Statistical Analysis Plan I8G-MC-LMDA Version 1

Single-Dose, Dose-Escalation Study with LY3303560 to Evaluate the Safety, Tolerability, and Pharmacokinetics in Healthy Subject and Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease

NCT02754830

Approval Date: 14-Apr-2016

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LY3303560

Single-Dose, Dose Escalation Study with LY3303560 to Evaluate the Safety, Tolerability and Pharmacokinetics in Healthy Subjects and Patients with MCI and AD to mild/moderate AD.

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Protocol I8G-MC-LMDA
Phase 1

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 14-Apr-2016 GMT

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2. Revision History

This is SAP Version 1

3. Study Objectives

Objectives	Endpoints
Primary The primary objective of this study is to assess the safety and tolerability following single doses of LY3303560 in healthy subjects and patients with Mild Cognitive Impairment due to Alzheimer's Disease (AD) or Mild to Moderate AD.	Safety and tolerability will be assessed by monitoring adverse events (AEs).
Secondary • To assess the serum pharmacokinetics (PK) of LY3303560 in healthy subjects, including those of Japanese origin, following single doses of LY3303560.	The primary parameters for analysis will be maximum drug concentration (C_{max}) and area under the concentration versus time curve from time 0 to infinity (AUC0-∞) of LY3303560.
• To assess the cerebrospinal fluid (CSF) PK of LY3303560 in patients with AD following single doses of LY3303560.	
• To assess the effect of single doses of LY3303560 on the QTc interval in healthy subjects and patients with AD.	QT/QTc interval mean change from baseline

