2. LZAN Synopsis

Clinical Study Report Synopsis: Study H8A-MC-LZAN

Title of Study: Effect of Passive Immunization on the Progression of Alzheimer's Disease: Solanezumab (LY2062430) versus Placebo

Number of Investigator(s): This multicenter study included 111 principal investigators.

Study Center(s): This study was conducted at 111 study centers in 13 countries.

Publication(s) Based on the Study: None at this time.

Length of Study:
Date first subject enrolled (assigned to therapy): 11 June 2009
Date of last subject visit: 20 June 2012

Phase of Development: 3

Study H8A-MC-LZAN (LZAN) was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study comparing solanezumab and placebo for 18 months in 1040 subjects with mild-to-moderate Alzheimer's disease (AD). Originally, Study LZAN was designed with coprimary cognitive and functional outcome measures (the 11-item Alzheimer's Disease Assessment Scale-Cognitive subscale [ADAS-Cog_{11}] and the Alzheimer's Disease Cooperative Study-Activities of Daily Living [ADCS-ADL]) in a mild-to-moderate study population (defined in the protocol as subjects with a baseline Mini-Mental Status Examination [MMSE] score of 16 to 26). Because a previously completed study, Study H8A-MC-LZAM (LZAM), did not meet these same coprimary objectives, but did demonstrate cognitive effects in a prespecified population with mild AD (defined in the protocol as baseline MMSE score of 20 to 26), a draft of the statistical analysis plan (SAP) for LZAN was revised to prespecify the mild population as the primary analysis population prior to database lock. The primary outcome measure was also revised to the 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog_{14}), which includes 3 additional items, compared to the ADAS-Cog_{11}, considered relevant for patients with mild AD.

Primary Objective:

The primary objective of this study was to test the hypothesis that intravenous infusion of solanezumab would slow the decline of AD, compared with placebo, in subjects with mild AD at baseline (Visit 1 MMSE 20 to 26) over 80 weeks of treatment. The primary objective was assessed using a mixed-model repeated-measures (MMRM) analysis of the ADAS-Cog_{14}. The specific hypothesis was that the decline at the end of the treatment phase for solanezumab would be significantly less than that for placebo.

Secondary Objectives:

The secondary objectives of this study were to further assess solanezumab versus placebo in subjects with mild AD at baseline as follows:

- To test the hypothesis that solanezumab would slow the cognitive decline associated with AD, compared with placebo, using the MMSE.
- To test the hypothesis that solanezumab would slow the functional decline associated with AD, compared with placebo, using the ADCS-ADL.
- To assess the functional decline with solanezumab, compared with placebo, using a subset of items from the ADCS-ADL for basic activities of daily living (ADLs) (Items 1 through 6) and also for instrumental activities of daily living (Items 7 through 23). In addition, the following ADCS-ADL factors were also assessed: household activities, basic ADLs (modified), communication/engagement, and outside activities.
- To test the hypothesis that solanezumab would slow the cognitive decline associated with AD, compared with placebo, using the ADAS-Cog_{11} and the 12-item extended version of the ADAS-Cog (ADAS-Cog_{12}).
- To assess the global clinical benefit of treatment with solanezumab as demonstrated through the Clinical Dementia Rating—Sum of Boxes (CDR-SB) and the Neuropsychiatric Inventory (NPI).
- To further assess differences between treatment groups in ADAS-Cog_{14}, ADAS-Cog_{11}, MMSE, and ADCS-ADL using the last-observation-carried-forward (LOCF) method of imputing missing data.
- To test the hypothesis that solanezumab will slow the rate of decline associated with AD, compared with placebo, assessed by using a slope analysis for the ADAS-Cog_{11}, ADAS-Cog_{12}, ADAS-Cog_{14}, MMSE,

CDR-SB, and ADCS-ADL.

- To assess the clinical benefit of treatment with solanezumab, as demonstrated through the Resource Utilization in Dementia—Lite (RUD-Lite), EuroQol 5-Dimensional Health-related Quality of Life Scale Proxy version (EQ-5D Proxy), and the Quality of Life in Alzheimer's Disease (QoL-AD) scales.
- To assess differences between solanezumab and placebo on the ADAS-Cog_{11}, ADAS-Cog_{12}, ADAS-Cog_{14}, ADCS-ADL, MMSE, and CDR-SB for completers of treatment.
- To assess the effect of solanezumab on the ADAS-Cog_{14}, ADCS-ADL, MMSE, and CDR-SB in subjects who completed the study and received complete infusions at each visit.
- To assess the effects of APOE*E4 carrier (E2/E4, E3/E4, E4/E4) and noncarrier (E3/E3, E2/E2, E3/E2) on treatment differences on the ADAS-Cog_{11}, ADAS-Cog_{12}, ADAS-Cog_{14}, ADCS-ADL, CDR-SB, and MMSE.
- To assess the effects of various other demographic and baseline characteristics on the treatment differences on the ADAS-Cog_{11}, ADAS-Cog_{12}, ADAS-Cog_{14}, ADCS-ADL, CDR-SB, and MMSE. Subgroups were based on: (1) gender; (2) race (dichotomized based on distribution of race in study); (3) family history of AD; (4) depression; (5) anticholinergic medication use; and (6) age group.
- To assess the treatment differences on the ADAS-Cog_{11}, ADAS-Cog_{12}, ADAS-Cog_{14}, ADCS-ADL, CDR-SB, and MMSE based on standard of care (StOC) medications at baseline. This was assessed by comparing subjects receiving (at baseline): (i) neither acetylcholinesterase inhibitors (AChEI) concomitant medications nor memantine; versus (ii) those receiving only AChEI medications; versus (iii) those receiving both AChEI medication(s) and memantine; versus (iv) those receiving memantine only.
- To assess treatment differences on the ADAS-Cog_{14} and ADCS-ADL for completers of treatment, excluding subjects who had changed doses of AChEI medication(s) and/or memantine, or who have started/stopped AChEI medication(s) and/or memantine anytime during the study.
- To provide supporting evidence that solanezumab attenuated the underlying pathologic process in AD, as measured by changes in plasma Aβ analyte levels and by using volumetric magnetic resonance imaging (vMRI) to assess the decline in brain volume.
- To provide further supporting evidence that solanezumab attenuates the underlying pathologic process in AD, as measured by several additional biomarkers that were collected via optional study addenda. Because these biomarkers were collected only in subsets of subjects, they are mentioned only briefly in the protocol to contribute to greater understanding of the study objectives. Specifically,
    - Addendum (2) tested the hypothesis that solanezumab would reduce the elevated concentrations of CSF tau proteins known to exist in patients with AD and evaluate the effect of solanezumab on CSF free (unbound to antibody) and total (sum of unbound and bound to antibody) $A\beta_{1-40}$ and $A\beta_{1-42}$, collected via lumbar punctures.
    - Addendum (3) tested the hypothesis that solanezumab would reduce brain amyloid burden as compared with placebo, as assessed using an amyloid-imaging agent.
- To compare the safety of solanezumab and placebo, through assessment of treatment-emergent adverse events (TEAEs), magnetic resonance imaging (MRI), vital signs, laboratory evaluations, electrocardiograms (ECGs), and immunogenicity measures.
- To assess the relationships between the change from baseline in plasma amyloid beta (Aβ) analytes and the change from baseline on the ADAS-Cog and ADCS-ADL.
- To assess the efficacy of solanezumab as compared to placebo in subjects with moderate AD at baseline (Visit 1 MMSE 16 to 19) and in the overall population by repeating all of the above-described analyses in those populations. Note that most of the analyses of ADAS-Cog will use the ADAS-Cog_{14} for the population with mild AD, and ADAS-Cog_{11} for the population with moderate AD and overall population.

