Statistical Analysis Plan Version 2 LMDD

Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LY3303560 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease

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Statistical Analysis Plan for Clinical Studies:
I8G-MC-LMDD: Study Title Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LY3303560 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease

LY3303560

Phase 1 MAD study to assess the safety, PK and PD of LY3303560 in patients in MCI and AD.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I8G-MC-LMDD
Phase 1

Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.
Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 20-December-2016.

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2. Revision History

SAP Version 1 was approved prior to first patient visit and prior to unblinding

SAP Version 2 was approved prior to prior to unblinding and final database lock. Changes reflect the changes made to the LMDD protocol as defined in LMDD (b) and (d).

Briefly, in amendment (b), the higher dose cohorts of LY3303560 (700 and 1400 mg) have been removed based on an update to the PK/PD model originally used to predict the LY3303560 efficacious dose range. In addition, the duration of dosing in the LMDD study has been reduced from 12 months to 6 months, based on emerging longitudinal and baseline data using tau positron emission tomography (PET) imaging, which suggests that the Part B of the study is now insufficiently powered to assess the effects of LY3303560 on progression of tau pathology using the tau tracer flortaucipir F 18 PET over 12 months. However the effects using the tau tracer on tau pathology of repeated every 4 week (Q4W) administrations in patients over approximately 6 months (7 doses), with the option of extending the treatment period to up to 12 months (up to 6 further doses), in the two remaining doses of Part A.

A decision was made by the team to not implement amendment c because the cohort 2 subjects would have had a LP at V13 per amendment b after which amendment c would be implemented and another LP would have been required at V20 per amendment c. This is would have meant an extra LP for these subjects.

The overall changes made to protocol amendment b to create LMDD (d) are as follows:

- In the Schedule of Activities in Section 2, the lumbar puncture at Visit 13, which was removed in protocol amendment (c), has been reinstated to accommodate patients who are following the 25-week dosing period. A flortaucipir F 18 PET scan has been added to Visit 13 for the same reason.
- The Schedule of Activities in Section 2 has been amended to show the LP and flortaucipir F 18 PET scan are not required at Visit 20 for patients who have had an LP or PET scan at Visits 13 or 19. A flortaucipir F 18 PET scan has been added to Visit 19 for patients following the 25-week treatment period.
- The Schedule of Activities (Section 2) has been amended to show that, after a patient has had 6 infusions with no infusion reaction, the observation period for subsequent infusions has been reduced to 2 hours. However, should any infusion reaction occur for any patient, the monitoring period will be increased to at least 8 hours for all subsequent infusions. To date, there have been no infusion reactions observed in 9 subjects in Cohort 1 (70 mg LY3303560) who have reached at least 6 months of dosing and 9 subjects in Cohort 2 (210 mg LY3303560) who have reached at least 3 months of dosing.

3. Study Objectives

Primary The primary objective of this study is to assess the safety and tolerability after 16 weeks of multiple doses of LY3303560 in patients with MCI due to AD or mild to moderate AD	Safety and tolerability will be assessed by monitoring treatment-emergent adverse events (TEAEs)
Secondary	
• To assess the PK of LY3303560 in serum following multiple IV doses of LY3303560 in patients with MCI due to AD or mild to moderate AD	Maximum serum concentration (C_{max}) and the area under the serum concentration time curve during the dosing interval ($AUC\tau$)
Exploratory Objectives	
• To evaluate the effects of multiple doses of LY3303560 on cognitive function in patients with MCI due to AD or mild to moderate AD	ADAS-Cog_{14}, ADCS-MCI-ADL24, NTB, MMSE, dCDT
• To evaluate the effects of multiple doses of LY3303560 on brain atrophy in patients with MCI due to AD or mild to moderate AD	Quantitative measures of brain atrophy derived from volumetric MRI scans
• To evaluate the effects of multiple doses of LY3303560 on brain functional connectivity in patients with MCI due to AD or mild to moderate AD	Quantitative measures of brain functional connectivity derived from functional MRI scans
• To evaluate the immunogenicity of multiple doses of LY3303560 in patients with MCI due to AD or mild to moderate AD	Detection of anti-drug antibodies (ADA)
• To evaluate the effects of multiple doses of LY3303560 on plasma and CSF biomarkers in patients with MCI due to AD or mild to moderate AD	Plasma tau concentration; CSF concentration of tau, p-tau, Aβ1-42, and neurogranin
• To evaluate the effects of multiple doses of LY3303560 on tau pathology using the tau tracer flortaucipir F 18 in patients with MCI due to AD or mild to moderate AD	Quantitative endpoints from flortaucipir F 18 PET scans
• To determine the CSF concentration of LY3303560 following multiple IV doses in patients with MCI due to AD or mild to moderate AD	Mean LY3303560 concentrations in CSF

