervous system (CNS) trauma
- Contraindication to magnetic resonance imaging (MRI) or inability to tolerate MRI
- QTcF >470 ms for male participants and >480 ms for female participants, demonstrated by ≥2 ECGs >30 minutes apart

Safety endpoints

- Incidence, nature, severity, and seriousness of all adverse events (AEs) and all treatment-emergent AEs (TEAEs)
- Incidence of dose-limiting AEs (DLAEs), treatment discontinuations due to AEs, and dose reductions due to AEs
- Mean changes in clinical laboratory tests and vital signs from baseline over time
- Incidence of treatment-emergent abnormal laboratory values and abnormal vital sign measurements
- Incidence of suicidal ideation/behavior (MD patient cohort only) determined using the Sheehan Suicidality Tracking Scale

PK and fluid biomarker endpoints

- Serum and CSF concentration profiles of AL003 and relevant PK parameters
- Incidence of treatment-emergent antidrug antibodies (ADAs)
- CD33 surface expression on monocytes
- CSF concentrations of soluble (s)CD33

Results

- Among 38 enrolled HVs, 29 participants received SD AL003, and 9 participants received placebo (**Table 1**)
  - Actual enrollment for Cohort H (60 mg/kg) included 2 participants who received AL003 and 1 who received placebo
- Among HVs, 3 participants in the AL003 group withdrew from the study
  - One participant in the 30 mg/kg group and 1 participant in the 60 mg/kg group withdrew consent
  - One participant in the 0.05 mg/kg group discontinued the study due to relocation
- Of the 12 patients with AD, 10 received MD AL003 15 mg/kg and 2 received placebo
- All patients with AD completed the study

Table 1. Baseline Demographics

	SAD HVs		MD patients with AD	
	Total AL003 (n=29)	Pooled placebo (n=9)	AL003 15 mg/kg (n=10)	Pooled placebo (n=2)
Female sex, n (%)	19 (65.5)	2 (22.2)	5 (50.0)	2 (100.0)
Age, years, mean (SD)	27.1 (8.48)	34.6 (15.07)	77.6 (4.06)	76.0 (4.24)
Race, n (%)				
White	16 (55.2)	6 (66.7)	9 (90.0)	2 (100.0)
Asian	8 (27.6)	3 (33.3)	0	0
Black/African American	1 (3.4)	0	0	0
Other	4 (13.8)	0	1 (10.0)	0
Hispanic/Latino ethnicity, n (%)	1 (3.4)	0	0	0
BMI at screening, kg/m², mean (SD)	25.50 (5.251)	24.63 (3.002)	26.65 (5.031)	23.65 (1.061)
Day 1 predose body weight, kg, mean (SD)	71.91 (14.228)	73.09 (11.564)	74.00 (17.778)	59.95 (0.071)

AD, Alzheimer's disease; BMI, body mass index; HV, healthy volunteer; MD, multiple-dose; SAD, single ascending dose; SD, standard deviation.

Safety

- Overall, 79.3% of HVs in the total AL003 group experienced TEAEs compared with 77.8% of HVs in the pooled placebo group (**Table 2**)
  - Dose levels up to 15 mg/kg were well tolerated in HVs with immune-related AEs seen at higher dose levels (30 and 60 mg/kg)
    - The most frequently reported TEAEs in HVs receiving AL003 were headache (20.7%), post-LP syndrome (ie, headache after LP; 17.2%), nausea (13.8%), upper respiratory tract infection (13.8%), and puncture-site pain (10.3%)
    - 2 HVs experienced SAEs considered related to the study drug. One participant (AL003 30 mg/kg) reported aseptic arthritis of the hip 15 days after receiving study drug and required hospitalization and treatment with oral corticosteroids for 4 days. One participant (AL003 60 mg/kg) reported severe hypersensitivity characterized by rash, fever, thrombocytopenia, and elevated c-reactive protein 9 days after receiving study drug; this participant required hospitalization and treatment with oral corticosteroids, analgesics, and antihistamines
    - The AE of hypersensitivity in the 60 mg/kg cohort (Cohort H) met the protocol-defined criteria for a DLAE and led to discontinuation of further enrollment in this cohort
- Among the MD cohort of patients with AD, 70.0% of patients in the AL003 group (15 mg/kg) experienced TEAEs compared with 100.0% of patients in the placebo group
  - One patient with AD in the AL003 group (15 mg/kg) experienced an unrelated SAE (cerebrovascular accident)
- No TEAEs leading to study drug withdrawal or early discontinuation occurred during the study among the SAD HVs or MD patients with AD