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study comparing 400-mg solanezumab with placebo, given as an intravenous infusion once every 4 weeks (Q4W) over 18 months in 1040 outpatients with mild (baseline MMSE ≥20 and ≤26) to moderate (baseline MMSE ≥16 and ≤19) AD. Concomitant treatment with AChEIs and/or memantine at stable doses was allowed.

Number of Subjects:
Planned: 500 solanezumab and 500 placebo
Randomized: 521 solanezumab (322 mild AD, 196 moderate AD); 519 placebo (325 mild AD, 194 moderate AD)
Treated : 518 solanezumab (321 mild AD; 194 moderate AD), 518 placebo (324 mild AD; 194 moderate AD)
Completed: 406 solanezumab (252 mild AD, 152 moderate AD); 400 placebo (259 mild AD; 141 moderate AD)

Diagnosis and Main Criteria for Inclusion: Subjects were male or female at least 55 years old with AD, as demonstrated by meeting National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD; had a Modified Hachinski Ischemia Scale (MHIS) score of ≤4, an MMSE score of 16 through 26, and a Geriatric Depression Scale (GDS) short-form score of ≤6; and having an MRI or computerized tomography (CT) scan performed within the past 2 years with no findings inconsistent with a diagnosis of AD.

Test Product, Dose, and Mode of Administration: Solanezumab 400 mg given as an intravenous infusion once every 4 weeks over approximately 18 months (Week 0 [Visit 2] to Week 76 [Visit 22]).

Reference Therapy, Dose, and Mode of Administration: Placebo given as an intravenous infusion once every 4 weeks over approximately 18 months (Week 0 [Visit 2] to Week 76 [Visit 22]).

Duration of Treatment: Study medication was given once every 4 weeks through Week 76, with final evaluations occurring 4 weeks later at Week 80, such that total duration was approximately 18 months.

Variables:

Efficacy Scales:
- Alzheimer's Disease Assessment Scale-Cognitive Scale (11-item, 12-item, and 14-item scales)
- Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory
- Mini-Mental State Examination
- Clinical Dementia Rating—Sum of Boxes

Efficacy Biomarkers:
- Plasma Aβ (including assayed plasma $A\beta_{1-40}$ and $A\beta_{1-42}$)
- Volumetric MRI parameters (right hippocampal volume, left hippocampal volume, right + left hippocampal volume, right entorhinal cortex, left entorhinal cortex, atrophy of total whole brain volume, enlargement of ventricular volume)
- Composite summary standard uptake value ratio (SUVr) of AV-45 (amyloid imaging agent)
- Cerebrospinal fluid parameters (free $A\beta_{1-40}$, free $A\beta_{1-42}$, total tau, p-Tau, total $A\beta_{1-40}$, total $A\beta_{1-42}$).

Health Outcomes/Quality of Life:
- Neuropsychiatric Inventory (including subdomains)
- Resource Utilization in Dementia—Lite
- EuroQoL 5-Dimensional Health-related Quality of Life Scale Proxy version
- Quality of Life in Alzheimer's Disease

Safety:
- Serious adverse events (SAEs), adverse events (AEs) reported as reason for study discontinuation, and TEAEs
- Laboratory measurements including hematology, blood chemistry, and urine analytes
- Vital signs (sitting and standing pulse and blood pressure [BP]) and body weight and temperature
- Electrocardiograms
- Immunogenicity (anti-solanezumab, hamster anti-Aβ, and human anti-Aβ)
- Magnetic resonance imaging for detection of amyloid-related imaging abnormality – edema (ARIA-E, also known as vasogenic edema) and amyloid-related imaging abnormality – hemorrhage (ARIA-H, also known as microhemorrhage)

Statistical Evaluation Methods:

General Considerations: All analyses followed the intent-to-treat (ITT) principle unless otherwise specified.