Exploratory Objectives (continued)	
• To explore the safety and tolerability of LY3303560 in Japanese subjects in relation to non-Japanese subjects	Safety and tolerability will be assessed by monitoring TEAEs
• To explore the PK of LY3303560 in Japanese subjects in relation to non-Japanese subjects	C_{max} and AUCτ

4. Study Design

This is a Phase 1b, multi-site, patient- and investigator-blind, placebo-controlled, parallel-group study in patients with MCI due to AD or mild to moderate AD to assess the safety, tolerability, PK and PD following multiple IV doses of LY3303560.

The planned doses of LY3303560 are: 70 and 210, mg; however, dose levels may be adjusted based on emerging data from Study LMDA and from this current study, if indicated.

Dose escalation decisions will be made following a review of the safety data from a minimum of 4 patients having received at least 2 doses of LY3303560 and 1 patient having received at least 2 doses of placebo at the prior dose level. The subsequent cohort will not begin dosing until all 8 patients from the previous cohort have started dosing. For each cohort, IADs for review of safety data, including ADA titres (if available), and PK data will be conducted at 16 weeks to evaluate the safety, PK and PD of LY3303560 at steady-state.

4.1. Method of Assignment to Treatment

Assignment to treatment groups will be determined by a computer-generated random sequence within each dose cohort using an interactive web response system (IWRS).

For Cohorts 1 to 2, up to 12 patients may be enrolled so that approximately 8 patients per cohort (6 LY3303560: 2 placebo) provide data to Day 113. The randomization will be such that the placebo assignments for the cohorts enrolling Japanese and non-Japanese subjects will be balanced between these 2 populations.

5. A Priori Statistical Methods

5.1. General Considerations

Pharmacokinetic analyses will be conducted on the full analysis set (not including placebo). This set includes all data from all subjects receiving at least one dose of the investigational product.

Safety analyses will be conducted for all enrolled subjects who took study medication, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. As this is a Phase 1 study and there will be no formal statistical hypothesis testing, any changes to the planned analysis will not necessitate a protocol amendment and will be detailed in the study report. Summary statistics, data tabulations, and data graphs by ethnicity (Japanese and non-Japanese, and combined) will be provided as appropriate.

Safety reporting will be conducted by Covance; with the exception of QTcF statistical analyses which will be conducted by Eli Lilly. All drug effects, PK, PD, imaging, cognition and exploratory reporting and analyses will be conducted by Eli Lilly.

Where two cohorts are given the same dose and formulation the patients will be pooled together and reported under the same dose levels. Placebo will be pooled across all cohorts.

In recognition that there are now only two dose cohorts in this study, any statistical models detailed in the analysis plan may still be carried out in order to estimate parameters, in particular where changes from baseline are being considered. Without recourse to statistical models, only those patients with both baseline and at least one post-baseline measurement can be included in any summary. Estimates from statistical models may provide additional information, if interpreted appropriately.

5.1.1. Handling of Dropouts or Missing Data

Subjects or patients who discontinue may be replaced at the discretion of the sponsor and investigator. The ethnicity of the replacement subject (Japanese or non-Japanese) should match the ethnicity of the discontinued patient, where possible. Replacement patients will be allocated the same treatment as the dropout patient.

There will be no imputation of missing data.

5.1.2. Multicentre Studies

Due to this being a safety and tolerability study with low patient numbers per dose there is no plan to fit centre as a covariate in any of the models. The demographic/disposition listings will make it clear which sites each patient were attributed to.

5.1.3. Multiple Comparisons/Multiplicity

No adjustments will be made for multiplicity.

5.2. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study. All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

5.2.1. Patient Characteristics

The patient's age, sex, race, weight, height, APOE4 status or other demographic characteristics will be recorded and may be used in the PK, PD, and safety analyses as quantitative or classification variables. These characteristics will be listed and summarised at baseline, with the exception of weight which will also be summarised over time.

5.3. Protocol deviations

All clinically relevant programmable protocol deviations will be listed by pre-determined categories (e.g., inclusion/exclusion criteria, non-compliance with protocol procedures, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, or other). The following protocol deviations relevant to this study have been identified in Table LMDD.1.