Table 2. Safety[a]

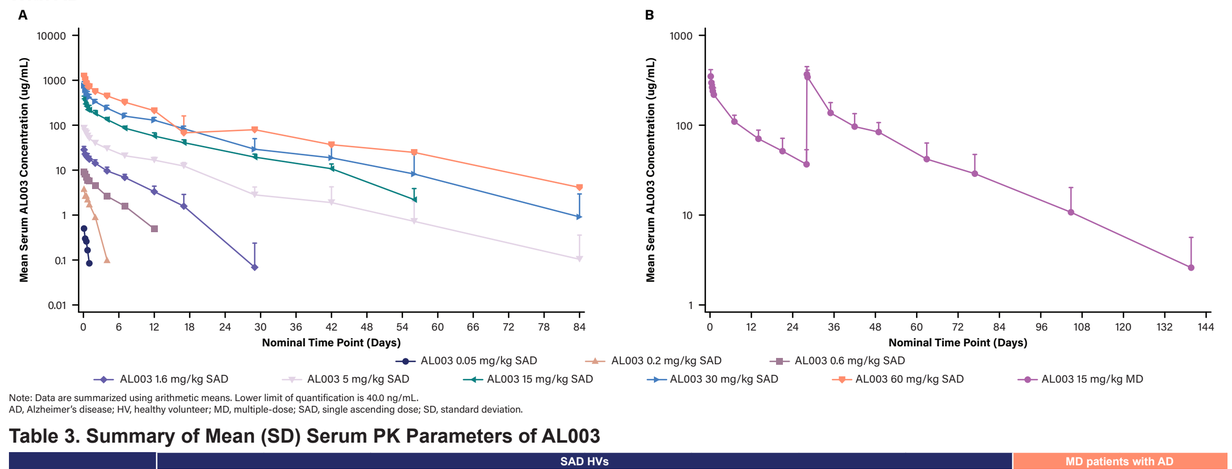
	SAD HVs							MD patients with AD	
System Organ Class Preferred Term	AL003 0.05-0.6 mg/kg (n=3) n (%)	AL003 1.6 mg/kg (n=6) n (%)	AL003 5 mg/kg (n=6) n (%)	AL003 15 mg/kg (n=6) n (%)	AL003 30 mg/kg (n=6) n (%)	AL003 60 mg/kg (n=2) n (%)	Pooled placebo (n=9) n (%)	AL003 15 mg/kg (n=10) n (%)	Pooled placebo (n=2) n (%)
Participants with ≥1 TEAE	2 (66.7)	5 (83.3)	5 (83.3)	5 (83.3)	4 (66.7)	2 (100.0)	7 (77.8)	7 (70.0)	2 (100.0)
TEAEs in ≥5% of total AL003 HVs									
Headache	0	1 (16.7)	0	3 (50.0)	1 (16.7)	1 (50.0)	4 (44.4)	1 (10.0)	0
Post-LP syndrome	0	0	1 (16.7)	2 (33.3)	2 (33.3)	0	1 (11.1)	0	0
Nausea	0	1 (16.7)	1 (16.7)	0	2 (33.3)	0	3 (33.3)	0	0
URTI	1 (33.3)	1 (16.7)	1 (16.7)	0	0	1 (50.0)	1 (11.1)	0	0
Puncture-site pain	0	0	1 (16.7)	1 (16.7)	1 (16.7)	0	0	0	0
Arthralgia	0	0	0	0	1 (16.7)	1 (50.0)	0	0	0
Arthritis	0	0	0	0	2 (33.3)	0	0	0	0
Dizziness	0	0	1 (16.7)	1 (16.7)	0	0	0	0	1 (50.0)
Gastroenteritis	0	0	0	1 (16.7)	0	1 (50.0)	1 (11.1)	0	1 (50.0)
Oral herpes	0	1 (16.7)	1 (16.7)	0	0	0	0	0	0
Orthostatic hypotension	0	1 (16.7)	1 (16.7)	0	0	0	0	0	0
Viral URTI	0	0	1 (16.7)	1 (16.7)	0	0	0	0	0
Participants with ≥1 SAE	0	0	0	0	1 (16.7)	1 (50.0)	0	1 (10.0)	0