When change from baseline was assessed, patients were included in the analysis only if both a baseline and a

postbaseline measure were available. For analyses using MMRM, an unstructured covariance matrix was used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure followed by the heterogeneous autoregressive covariance structure was used. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. For analyses using LOCF, the last non-missing observation post-baseline was used to calculate change from baseline. All efficacy and safety hypothesis tests used a two-sided 0.05 significance level unless otherwise stated.

Primary Endpoint: To assess the primary objective, an MMRM analysis of the ADAS-Cog_{14} was performed in subjects with mild AD at baseline (Visit 1 MMSE 20 to 26). The mean change from baseline score on the ADAS-Cog_{14} at each scheduled postbaseline visit during treatment was the dependent variable. The model for the fixed effects included terms for 7 effects: baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, concomitant AChEI and/or memantine use at baseline (Yes/No), and age at baseline. Visit was considered a categorical variable with values equal to the visit numbers at which the scales were assessed. The null hypothesis was that the contrast between the solanezumab- and placebo-treatment groups at the last visit (Week 80 [Visit 23]) would equal zero. A rejection of the null hypothesis in favor of the alternative, showing that solanezumab was superior to placebo, demonstrated a treatment effect.

Secondary Endpoints: A sequential gatekeeping strategy was used for hypothesis testing to protect against type I error of falsely rejecting the null hypothesis. Although the primary endpoint was not met for the gatekeeping strategy, the following secondary endpoints were analyzed: MMRM analysis of the MMSE in the mild population, and MMRM analysis of the ADCS-ADL in the mild population. Slopes of the primary measure (ADAS-Cog_{14}) and other clinical outcomes (MMSE, ADCS-ADL, ADAS-Cog_{11}, ADAS-Cog_{12}, and CDR-SB) were assessed separately using an MMRM analysis. Change from baseline was assessed using MMRM for the MMSE, ADCS-ADL, ADAS-Cog_{11}, ADAS-Cog_{12}, ADAS-Cog_{14}, ADCS-ADL subscores (basic ADL and instrumental ADL), CDR-SB, NPI, RUD-Lite, EQ-5D Proxy, and QoL-AD. Additionally, change from baseline to endpoint was assessed using a LOCF-approach for ADAS-Cog_{14}, ADAS-Cog_{11}, MMSE, and ADCS-ADL. Additional subgroup analyses were performed (eg, disease severity [mild AD = Visit 1 MMSE of 20 to 26; moderate AD = Visit 1 MMSE of 16 to 19], APOE*E4 carrier, APOE genotype, and/or demographics/baseline characteristics).

Safety: Safety was assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, ECGs, immunogenicity data, and brain MRIs.

Power of Primary Objective: Based on the observed treatment outcomes in subjects with mild AD in the first Phase 3 study for solanezumab (Study LZAM), a treatment difference of 2.6 (42% reduction in decline) with a standard deviation of 12 on the ADAS-Cog_{14} in subjects with mild AD was assumed. With this assumption, a sample size of 335 subjects with mild AD per treatment group were predicted to have approximately 80% power to detect a significant treatment difference on the ADAS-Cog_{14} (effect size 0.22) after 18 months of treatment using a 2-sided significance level of 0.05.

Disposition and Demographics:

In total, 1040 subjects were randomized to solanezumab (N = 521) or placebo (N = 519). The majority of subjects with mild AD (N = 647) were white (80.1%), female (53.0%), and the mean age was approximately 73 years. The respective mean times since diagnosis were 1.67 years and 1.78 years for solanezumab- and placebo-treated subjects with mild AD, respectively. The majority of subjects with mild AD (89.5%) were taking a StOC medication (AChEI and/or memantine). Similar results were observed for subjects with moderate AD (N = 390) and for the overall population (N = 1040). For subjects with mild AD, a statistically significant difference was observed between the solanezumab- versus placebo-treatment groups for Visit 1 MMSE scores (22.56 versus 23.03 years; p=.01) and AChEI/memantine use (p=.041). For most other demographic and baseline characteristics, no other statistically significant differences between the treatment groups were observed. No statistically significant treatment–group differences were observed for each reason for discontinuation for subjects with mild AD, for subjects with moderate AD, or for the overall population.

Efficacy Scales:

Table LZAN.2.1 summarizes the least-squares (LS) mean changes at Week 80 (Visit 23) from the MMRM analyses of the cognitive, functional, and health outcome/quality of life measure total scores for subjects with mild AD, for subjects with moderate AD, and for the overall population. The primary endpoint, as measured by MMRM analysis of the ADAS-Cog_{14} in subjects with mild AD receiving intravenous infusion of 400 mg solanezumab every 4 weeks for approximately 18 months was not met (p=.120), although there was a numerical reduction in decline among solanezumab-treated subjects with mild AD compared with placebo. Similar results were observed for the overall population (p=.075). There was no statistically significant difference for subjects with moderate AD (p=.395). Mean change from baseline to LOCF endpoint analysis of the ADAS-Cog_{14}, however, showed significantly less cognitive decline in solanezumab- versus placebo-treated subjects for the overall population (p=.048), but the treatment group differences were not statistically significant for subjects with mild AD (p=.128) or for subjects with moderate AD (p=.318). In addition, in solanezumab- versus placebo-treated subjects, there was a statistically significant difference in the slope of decline on the ADAS-Cog_{14} for subjects with mild AD (p=.030) and for the overall population (p=.041), but not for subjects with moderate AD (p=.340). With the exception of a statistically significant APOE*E4 carrier status-by-treatment (p=.021) and APOE genotype-by-treatment (p=.026) interactions in subjects with mild AD, no additional treatment-by-subgroup interactions were statistically significant for the ADAS-Cog_{14}.