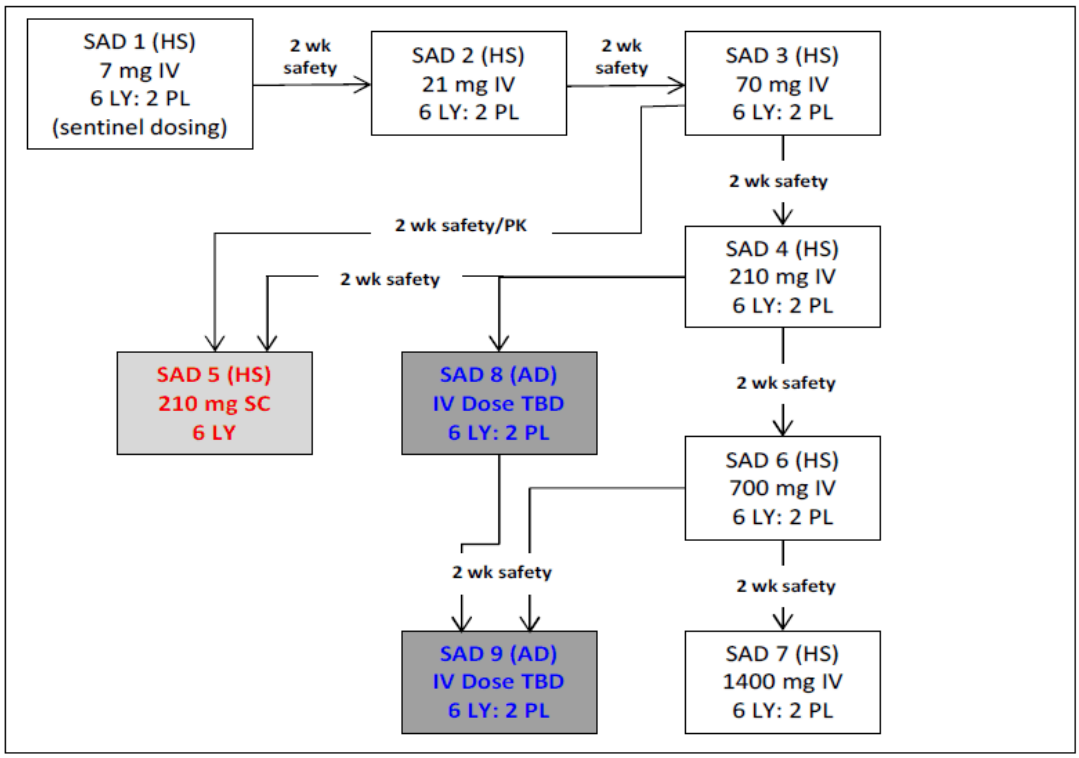
4. Study Design

4.1. Summary of Study Design

This is a Phase I, subject-/patient- and investigator-blind, placebo-controlled, randomized, parallel, single-ascending dose (SAD) study in healthy subjects and patients with mild cognitive impairment (MCI) due to AD or mild to moderate AD. The study has been designed to assess the safety, tolerability, and PK of single intravenous (IV) and subcutaneous (SC) doses of LY3303560. The planned doses to be explored are 7, 21, 70, 210, 700 and 1400 mg.

Cohorts 1 to 7 will consist of healthy subjects. The planned number of subjects per cohort will be 8 (6:2, LY3303560: placebo), except for Cohort 5 (6 subjects on LY3303560). For each IV cohort, the intention is to enroll 4 subjects of Japanese origin (first generation) and 4 subjects of non-Japanese origin, but enrollment to a cohort will not be contingent upon fulfilling these requirements. The minimum requirement is to enroll 4 Japanese subjects to at least 3 of the IV cohorts, including the highest dose level cohort (a minimum of 12 Japanese subjects in total). However, if enrollment of Japanese subjects is slower than anticipated, cohorts may complete enrollment with non-Japanese subjects and proceed to dose escalation without waiting for the desired number of Japanese subjects to be enrolled. If 4 subjects of Japanese origin are not included in a cohort initially, additional subjects may subsequently be enrolled to achieve a maximum of 4 subjects of Japanese origin, if agreed between the sponsor and investigator.

Cohorts 8 and 9 will consist of patients with MCI due to AD or mild to moderate AD. The number of patients (LY3303560: placebo) in each cohort will be 6:2 patients.



Abbreviations: AD = patients with Alzheimer's disease; HS = healthy subjects; IV = intravenous; LY = LY3303560; PK = pharmacokinetics; PL = placebo; SAD = single-ascending dose; SC = subcutaneous.

4.2. Determination of Sample Size

The sample size is customary for Phase 1 studies evaluating safety, PK, and/or PD parameters, and at the conclusion of the trial confidence intervals for PK, PD, and cognition endpoints may be computed in order to evaluate the precision of the estimates where appropriate.

Up to 70 healthy subjects may be enrolled to ensure that approximately 54 subjects (8 subjects per cohort, except for Cohort 5 [n=6]) reach at least Day 29 of the study.

For each of the IV healthy subject cohorts, the intention is to include at least 4 non-Japanese subjects (preferred non-Asian) and up to 4 Japanese subjects to support the development of LY3303560 in Japan.
Up to 20 patients with AD may be enrolled to ensure that 16 patients (8 patients in each cohort) complete Cohorts 8 and 9.

4.3. Method of Assignment to Treatment

Computer-generated randomization tables will be prepared by a statistician.

Cohorts 1-7 (Healthy Volunteers, Single Site): 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.

Cohorts 8-9 (AD Patients, 2 Sites): The randomization will be such that the placebo assignments for the patient cohorts will be balanced between these 2 populations. Japanese subjects are not required for these cohorts and hence no split for Japanese/Non-Japanese will be made in the randomisation.

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 allprotocol 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 and exploratory reporting and analyses will be conducted by Eli Lilly.

5.2. Handling of Dropouts or Missing Data

Subjects or patients who discontinue the study before completing the Day 29 assessment may be replaced at the discretion of the sponsor and investigator. Subjects or patients who discontinue after Day 29 may also be considered for replacement to ensure sufficient data are available for final data analysis.

The ethnicity of the replacement subject (Japanese or non-Japanese) should match the ethnicity of the discontinued subject, where possible. Replacement subjects will be allocated the same treatment as the dropout subject.

There will be no imputation of missing data.

5.3. Multicenter 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.

5.4. Multiple Comparisons/Multiplicity

No adjustments will be made for multiplicity.

5.5. Patient and Subject Disposition

A detailed description of healthy subject and patient disposition will be provided at the end of the

study.