[a]A TEAE is defined as an AE that commenced on or after the time of first study drug administration. If a participant has multiple occurrences of a TEAE, the subject is counted only once in the subject count (n) column for a given system organ class and preferred term. AEs were coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities Version 24.0.
AD, Alzheimer's disease; AE, adverse event; HV, healthy volunteer; LP, lumbar puncture; MD, multiple dose; SAD, single ascending dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

PK

- After a single IV infusion of AL003 0.05 to 60 mg/kg in HVs, mean serum concentrations of AL003 were consistently elevated in a dose-dependent manner (**Figure 2A**)
- AL003 has an approximately dose-proportional C_{max} and AUC_{0-inf} from 15 mg/kg to 30 mg/kg, with nonlinear exposures between dose levels of 1.6 mg/kg to 15 mg/kg (**Table 3**)
- In the MD patient cohort (15 mg/kg, 2 doses, q4w), C_{max} was similar to that of HVs in the AL003 15 mg/kg group (**Figure 2B**); patients with AD showed slightly slower clearance, which was reflected by a longer half-life at day 29 in patients with AD when compared with day 1 in HVs
- For both SAD HVs and MD patient cohorts, mean CSF concentration-time profiles for AL003 demonstrated CNS penetrance of AL003 (**Figure 3**) with geometric mean partition coefficients (CSF over serum) of 0.1% to 0.2%

Figure 2. Mean (SD) Serum AL003 Concentration Profiles Over Time by Treatment Group (semi-log) for (A) SAD HVs and (B) MD Patients With AD



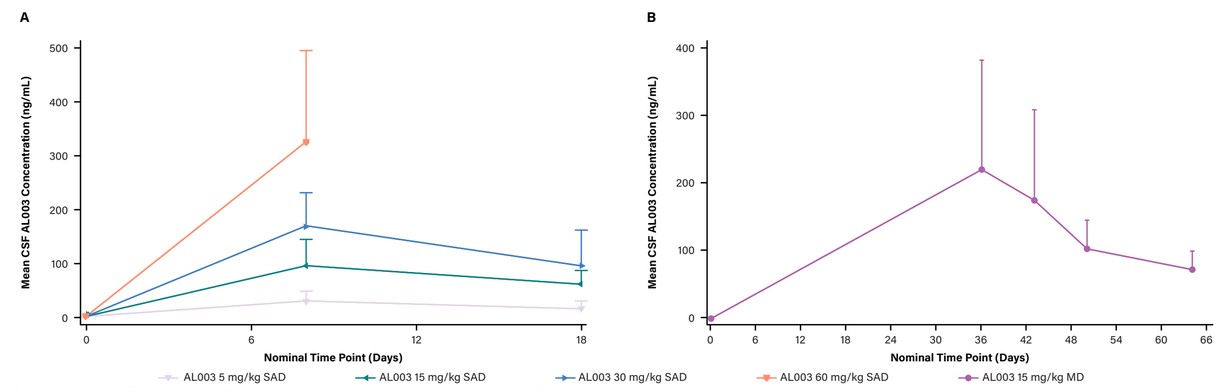
Note: Data are summarized using arithmetic means. Lower limit of quantification is 40.0 ng/mL.
AD, Alzheimer's disease; HV, healthy volunteer; MD, multiple-dose; SAD, single ascending dose; SD, standard deviation.