Table LZAN.2.1. Efficacy and Health Outcome/Quality of Life Measures Total Score Least-Squares Mean Changes at Week 80 (Visit 23) from Repeated Measures Analyses Intent-to-Treat Population

Measure	Mild[a]		Moderate[b]		Overall	
	SLZ	PBO	SLZ	PBO	SLZ	PBO
	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)
Cognitive						
ADAS-Cog$_{14}$	5.69 (0.762)	7.14 (0.764)	12.08 (1.147)	13.24 (1.177)	8.32 (0.628)	9.69 (0.633)
MMSE	-2.50 (0.361)	-3.17 (0.367)	-5.02 (0.477)	-5.97 (0.490)	-3.58* (0.274)	-4.42 (0.280)
ADAS-Cog$_{11}$	4.63 (0.637)	5.92 (0.638)	10.31 (0.959)	11.00 (0.980)	6.89 (0.529)	8.10 (0.533)
ADAS-Cog$_{12}$	4.98* (0.688)	6.62 (0.690)	11.02 (1.016)	11.78 (1.041)	7.24* (0.537)	8.65 (0.546)
Composite						
CDR-SB	1.62 (0.204)	1.99 (0.206)	3.44 (0.339)	3.79 (0.347)	2.33 (0.172)	2.70 (0.174)
Functional						
ADCS-ADL	-7.92 (0.848)	-9.79(0.846)	-15.77 (1.349)	-16.49 (1.379)	-10.54 (0.719)	-12.19 (0.724)
B-ADL	-1.77 (0.218)	-1.85 (0.219)	-3.82 (0.421)	-4.65 (0.432)	-2.53 (0.199)	-2.92 (0.202)
I-ADL	-5.71* (0.680)	-7.41 (0.687)	-11.69 (1.058)	-11.61 (1.082)	-7.88 (0.576)	-9.09 (0.581)
HO/QoL						
NPI	2.02 (0.887)	2.35 (0.905)	8.05 (1.467)	8.07 (1.509)	4.37 (0.729)	4.69 (0.749)
RUD-Lite						
B-ADL	0.40 (0.140)	0.44 (0.141)	0.96 (0.407)	1.77 (0.416)	0.69 (0.164)	0.94 (0.166)
I-ADL	0.24 (0.218)	0.29 (0.223)	0.98 (0.421)	0.93 (0.430)	0.45 (0.198)	0.41 (0.202)
EQ-5D Proxy	-1.34 (1.474)	-0.25 (1.506)	-0.74 (2.160)	-2.47 (2.229)	-1.03 (1.161)	-1.00 (1.193)
QoL-AD						
Subject	-0.91 (0.401)	-1.53 (0.413)	-1.76 (0.613)	-1.67 (0.639)	-1.20 (0.325)	-1.53 (0.337)
Caregiver	-2.52 (0.421)	-1.99 (0.436)	-1.93 (0.587)	-2.91 (0.608)	-2.69 (0.328)	-2.63 (0.341)

Abbreviations: AD = Alzheimer's Disease; $ADAS\text{-}Cog_{11}$ = Alzheimer's Disease Assessment Scale-Cognitive 11-item subscale; $ADAS\text{-}Cog_{12}$ = Alzheimer's Disease Assessment Scale-Cognitive 12-item subscale; $ADAS\text{-}Cog_{14}$ = Alzheimer's Disease Assessment Scale-Cognitive 14-item subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; B-ADL = basic activities of daily living (hours per day); CDR-SB = Clinical Dementia Rating—Sum of Boxes; EQ-5D Proxy = EuroQol 5-Dimensional Health-related Quality of Life Scale Proxy version; HO = health outcome; I-ADL = instrumental activities of daily living (hours per day); LS = Least-squares; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PBO = placebo; QoL = quality of life; QoL-AD = Quality of Life in Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia—Lite; SE = standard error; SLZ=solanezumab.

* Indicates statistically significant difference from placebo.

[a] Mild AD was determined by the Visit 1 MMSE score (20-26).

[b] Moderate AD was determined by the Visit 1 MMSE score (16-19).

Sources: LTRM_A210.rtf, MTRM_A210.rtf, TRM_A210.rtf, LTRM_A250.rtf, MTRM_A250.rtf, TRM_A250.rtf, LTRM_A010.rtf, MTRM_A010.rtf, TRM_A010.rtf, LTRM_A180.rtf, MTRM_A180.rtf, TRM_A180.rtf, LTRM_A160.rtf, MTRM_A160.rtf, TRM_A160.rtf, LTRM_A030.rtf, MTRM_A030.rtf, TRM_A030.rtf, LTRM_A230.rtf, MTRM_A230.rtf, TRM_A230.rtf, LTRM_A240.rtf, MTRM_A240.rtf, TRM_A240.rtf, LTRM_A260.rtf, MTRM_A260.rtf, TRM_A260.rtf, LTRM_C020.rtf, MTRM_C020.rtf, TRM_C020.rtf, LTRM_C030.rtf, MTRM_C030.rtf, TRM_C030.rtf, LTQL_A010.rtf, MTQL_A010.rtf, TQL_A010.rtf

No significant effect of solanezumab was observed for the MMSE when compared with placebo in subjects with mild AD at Week 80 (Visit 23 [p=.099]), although there was a numerical reduction in decline among solanezumab-treated subjects with mild AD compared with placebo; this scale served as a secondary gatekeeper measure in subjects with mild AD (see Table LZAN.2.1). Similar results, but with smaller differences between active treatment and placebo, were observed for subjects with moderate AD (p=.053). For the overall population, however, solanezumab demonstrated a statistically significant reduction in cognitive decline compared with placebo (p=.004). Mean change from baseline to LOCF endpoint analyses of the MMSE yielded generally similar results to those of the MMRM analyses for subjects with mild AD (p=.342), for subjects with moderate AD (p=.203) and for the overall population (p=.039). In addition, in solanezumab- versus placebo-treated subjects, there was a statistically significant difference in the slope of decline on the MMSE for the overall population (p=.017), but not for subjects with mild AD (p=.060) or for subjects with moderate AD (p=.105). Most treatment-by-subgroup interactions were not statistically significant for the MMSE, with the exception of the statistically significant treatment-by-anti-cholinergic medication interaction in the overall population (p=.015).