Table LMDD.1. Description of Programmable Protocol Deviations

Category	Source	Methods of Identification
Category: Informed Consent		
Informed Consent Not Obtained/Missing/Late	Programmable (clinical database)	Compare all assessment dates to ICD date (except those assessments that may occur before ICD, e.g., disease assessments) from SDTM datasets
Category: Eligibility		
Participation of a subject(s) that did not meet study inclusion/exclusion criteria	Mixed (Monitoring and clinical database)	Review of the following programmable and relevant protocol inclusion/exclusions criteria: [1] CDR, FSCRT, MMSE and amyloid, [3] Age [4] BMI [29]C- SSRS [35] stable concomitant medications.
Discontinuation due to protocol violation during the study	Mixed (Monitoring and clinical database)	Review of reasons for discontinuation
Category: Study Procedures		
Excluded concomitant medications	Mixed (Monitoring and clinical	Study specific definition: a list with all concomitant medication will be generated, and CRP will flag those

	database)	excluded (the flagged medications will be used in programming to flag important protocol deviations)

Abbreviations: CRP = clinical research physician; ICD = informed consent document.

5.3.1. Japanese and non-Japanese Patients

In addition to combined summaries selected TFLs will be reproduced in triplicate for Japanese and non-Japanese subjects (All subjects, Japanese only subjects and Non-Japanese only subjects.). These will include demography and baseline characteristics, AE summaries, frequency of increases in QTc intervals (greater than 30msec and greater than 60msec) and maximum QTc values exceeding 450msec, 480msec and 500msec. If differences are observed between Japanese and non-Japanese then further analyses and/or split summaries maybe produced.

5.3.2. Subgroup Analyses

Any subgroup analyses will be exploratory (posthoc) in nature.

5.3.3. Concomitant Therapy

Concomitant medication will be coded using the WHO drug dictionary. Concomitant medications will be listed and summarised by treatment.

5.3.4. Extent of Exposure

Dosing information for each individual subject will be listed.

5.4. Safety Analyses

Safety parameters that will be assessed include AEs, MRI, safety laboratory parameters, vital signs, and ECG parameters. The parameters will be listed and summarised using standard descriptive statistics for values at each time point as well as changes from baseline. A listing of all patients' lab values and a listing of abnormal lab values (for that parameter) during the treatment period will be provided and results will be summarised. Outliers will also be identified and listed where appropriate. Additional analyses may be performed if warranted upon review of the data.

5.4.1. Adverse Events

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with IP as perceived by the investigator. Symptoms reported to occur prior to randomization will be distinguished from those reported as new or increased in severity during the study. Each

symptom will be classified by the most suitable term from the medical regulatory dictionary. The number of IP-related SAEs will be reported.

5.4.2. Safety MRI

Shift tables will be constructed for each dose group to assess the incidence of and changes in vasogenic oedema and microhaemorrhage counts pre- and post-dose (by time) based on MRI.

5.4.3. Evaluation of Immunogenicity

Antibody formation will be listed and summarized as well as presented graphically over time by patient and treatment. Exposure and antibody formulation may also be explored graphically. If a neutralization assay is performed, the frequency of neutralizing antibodies will be determined. The relationship between the presence (or absence) of antidrug antibodies and clinical parameters (e.g., infusion reaction AEs) may be assessed. Likewise, the relationship between the presence of antidrug antibodies and the PK parameters and PD response to LY3303560 may be assessed.

5.4.4. C-SSRS

Suicide-related thoughts and behaviours based on the C-SSRS will be listed by patient. Only time points and patients that show suicidal ideation/behaviour will be displayed (i.e., not all of the "no" responses will be displayed).

5.4.5. QTcF

The number of patients experiencing a maximum increase from baseline in QTcF interval will be summarised for each treatment according to the following categories: >30 ms and >60 ms. In addition, the number of patients with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarised by treatment.

Analyses of QTc using QTcF from ECG monitoring will be performed to judge the extent and/or risk of QT prolongation. An assessment of potential QTc prolongation will be performed using plots of PK data versus QTc values. Scatter plots will be created of QTcF versus LY3303560 concentration and change from baseline QTcF versus LY3303560 concentration (for timepoints where there is matched LY3303560 concentration and QTcF available). Placebo data will be included in the plot with concentration imputed to zero. The reference line of 450, 480, and 500 ms will be used for the QTcF versus concentration plot; while 10, 30 and 60 ms for QTcF change from baseline versus concentration plot. Analysis will be performed to assess the mean change in QTcF as a function of plasma drug concentration. The average of the triplicate QTcF measurements will be computed at each of the scheduled time points, and baseline will be the mean of the triplicate measurements collected prior to dosing at time 0 in each treatment period.