Table 3. Summary of Mean (SD) Serum PK Parameters of AL003

	SAD HVs								MD patients with AD	
	AL003 0.05 mg/kg (n=1)	AL003 0.2 mg/kg (n=1)	AL003 0.6 mg/kg (n=1)	AL003 1.6 mg/kg (n=6)	AL003 5 mg/kg (n=6)	AL003 15 mg/kg (n=6)	AL003 30 mg/kg (n=6)	AL003 60 mg/kg (n=2)	AL003 15 mg/kg (n=9) Day 1	AL003 15 mg/kg (n=10) Day 29
AUC_{0-inf} (h*ug/mL)	NA	NA	811 (NC)	3290 (673)	13 900 (2890)	58 600 (7610)	111 000 (25 100)	175 000 (44 900)		
CL (mL/h)	NA	NA	44.4 (NC)	35.7 (5.41)	23.9 (3.53)	19.5 (3.39)	21.7 (6.97)	22.5 (6.75)		
AUC_{tau} (h*ug/mL)									NA	84 300 (25 000)
CLss (mL/h)									NA	14.8 (6.90)
C_{max} (ug/mL)	0.502 (NC)	3.87 (NC)	9.00 (NC)	28.5 (5.20)	86.2 (11.0)	387 (57.2)	773 (147)	1250 (104)	348 (65.3)	370 (78.2)
t_{max} (h)	1.43 (NC)	1.17 (NC)	1.38 (NC)	1.18 (0.03)	1.19 (0.15)	1.45 (0.55)	1.90 (1.53)	2.20 (0.02)	1.29 (0.10)	1.68 (1.17)
$t_{1/2}$ (h)	NA	NA	88.9 (NC)	119 (31.3)	184 (75.3)	244 (45.8)	195 (89.2)	177 (191)	241 (52.6)	375 (173)

AD, Alzheimer's disease; AUC_{0-inf}, area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{tau}, areas under the drug concentration-time curve over the interdosing interval; CL, total body clearance; CLss, steady state clearance; C_{max}, maximum observed concentration; HV, healthy volunteer; MD, multiple-dose; NA, not available; NC, not calculable; PK, pharmacokinetic; SAD, single ascending dose; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; t_{max}, time of maximum observed concentration.

Figure 3. Mean (SD) CSF AL003 Concentration Profiles Over Time by Treatment Group (Linear) for (A) SAD HVs and (B) MD Patients With AD

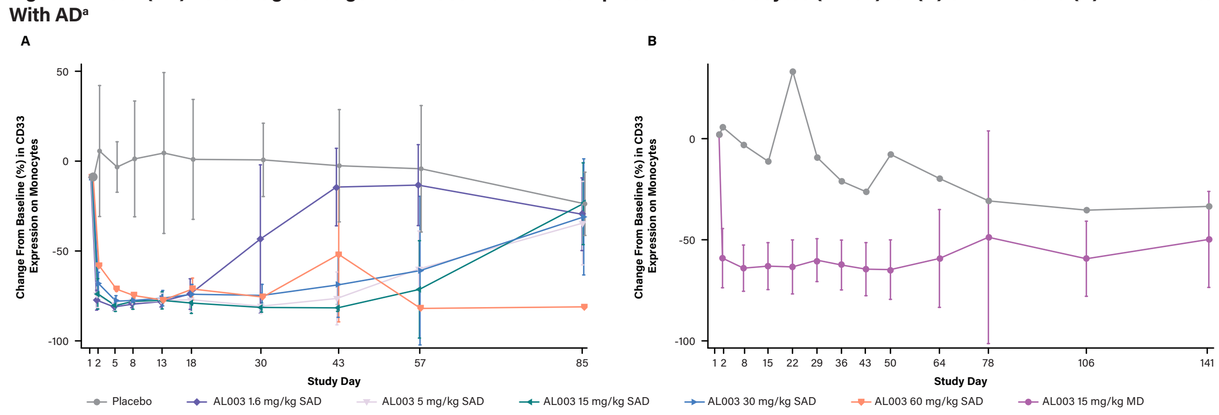


AD, Alzheimer's disease; CSF, cerebrospinal fluid; HV, healthy volunteer; MD, multiple-dose; SAD, single ascending dose; SD, standard deviation.