No significant effect of solanezumab was observed for the ADCS-ADL when compared with placebo for subjects with mild AD (p=.076) at Week 80 (Visit 23; see Table LZAN.2.1), although there was a numerical reduction in decline among solanezumab-treated subjects with mild AD compared to placebo; the ADCS-ADL served as a secondary gatekeeper measure in subjects with mild AD. Similar results were observed for the overall population (p=.062). There were no significant treatment differences for subjects with moderate AD (p=.647). Mean change from baseline to LOCF endpoint analyses of the ADCS-ADL yielded generally similar results to those of the MMRM analyses for subjects with mild AD (p=.211), for subjects with moderate AD (p=.548), and for the overall population (p=.053). In addition, in solanezumab- versus placebo-treated subjects, there was no statistically significant difference in the slope of decline on the ADCS-ADL for subjects with mild AD (p=.068), for subjects with moderate AD (p=.626), or for the overall population (p=.105). When the basic component of the ADCS-ADL was analyzed, there were no statistically significant treatment group differences for subjects with mild AD (p=.766), for subjects with moderate AD (p=.105) and for the overall population (p=.097) at Week 80 (Visit 23; see Table LZAN.2.1). When the instrumental component of the ADCS-ADL was analyzed, however, significantly less functional decline as measured in hours per day in instrumental ADL was observed in solanezumab- versus placebo-treated subjects with mild AD (p=.029); the treatment-group differences were not statistically significant for subjects with moderate AD (p=.949) or for the overall population (p=.080) (see Table LZAN.2.1). No treatment-by-subgroup interactions were statistically significant for the ADCS-ADL.

Analyses of the ADAS-Cog_{11} yielded similar results to the MMRM analyses of the ADAS-Cog_{14} for subjects with mild AD (p=.097) and for the overall population (p=.060) at Week 80 (Visit 23). There were no significant treatment-group differences for subjects with moderate AD (p=.536). Furthermore, mean change from baseline to LOCF endpoint analyses of the ADAS-Cog_{11} showed significantly less cognitive decline in solanezumab- versus placebo-treated subjects in the overall population (p=.025), but the treatment group differences were not statistically significant in subjects with mild AD (p=.068) or in subjects with moderate AD (p=.351). In solanezumab- versus placebo-treated subjects, there was a statistically significant difference in the slope of decline on the ADAS-Cog_{11} for subjects with mild AD (p=.035), but not for subjects with moderate AD (p=.373) or for the overall population (p=.051). For the ADAS-Cog_{12}, the MMRM showed significantly less cognitive decline in solanezumab- versus placebo-treated subjects with mild AD (p=.05) and in the overall population (p=.019), but the treatment group differences were not statistically significant for subjects with moderate AD (p=.519). There was also a statistically significant difference in solanezumab- versus placebo-treated subjects in the slope of decline on the ADAS-Cog_{12} in subjects with mild AD (p=.015) and in the overall population (p=.013), but not in subjects with moderate AD (p=.228).

The LS mean changes in the CDR-SB, a composite measure of cognition and function, were not significantly different between the treatment groups for subjects with mild AD (p=.123), for subjects with moderate AD (p=.352), and for the overall population (p=.055) at Week 80 (Visit 23). In addition, there was no statistically significant difference in the slope of decline on the CDR-SB in solanezumab- versus placebo-treated subjects with mild AD (p=.709), with moderate AD (p=.296), or for the overall population (p=.351).

No statistically significant difference in neuropsychiatric disturbance was observed in the solanezumab-treatment group compared with the placebo-treatment group as shown by the LS mean changes in the NPI for subjects with mild AD (p=.734), for subjects with moderate AD (p=.990), or for the overall population (p=.656) at Week 80 (Visit 23). For the RUD-Lite, no statistically significant treatment-group differences were observed in the change in time spent by the caregiver performing basic ADL (p=.796) and instrumental ADL (p=.828), or in supervising the subject (p=.883) for subjects with mild AD. Similar results for the RUD-Lite were observed for subjects with moderate AD and for the overall population. For the EQ-5D Proxy Health State score, no statistically significant treatment-group differences were observed for subjects with mild AD (p=.478), for subjects with moderate AD (p=.419), or for the overall population (p=.979). Likewise, for the QoL-AD subject and caregiver total scores, no statistically significant treatment-group differences were observed for subjects with mild AD (p=.138 and p=.230), for subjects with moderate AD (p=.895 and p=.092), or for the overall population (p=.319 and p=.854).

Efficacy Biomarkers:
Table LZAN.2.2 summarizes the LS mean change at endpoint (Week 80 [Visit 23]) from MMRM and analysis of covariance (ANCOVA) of plasma Aβ and cerebrospinal fluid (CSF) analytes in subjects with mild AD, in subjects moderate AD, and in the overall population. Statistically significant elevations in plasma Aβ analytes were observed at Week 80 (Visit 23) in solanezumab- versus placebo-treated subjects with mild AD, with moderate AD, and overall as measured by the respective LS mean changes in $Aβ_{1-40}$ (p<.001) and in $Aβ_{1-42}$ (p<.001). No treatment-by-subgroup interactions were statistically significant for plasma Aβ analytes for subjects with mild AD, for subjects with moderate AD, and overall.