All patients/healthy subjects 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.

5.6. Patient and Subject Characteristics

The patient's/healthy subject'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 summarized at baseline, with the exception of weight which will also be summarized over time.

5.7. Japanese and non Japanese subjects

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 30ms and greater than 60ms) 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.

5.8. Subgroup Analyses

Any subgroup analyses will be exploratory (posthoc) in nature

5.9. Concomitant Therapy

Concomitant medication will be coded using the WHO drug dictionary. Concomitant medications will be listed.

5.10. Safety Analyses

Safety parameters that will be assessed include safety laboratory parameters, vital signs and ECG parameters. The parameters will be listed and summarized 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.

5.10.1. Extent of Exposure

Dosing information for each individual subject will be listed.

5.10.2. 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.

5.10.3. Safety MRI

A shift table for each IV dose will be constructed to assess the MRI measurement pre- and postdose for changes and additions of vasogenic edema and microhemorrhages in AD Cohorts 8/9 and for clinically significant changes including potentially vaogenic edema and microheamorrhages in HVs.

5.10.4. Evaluation of Immunogenicity

Antibody formation will be listed and summarized as well as presented graphically over time by subject/patient and treatment. If trends following the dosing of LY3303560 are observed, then a mixed effect model will be used, fitting dose and day and the interaction between day and dose as a fixed effects and the dependent variable as the log transformed change from baseline in antibody formulation following dosing of LY3303560. 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.

5.10.5. C-SSRS

For Cohorts 8 and 9, suicide-related thoughts and behaviors based on the C-SSRS will be listed by patient. Only time points and patients that show ideation/behavior of suicide will be displayed, that is, all ‘no’s will not be displayed.

5.10.6. Electrocardiograms

An assessment of potential prolongation will be performed using plots of PK data versus QTc values. The frequency of subjects with a maximum increase from baseline in QTcF interval will be summarized for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.
Analyses of QTc using QTcF from ECG monitoring in a Phase 1 trial will be performed to judge the extent and/or risk of QT prolongation. Scatter plots will be created of QTcF versus LY3303560 concentration and change from baseline QTcF versus LY3303560 concentration for matched timepoints.

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

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 following SAS code may be utilized:

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

Further exploratory analyses may be conducted if required. Separate analysis may be conducted for healthy subjects and patients with AD as required.

5.11. Pharmacokinetic Parameter Estimation

It is intended that PK parameter estimates for LY3303560 in serum and CSF will be calculated by standard noncompartmental methods of analysis. The primary serum and CSF parameters for analysis will be maximum drug concentration (C_{max}), area under the concentration versus time curve from time 0 to infinity ($AUC_{0-\infty}$) and AUC from time 0 to the last measurable concentration (AUC0-tlast) of LY3303560. Other serum PK parameters, such as half-life, clearance, and volume of distribution may be reported after IV administration of LY3303560. Serum PK parameters such as bioavailability, apparent clearance, apparent volume of distribution and half-life may be reported after SC administration.

A model-based approach may also be implemented using nonlinear mixed effects modeling (NONMEM) or other appropriate software to estimate serum and/or CSF PK parameters. Exploratory analyses of the effect of dose, route of administration, concentration or demographic factors, including healthy subjects versus patients, on the PK parameters may be conducted, and modeling analyses may be performed for characterization purposes. Exploratory analyses relating LY3303560 serum exposure versus LY3303560 CSF concentrations may be conducted.

5.11.1. Pharmacokinetic Statistical Inference

The serum PK parameters, C_{max} and $AUC_{0-\infty}$ or AUC0-tlast, for LY3303560 obtained for healthy subjects (IV only) will be evaluated to estimate the dose-exposure proportionality of LY3303560 using a linear effects power model (Smith et al. 2000). In this model, log transformed dose will be the independent variable, and subject will be a random effect. Both C_{max} and AUC will be log-transformed prior to analysis. The least-square means for each treatment together with the treatment differences and associated 90% confidence intervals (CIs) will be estimated from the model. These estimates will be back-transformed to present geometric means, the ratios of geometric means, and the corresponding 90% CIs. Dose-exposure

analysis will be conducted using the healthy subject IV cohorts (Cohorts 1, 2, 3, 4, 6, and 7).