A mixed-effect model may be fitted to the QTcF change from baseline, with log –transformed plasma-drug concentration and dose included as fixed effects. The model will be run for the following ECG/PK time matched visits and time points in separate models; Visit 3(Day 1), Visit 8 (Day 27), Visit 9 (Day 57), Visit 13 (Day 169), Visit 19 (Day 337).

The following SAS code may be utilized:

```
proc mixed data=dose_sim;
by visit;
class patient;
model qtcresult = pkresult / outp=resdat s cl alpha=0.1;
random patient;
ods output solutionf=sol;
run;
```

A second model may be run following the same model but combining all the visits above together. Other time matched measures from non PK/ECG intensive days may also be considered for inclusion.

Further exploratory analyses may be conducted if required.

5.5. Pharmacokinetic Parameter Estimation

Standard non-compartmental methods of analysis and model-based approaches using non-linear mixed effects modeling (NONMEM) or other appropriate software may be implemented to estimate PK parameters including maximum drug concentration (C_{max}), area under the concentration curve during the dosing interval ($AUC\tau$), half-life, clearance and volume of distribution after IV administration of LY3303560. Parameters such as time to C_{max} (t_{max}), C_{max}, bioavailability, apparent clearance, apparent volume of distribution and half-life after SC administration may be reported. The accumulation ratio, expressed as either $AUC\tau$ or minimum observed drug concentration (C_{min}), following IV and SC routes may be reported.

When plotted Japanese and non-Japanese subjects will be identified in the same plot with different symbol types.

An analysis of the effect of dose, route of administration, concentration or demographic factors on the PK parameters may be conducted.

An analysis relating LY3303560 serum exposure versus LY3303560 CSF concentrations may be conducted.

5.5.1. Pharmacokinetic Statistical Inference

With just two doses no statistical inferential analyses will be carried out on PK parameters.

5.6. Imaging Analyses

5.6.1. Flortaucipir SUVr

Whilst the following proposed analyses are not intended to test any hypotheses, they will be carried out to estimate the extent of changes from baseline of the flortaucipir F 18 SUVr after treatment with LY3303560.

The data will be analysed by an Analyses of Covariance (ANCOVA). Fixed effects of treatment doses (LY3303560 and placebo) will be fitted and a baseline covariate adjustment will be used.

The primary comparison is between LY3303560 and placebo for change from baseline in composite SUVr at last flortaucipir F 18 imaging visit. Covariates such as (but not limited to) APOE status, MMSE baseline score, diagnosis and age may be explored.

The following SAS code may be utilized:

```
proc mixed data=tau_sim;
class patient treatment;
model change_from_baseline_SUVR_month12 = treatment baseline_SUVR APOE, MMSE_baseline
diagnosis age / outp=resdat s cl solution residual;
lsmeans treatment /pdiff cl alpha=0.05;
ods output lsmeans=lsmean1 diffs=diff1  covparms=cov1;
run;
```

In addition to the ANCOVA analysis, a Bayesian posterior probability may be computed for each LY3303560 dose compared to placebo, it is essentially a Bayesian interpretation of the results assuming a non-informative prior. The credible interval will be computed for each dose relative to placebo. For each dose of LY3303560, the posterior probability that the SUVr difference to placebo is less than or equal to a certain value (X) will be calculated as the appropriate tail area in the t distribution, e.g., Prob(LY xmg - Placebo <=X) = prob t ((X– d) / sed, df) where d is the estimated difference, sed is the standard error of the estimated difference and df is the degrees of freedom associated with this difference. This Bayesian inference is justified on the assumption of vague priors for all parameters in the model. Values of interest for X may be a 0%, 10%, 30%, 50% and 100% reduction in accumulation of tau compared to placebo.

This analysis may be repeated for SUVrs in individual and other composite brain regions if needed.

Additional analyses may explore if there is an optimum baseline SUVr value that can be used as an inclusion criterion for future studies, i.e., do those with a higher baseline SUVr accumulate more tau burden over time and hence have high propensity to respond to treatment. To investigate this, the above analyses may be conducted on; all patients, patients with baseline SUVrs >1.05, SUVrs >1.1 and SUVrs >1.2. These cutoffs are subject to change based on data received and any analyses will consider the current literature and the in-house method study findings (A05 from AVID). Given the small sample sizes this is very exploratory and the findings may not be reported in the CSR.