Table LZAN.2.2. Plasma and Cerebrospinal Fluid β-Amyloid Least-Squares Mean Changes at Week 80 (Visit 23) from Repeated Measures Analysis or Analysis of Covariance Intent-to-Treat Population

	Mild[a]		Moderate[b]		Overall	
	SLZ	PBO	SLZ	PBO	SLZ	PBO
Measure	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)
Plasma Aβ[c]						
Total $A\beta_{1-40}$ (pg/mL)	157335.12* (1985.951)	1125.35 (1958.108)	166324.77* (4799.818)	1057.52 (5005.078)	161254.05* (2161.525)	801.29 (2161.679)
Total $A\beta_{1-42}$ (pg/mL)	19387.59* (231.084)	136.97 (227.998)	18920.81* (319.422)	91.43 (330.961)	19230.72* (185.926)	68.57 (186.350)
CSF[d]						
Total $A\beta_{1-40}$ (pg/mL)	2807.65* (679.902)	-448.88 (679.289)	1271.66 (967.303)	-949.99 (1254.737)	2337.60* (591.995)	-675.54 (591.922)
Total $A\beta_{1-42}$ (pg/mL)	422.19* (51.545)	-2.23 (51.794)	657.18* (117.546)	-225.88 (158.546)	453.62* (49.622)	48.12 (50.118)
Free $A\beta_{1-40}$ (pg/mL)	-528.44 (284.290)	-69.12 (290.509)	-1269.05 (809.333)	884.24 (1045.071)	-699.01 (273.170)	-156.74 (272.361)
Free $A\beta_{1-42}$ (pg/mL)	14.97* (14.508)	-36.14 (14.854)	-12.63 (32.795)	2.07 (43.560)	-3.88* (14.653)	-43.23 (14.734)
Total Tau (pg/mL)	-22.63 (31.389)	-29.71 (32.272)	-135.94 (42.177)	78.51 (51.153)	-54.54 (27.693)	-31.66 (27.952)
p-Tau (pg/mL)	-3.50 (2.922)	-4.25 (3.000)	-12.18 (7.963)	1.80 (9.607)	-6.38 (2.731)	-3.20 (2.766)

Abbreviations: Aβ = amyloid-β; AD = Alzheimer's Disease; ANCOVA = analysis of covariance; CSF = cerebrospinal fluid; LS = least-squares; MMRM = mixed-model repeated measures; MMSE = Mini-Mental State Examination; PBO = placebo; SE = standard error; SLZ = solanezumab.

* Indicates statistically significant difference from placebo.

[a] Mild AD was determined by the Visit 1 MMSE score (20-26).

[b] Moderate AD was determined by the Visit 1 MMSE score (16-19).

[c] Results for plasma Aβ analytes are from an MMRM analysis.

[d] Results for CSF Aβ analytes are from an ANCOVA.

Sources: LTPL_A010.rtf, MTPL_A010.rtf, TPL_A010.rtf, LTCS_A010.rtf, MTCS_A010.rtf, TCS_A010.rtf

For analyses of CSF parameters in the overall population, statistically significant baseline-to-endpoint LS mean increases were observed in solanezumab- versus placebo-treated subjects for CSF total (bound plus unbound to solanezumab) $A\beta_{1-40}$ ($p<.001$) and for CSF total $A\beta_{1-42}$ ($p<.001$) There were also LS mean decreases in CSF free $A\beta_{1-40}$ observed in the solanezumab-treatment group, which were accompanied by relatively smaller decreases in CSF free $A\beta_{1-42}$. Annualized baseline-to-endpoint analyses revealed similar respective results for each CSF parameter in the overall population (CSF total $A\beta_{1-40}$ [$p<.001$]; CSF total $A\beta_{1-42}$ [$p<.001$]). Similar results were also observed in subjects with mild AD, but not always in subjects with moderate AD for these CSF parameters. Note that mild and moderate population analyses of CSF parameters should be interpreted cautiously given the small sample sizes.

No statistically significant treatment-group differences were observed for baseline-to-endpoint analyses of each vMRI parameter in subjects with mild AD, in subjects with moderate AD, or in the overall population. Annualized baseline-to-endpoint analyses for each vMRI parameter in solanezumab- versus placebo-treated subjects with mild AD showed a significantly larger LS mean decrease in right hippocampal volume (-99.19 versus -75.71 mm^3; p=.048) and in right entorhinal cortex (-21.07 versus -16.48 mm^3; p=.047), but not for any other vMRI parameter. In subjects with moderate AD and in the overall population, annualized baseline-to-endpoint analyses for each vMRI parameter were not significantly different between the treatment groups. No treatment-by-subgroup interactions (eg, Visit 1 MMSE status, APOE*E4 carrier status, and APOE genotype) were statistically significant for each vMRI parameter.

Table LZAN.2.3 shows the relationship between selected vMRI parameters and the ADAS-Cog_{14} in subjects with mild AD, in subjects with moderate AD, and in the overall completer population. The correlations between the change from baseline in each vMRI parameter and the change from baseline in the ADAS-Cog_{14} were statistically significant in both solanezumab-and placebo-treated subjects with mild AD, with moderate AD, and overall, with several exceptions. The correlations between the change from baseline in right-hippocampal volume and the change from baseline in the ADAS-Cog_{14} were not statistically significant in solanezumab- and placebo-treated subjects with moderate AD, and the correlation between the change from baseline in left hippocampal volume and the change from baseline in the ADAS-Cog_{14} were not statistically significant in placebo-treated subjects with mild AD.