Fluid biomarkers

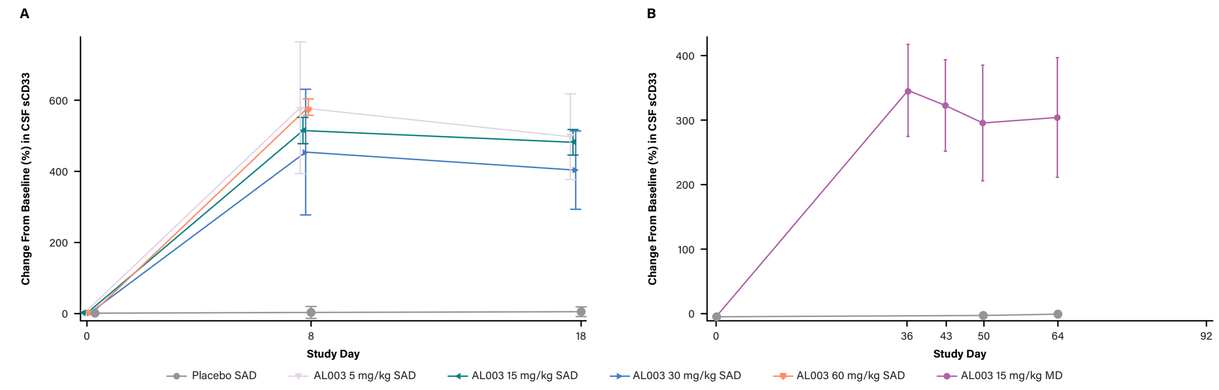
- SD AL003 treatment reduced CD33 expression on peripheral monocytes in HVs at dose levels of 1.6 mg/kg and greater (**Figure 4A**)
- MD AL003 treatment reduced CD33 expression on peripheral monocytes in patients with AD and was sustained for nearly the entire study duration (**Figure 4B**)
- SD AL003 treatment increased CSF levels of sCD33 in HVs, providing evidence of AL003 CNS target engagement (**Figure 5A**)
- MD AL003 treatment increased CSF levels of sCD33 in patients with AD, and sCD33 remained elevated from baseline at day 64, supporting MD dosing intervals of 4 weeks or longer (**Figure 5B**)

Figure 4. Mean (SD) Percentage Change From Baseline in CD33 Expression on Monocytes (MESF) for (A) SAD HVs and (B) MD Patients With AD[a]



[a]One patient with AD in the placebo group was not included due to missing baseline values.
AD, Alzheimer's disease; HV, healthy volunteer; MD, multiple-dose; MESF, molecules of equivalent soluble fluorochrome; SAD, single ascending dose; SD, standard deviation.

Figure 5. Mean (SD) Percentage Change From Baseline in CSF Concentration of sCD33 for (A) SAD HVs and (B) MD Patients With AD



AD, Alzheimer's disease; CSF, cerebrospinal fluid; HV, healthy volunteer; MD, multiple-dose; SAD, single ascending dose; sCD33, soluble cluster of differentiation 33; SD, standard deviation.

Conclusions

- In this first-in-human study, AL003 was found to be generally safe and well tolerated in healthy volunteers and patients with AD up to and including doses of 15 mg/kg
- The phase 1 data demonstrated target engagement of AL003 in both blood and CNS compartments across the tolerated dose range
- The favorable safety profile and evidence of CD33 target engagement support further clinical development of AL003 for the treatment of AD
- A phase 2 proof of concept study is being planned

References

1. Crocker PR, et al. *Nat Rev Immunol.* 2007;7(4):255-266.
2. Griciuc A, et al. *Neuron.* 2013;78(4):631-643.
3. Walker DG, et al. *Neurobiol Aging.* 2015;36(2):571-582.
4. Naj AC, et al. *Nat Genet.* 2011;43(5):436-441.
5. Hollingworth P, et al. *Nat Genet.* 2011;43(5):429-435.
6. Jiang YT, et al. *Ann Transl Med.* 2018;6(10):169.
7. Bradshaw EM, et al. *Nat Neurosci.* 2013;16(7):848-850.
8. Malik M, et al. *J Neurosci.* 2013;33(33):13320-13325.
9. Raj T, et al. *Hum Mol Genet.* 2014;23(10):2729-2736.
10. Bhattacherjee A, et al. *Commun Biol.* 2019;2(450).

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