Early withdrawals

It is anticipated that each patient has a baseline (screening) and week 51 value. All postbaseline scans from the screening scan will be considered to be included in the analyses. If the data suggest it is appropriate, a calculated annualized rate of change may be considered and analyses will be done with and without these dropouts included.

5.6.2. Brain volume and functional connectivity

If data is available then changes in regional brain volume and functional connectivity in brain networks captured by MRI over the course of the study will be explored and summarised. MRI will be obtained every 8-12 weeks; therefore, an MMRM may be conducted fitting treatment and study visit and the interaction as fixed effects, the baseline will also be included and the baseline*visit interaction will be assessed for potential inclusion. The following SAS code may be utilized for each relevant endpoint:

```
proc mixed data=MRI_sim;
class patient treatment visit;
model change_from_baseline_volume = treatment treatment*visit baseline_volume visit
baseline*visit / outp=resdat s cl solution residual;
random intercept/subject= patient type=un;
lsmeans treatment*visit treatment /pdiff cl alpha=0.05;
ods output lsmeans=lsmean1 diffs=diff1  covparms=cov1;

run;
```

Additionally, the relationship between LY3303560 serum exposure and imaging endpoints may be explored graphically or by a modeling approach.

5.6.3. Amyloid scans

Patients require an amyloid scan at screening (if they haven't previously had one for another purpose). This data will listed; it will be stated if the scan is historic or denovo. If numeric SUVr data is available this data may also be summarised and potential explored by correlations to tau burden and/or disease status.

5.7. Exploratory Pharmacodynamic Analyses

5.7.1. Pharmacodynamic Parameter Estimation

The concentration of plasma tau, and the concentration of CSF biomarkers, including tau, p-tau, Aβ1-42 and neurogranin, will be determined. Since protocol approval an additional parameter will be added to the assay; neurofilament light chain in CSF, this measure will be collected and treated as per the other parameters. Plasma and CSF biomarker data will be summarised statistically and/or illustrated graphically by time and dose. The mean change in concentration of the plasma and CSF biomarkers from predose will be evaluated.

No formal statistical analyses of these exploratory CSF/plasma biomarkers are planned.

5.7.2. Cognition Analyses

ADAS-Cog_{14}, NTB, MMSE, dCDT, and ADCS-MCI-ADL24 will all be summarised and may be analysed using an MMRM with preinfusion cognitive measures as a baseline covariate and fixed effects of dose and study visit. All cognition analyses are exploratory and underpowered to detect a clinically meaningful effect.

The digital clock test (dCDT) will be summarised by parameter and treatment, an MMRM may be applied.

Correlations between cognition endpoints (including dCDT) and flortaucipir F 18 SUVr, other imaging endpoints and plasma tau may be explored.

5.7.3. Exploratory Pharmacokinetic/Pharmacodynamic Analyses

A model-based approach may be implemented using NONMEM or other appropriate software to estimate PK/PD parameters. Exploratory analyses may be conducted to characterise the relationship between changes in cognition endpoints, plasma and/or CSF biomarkers and exposure of LY3303560.

5.7.4. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, clinical research physician/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

The Lilly study team will review safety data obtained on an ongoing basis, to assure patient safety. Safety and/or PK interim access to data (IAD) reviews are scheduled to occur throughout the study.

Changes to any Safety reviews/IADs will not constitute a SAP amendment.

5.7.4.1. Safety reviews for dose escalation, 16 week reviews per cohort, quarterly safety reviews and end of cohort reviews

For safety reviews it is planned that the draft site data will be loaded into Spotfire to look for trend over time and treatment. The endpoints to review will include (but not restricted to): vital signs, QTc, laboratory values, PK, and MRI scans. ADA titres will be reviewed as and when available. AEs, Conmeds and site feedback will also be reviewed (not in Spotfire)

The investigator will remain blinded and the Lilly study team will be unblinded during these reviews for dose escalation.

5.7.4.2. Internal decision making IAD for Phase 2/3 trigger

No longer applicable.

5.7.5. Other IADs

Additional IADs may also be conducted to summarise data for internal decision making and/or supporting subsequent clinical studies/regulatory agency/IB annual updates, as required by the Lilly study team and will be articulated in the snapshot plan.

5.8. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarised: by treatment group, by MedDRA preferred term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

6. References

Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST.Confidence interval criteria for assessment of dose proportionality. *PharmRes*.2000;17(10):1278-1283.

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