Table LZAN.2.3. Relationship between vMRI Parameters and the 14-Item Alzheimer's Disease Assessment Scale-Cognitive Subscale Spearman's Rank Correlation Coefficient (Rho) on Changes from Baseline to Week 80 Completer Population

	Mild[a]		Moderate[b]		Overall	
	SLZ	PBO	SLZ	PBO	SLZ	PBO
Measure	rho (p-value)	rho (p-value)	rho (p-value)	rho (p-value)	rho (p-value)	rho (p-value)
ADAS-Cog_{14}						
R Hippocampus (mm^3)	-0.177 (.011)	-0.202 (.004)	-0.162 (.078)	-0.124 (.182)	-0.152 (.006)	-0.193 (<.001)
L Hippocampus (mm^3)	-0.191 (.006)	-0.098 (.163)	-0.210 (.022)	-0.245 (.008)	-.211 (<.001)	-0.174 (.002)
R+L Hippocampus (mm^3)	-0.209 (.003)	-0.170 (.014)	-0.200 (.029)	-0.187 (.042)	-0.205 (<.001)	-0.202 (<.001)
W Brain Atrophy (cm^3)	0.412 (<.001)	0.412 (<.001)	0.529 (<.001)	0.496 (<.001)	0.464 (<.001)	0.467 (<.001)

Abbreviations: L = left; PBO = placebo; R = right; SLZ = solanezumab; W = Whole.

[a] Mild AD was determined by the Visit 1 MMSE score (20-26).

[b] Moderate AD was determined by the Visit 1 MMSE score (16-19).

Sources: LTPK_A006.rtf, MTPK_A006.rtf, TPK_A006.rtf.

No statistically significant treatment-group differences were observed for baseline-to-endpoint analyses of amyloid burden by AV-45 positron emission tomography (PET) using composite summary SUVr normalized to mean whole cerebellum in subjects with mild AD, in subjects with moderate AD, and in the overall population. Annualized baseline-to-endpoint analyses yielded similar results for this AV-45 parameter in subjects with mild AD, in subjects with moderate AD, and in the overall population. Note that a numeric baseline-to-endpoint increase in SUVr normalized to mean whole cerebellum was present for placebo-treated subjects with mild AD; no numeric baseline-to-endpoint increase in SUVr normalized to mean whole cerebellum was present for placebo-treated subjects with moderate AD.

Safety:
Overall, 518 subjects were exposed to solanezumab and 518 subjects were exposed to placebo for 6 months or less of treatment. By 12 months or less, 477 subjects were exposed to solanezumab and 482 subjects were exposed to placebo. By 18 months or less, 437 subjects were exposed to solanezumab and 447 subjects were exposed to placebo. After 18 months of treatment, 404 subjects were exposed to solanezumab and 400 subjects were exposed to placebo.

No statistically significant differences were observed between the treatment groups in the percentage of complete infusions at each visit (overall range 96.9% to 99.8%). A significantly higher LS mean volume of complete infusions was observed in solanezumab- versus placebo-treated subjects at Week 52 (Visit 16 [p=.050]), but not at the other visits (overall range 69.88 to 70.10 mL). A significantly lower LS mean duration in complete infusions was observed in solanezumab- versus placebo-treated subjects at Week 4 (Visit 4 [p=.017]), at Week 28 (Visit 10 [p=.027]), at Week 52 (Visit 16 [p=.050]), and at Week 56 (Visit 17 [p=.048]), but not at the other visits (overall range 30.99 to 32.35). The percentages of subjects with incomplete infusions (including subjects with no infusions) by reason across visits ranged from 0.0% to 1.4% in the solanezumab-treatment group and from 0.2% to 1.4% in placebo-treatment group.

Overall, solanezumab was well-tolerated. Although the number of deaths was higher in the solanezumab- versus placebo-treatment groups (13 [2.5%] versus 12 [2.3%]), the difference was not statistically significant. Of the 13 deaths in the solanezumab-treatment group, 3 deaths (B-cell lymphoma, death-unknown reason, and respiratory failure) were judged by the investigator to be related to study drug. Of the 12 deaths in the placebo-treatment group, 3 deaths (respiratory arrest, renal failure chronic, and death-unknown reason) were judged by the investigator to be related to study drug. There were no significant difference between solanezumab- and placebo-treated subjects in the incidence of overall SAEs (18.0% versus 19.5%) or in the incidence of any individual SAE. The most common SAEs in solanezumab-treated subjects were fall and syncope (1.2% each) and in placebo-treated subjects were fall, subdural hematoma, hyponatremia, and pulmonary embolism (0.6% each). There were no significant differences between solanezumab- and placebo-treated subjects in the overall incidence of AEs leading to study discontinuation (10.0% versus 10.2%) or in the incidence of any individual AE leading to study discontinuation. The most common AE leading to study discontinuation in solanezumab-treated subjects was cerebral hemorrhage (0.8%) and in placebo-treated subjects was cerebral microhemorrhage (1.0%).

In total, 846 of 1036 (81.7%) subjects had ≥1 TEAE(s). No statistically significant differences were observed between the solanezumab- and placebo-treatment groups in the percentage of subjects with mild AD who had ≥1 TEAE(s) (82.6% versus 82.1) and in the percentage subjects from the overall population who had ≥1 TEAE(s) (79.5% versus 83.8%); however, significantly fewer solanezumab- versus placebo-treated subjects with moderate AD had ≥1 TEAE(s) (74.7% versus 86.6%; p=.004). For solanezumab- and placebo-treated subjects from the overall population who experienced a TEAE, the investigator considered most to be mild (36.9% versus 34.4%) or moderate (27.2% versus 34.6%) in severity, and a smaller percentage were considered severe (15.4% versus 14.9%). By system organ class (SOC), significantly fewer solanezumab- than placebo-treated subjects from the overall population experienced “Injury, poisoning, and procedural complications” (15.4% versus 21.8%; p=.011), “Nervous system disorders” (25.7% versus 34.2%; p=.003), and “Psychiatric disorders” (21.4% versus 27.6%; p=.025). The

incidence of any individual TEAE within these SOCs was not significantly different between the treatment groups, with the exception of somnolence in "Nervous system disorders" SOC, which was significantly lower in solanezumab- versus placebo-treated subjects (0.4% versus 2.3%; p=.012). By preferred term, significantly more solanezumab- than placebo-treated subjects experienced angina pectoris (1.2% versus 0.0%; p=.031). For all other TEAEs, there were no statistically significant treatment group differences observed for any individual TEAE in any SOC. For TEAEs of special interest such as infusion-related reactions, suicidal ideation, and behavior events, hemorrhagic stroke events, and cardiac ischaemic-related events, the overall incidence for each type of event was not significantly different between the treatment groups. When cardiac arrhythmia-related TEAEs were clustered together, the overall incidence was not significantly different between the treatment groups.

The mean changes in each hematology, blood chemistry, and urine analyte were not significantly different between the treatment groups at Week 80 (Visit 23) and most other scheduled visits. For treatment-emergent abnormal low or high hematology, blood chemistry, and urine values at any time, a statistically significant difference was observed between solanezumab- versus placebo-treated subjects in abnormally high erythrocyte count (1.6% versus 0.2%; p=.038). For all other hematology, blood chemistry, and urine analytes, there were no statistically significant differences between the treatment groups in the percentage of subjects with treatment-emergent abnormal high or low values at any time. Furthermore, there were no statistically significant differences between the treatment groups in the percentage of subjects with abnormal ALT or total bilirubin at any time. The small numbers of significantly different laboratory values did not appear to have any clinically important consequences.

The mean changes in each vital sign and body weight parameter were not significantly different between the treatment groups at Week 80 (Visit 23). At the other scheduled visits, however, statistically significant differences were observed between solanezumab- versus placebo-treated subjects in pulse at Week 12 (Visit 6 [-0.54 versus 0.24 bpm; p=.028]), in systolic BP at Week 4 (Visit 4 [-4.23 versus -5.66 mm Hg; p=.050]), at Week 16 (Visit 7 [-3.80 versus -5.76 mm Hg; p=.022]), and at Week 44 (Visit 14 [-4.31 versus -7.03 mm Hg; p=.021]), and in diastolic BP at Week 36 (Visit 12 [-2.92 versus -3.84 mm Hg; p=.044]) and at Week 44 (Visit 14 [-2.39 versus -3.47 mm Hg; p=.018]). At every scheduled visit, the mean changes in orthostatic systolic BP, orthostatic pulse, body weight, and temperature were not significantly different between the treatment groups. There were no statistically significant differences between the treatment groups in the percentage of subjects with treatment-emergent abnormally high or low vital signs and weight, or high temperature at any time.

The LS mean changes in each ECG parameter including Fridericia corrected QT (QTcF), were not significantly different between the treatment groups at Week 80 (Visit 23) and most other scheduled visits. Statistically significant differences were observed between solanezumab- versus placebo-treated subjects for heart rate at Week 12 (Visit 6 [-1.18 versus 0.04 bpm; p=.008]) and for the RR interval at Week 12 (Visit 6 [16.32 versus -2.55 msec; p=.003]). No statistically significant differences were observed between solanezumab- and placebo-treated subjects in QTcF duration ≥500 msec at any time (0.0% versus 0.0%), in increases from baseline in QTcF >60 msec at any time (0.4% versus 0.6%), and in both an increase from baseline in QTcF >60 msec and a QTcF duration of ≥500 msec at any time (0.0% versus 0.0%).

For subjects with positive immunogenicity results (anti-solanezumab, anti-hamster Aβ, or anti-human Aβ), no statistically significant differences were observed between the treatment groups at Week 80 (Visit 23) or the other scheduled visits. There was a low incidence of treatment-emergent immunogenicity: For subjects with positive "treatment-emergent" immunogenicity results, no statistically significant differences were observed between the treatment groups at Week 80 (Visit 23) or the other scheduled visits. Among those subjects with treatment-emergent immunogenicity, 2 placebo-treated subjects experienced a TEAE (arthralgia and hypotension) from a set of predefined TEAEs potentially related to immunogenicity (eg, arthralgia, bronchospasm, drug hypersensitivity, face oedema, haematuria, hypotension, myalgia, pruritus, pyrexia, rash, rash erythematous, rash pruritic, and urticaria). No other subject who experienced any of these TEAEs had a treatment-emergent immunogenicity response.

There was a low incidence of ARIA-E. Of the 10 subjects who had ARIA-E, there were 7 in the solanezumab-treatment group (1.4%) and 3 in the placebo-treatment group (0.58%). Note that ARIA-E can occur in the absence of treatment with compounds that target Aβ. The majority of instance of ARIA-E occurred in subjects with at least 1 APOE*E4 allele and increased ARIA-H in proximity to the occurrence of ARIA-E. Although more solanezumab- than placebo-treated subjects had an increase in ARIA-H size or number, the difference between the treatment groups was not statistically significant overall (8.4% versus 6.9%; p=.402), in subjects with mild AD (7.7% versus 7.1%; p=.877) and in subjects with moderate AD (9.1% versus 6.6%; p=.441). Qualitatively, there was no significant difference in the degree of ARIA-H in solanezumab- versus placebo-treated subjects as the number of categorical shifts were similar between treatments.

Conclusions:

In this study, the primary objective (reduction in cognitive decline on the ADAS-Cog_{14} in subjects with mild AD) was not met, although there was a numerical reduction in decline on this measure among solanezumab- compared with placebo-treated subjects with mild AD (p=0.12). Similarly, there were numerical reductions in cognitive decline on the ADAS-Cog_{11} and MMSE, and numerical reductions in functional decline on the ADCS-ADL. These effects were not demonstrated in subjects with moderate AD. This study demonstrates that solanezumab, at the therapeutic dose studied, has an acceptable safety profile in a large international, multicenter sample of subjects with mild-to-moderate AD.