The following SAS code may be utilized:

```
proc mixed ;
class subject;
by day;
model log_pk= log_dose/ ddfm=kr s cl alpha=0.1;
random intercept/subject=subject;
estimate 'ldose' logdose 1 / cl alpha=0.10 e;
ods output estimates=est covparms=cov;
run;
```

When plotted Japanese and non Japanese subjects will be identified in the same plot with different symbol types. Exploratory analyses of Japanese and non-Japanese subjects may be conducted. Additional

dose-exposure analyses may be conducted using patient data.

5.12. Exploratory Pharmacodynamic Analyses

5.12.1. Pharmacodynamic Parameter Estimation

For the healthy subjects, if data are available, plasma tau will be summarized and/or illustrated graphically by time and dose/formulation.

For the patient cohorts (Cohorts 8 and 9), if data are available, the concentration of the plasma and/or CSF biomarkers, including tau, p-tau, Aβ, and neurograinin, will be summarized and/or illustrated graphically based on availability of data. The mean change in concentration of the biomarkers from predose will be evaluated. Further analyses may be conducted if trends are observed in the data.

5.12.2. Pharmacodynamic Statistical Inference

No statistical analysis of PD parameters are planned.

5.13. Pharmacokinetic/Pharmacodynamic Analyses (Cohorts 8 & 9)

Exploratory correlational analyses may be conducted to describe the relationship between systemic and/or central LY3303560 exposure and changes in the florbetapir SUVr; MRI of whole brain,ventricle, and hippocampus volumes; CSF concentrations of Aβ, tau and p-tau; and number AEs related to infusion reactions. It is intended that these analyses will initially be descriptive graphs in nature as a function of LY3303560 dose, exposure, and/or time from study entry. If appropriate,these relationships may also be described using a modeling approach.

5.13.1. Planned Exploratory Analyses (Cohorts 8 and 9)

5.13.2. Imaging

18F-AV-1451 SUVR data will be summarized and/or plotted by region of interest as appropriate. Change from baseline of tau burden within regions of interested will be calculated and summarised, however, no formal analyses is planned to be conducted due to single dose nature of the study.

Amyloid status at baseline will be summarized and may be used as a factor in plots of other endpoints.

In addition to these analyses, correlation analyses between changes in CSF biomarkers ($A\beta_{1-40}$, $A\beta_{1-42}$, total tau, phospho-tau), or imaging endpoints (MRI measures, or SUVr from florbetapir scans) with posthoc serum AUC estimates derived from the PK model (or an alternative measure of exposure if deemed appropriate) may be completed. For SUVr, this will be conducted for the individual regions (if collected) and the total SUVr. Additionally, CSF and/or serum LY3002813 exposures may be related to CSF biomarkers, as appropriate.

5.13.3. vMRI

Magnetic resonance imaging changes in volume over the course of the study will be explored, and exploratory evaluation of whole brain and anatomically localized structural changes will be summarized (including, but not limited to, whole brain, ventricle, and hippocampus). Magnetic resonance imaging volumetric assesssments will be obtained at baseline, Day 15 and end of study. If data warrants further analyses then an MMRM will be constructed by fitting treatment and study visit as fixed effects. Response variables are brain structural changes of whole brain, ventricle, and hippocampal volumes.

5.13.4. Cognition Analyses

Cognition endpoints collected at screening and Day 85 may be summarized and correlated with imaging and CSF endpoints. The data are collected to provide information on cognition changes in a 2-3 month timeframe will not be used to assess efficacy of the molecule.

5.14. Interim Analyses and Data Monitoring

Select individuals may gain access to unblinded data, prior to the interim data access review or final database lock, in order to initiate the final population PK/PD model development processes for interim or final analyses. The individuals and unblinded data are as specified in the unblinding plan.

Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

Safety and/or PK interim access to data (IAD) is scheduled to occur throughout the study. The purpose of these IAD reviews is to examine the safety data and guide dose selections. The investigator and the Lilly study team will make the determination regarding dose escalation based on their review of the safety and tolerability data, along with PK data, as applicable. An interim review of safety and PK data is planned after healthy subjects in Cohort 3 complete the 28-day postdose PK blood draw. Additional interim PK data reviews may be performed as required during study conduct. The PK data obtained during the study may be used to assist in

dose-escalation decisions, but such data are not required for dose escalation.]

5.15. Clinical Trial Registry Analyses

Additional analyses may 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 summarized: 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.

6. Unblinding Plan

This is a subject-/patient- and investigator-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Randomization tables for allocation of LY3303560 and placebo will be prepared by the Lilly statistician and provided to the study site pharmacists or pharmacy staff involved in dose preparation. Blinding will be maintained throughout the conduct of the trial until all data are cleaned to an acceptable level of quality and locked.

Emergency codes will be available to the investigator. A code, which reveals the treatment group for a specific study subject/patient, may be opened during the study only if the subject/patient's well-being requires knowledge of the subject/patient's treatment assignment.

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

Interim access to the data is detailed in the protocol.

7. References

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

8. Appendix

8.1. Derivations of Scores for Cognition Questionnaires

Note: These derivations are draft to facilitate programming and any changes will not warrant a SAP amendment

8.1.1. CDR Domain scores

6 domains scored by clinician (based on a structured interview) as follows:

CCI

8.1.1.1. CDR Global score

The global CDR is derived from the scores in each of the six categories ("box scores") as follows.

Memory (M) is considered the primary category and all others are secondary. CDR = M if at least three secondary categories are given the same score as memory. Whenever three or more secondary categories are given a score greater or less than the memory score, CDR = score of majority of secondary categories on whichever side of M has the greater number of secondary categories.

When three secondary categories are scored on one side of M and two secondary categories are scored on the other side of M, CDR=M. When M = 0.5, CDR = 1 if at least three of the other categories are scored one or greater. If M = 0.5, CDR cannot be 0; it can only be 0.5 or 1. If M = 0, CDR = 0 unless there is impairment (0.5 or greater) in two or more secondary categories, in which case CDR = 0.5

8.1.2. Mini Mental State Examination (MMSE)

MMSE Total score (range 0-30)
Sum of questions: Orientation (0-10), Registration (0-3), Attention and Calculation (0-5), Recall (0-3), Language (0-8) and Copying (0-1)

8.1.3. FCSRT-IR

The test provides two basic measures of memory and learning: Free Recall and Total Recall. Total Recall is obtained by adding Cued Recall to Free Recall on each trial.. Free Recall is a measure of self-organized retrieval. Total recall is a measure of maximum retrieval that provides an estimate of encoding and retention.

Free Recall
Enter the number of items retrieved by Free Recall on each trial.
Enter the sum of Free Recall on trials 1 + 2 + 3.

Cued Recall
Enter the number of items retrieved by Cued Recall on each trial.
Enter the sum of Cued Recall on trials 1 + 2 + 3.

Total Recall
Add Cued Recall to Free Recall on each trial. Enter the sum of Total Recall on trials 1 + 2+ 3.

Free Recall / Total Recall
The proportion of Total Recall obtained by Free Recall provides a measure of the efficacy of Free Recall or retrieval. Divide Free Recall on each trial by Total Recall on each trial. For “Sum 1+2+3” divide the sum of Free Recall on Trials 1 + 2 + 3 by the sum of Total Recall on Trials 1 + 2+ 3.

Total Recall / Maximum Possible Recall
The proportion of maximum possible recall obtained by Total Recall provides a measure of the

efficacy of Total Recall or encoding and retention. This proportion may also be regarded as a measure of the efficacy of Cued Recall, assuming that words retrieved by Free Recall would also have been retrieved by Cued Recall.
Divide Total Recall on each trial by 16. For "Sum 1+2+3" divide the sum of Total Recall on Trial 1 + 2 + 3 by 48.

Leo Document ID = ddcc1362-fe06-4d89-8879-98163d554f60

Approver: PPD
Approval Date & Time: 14-Apr-2016 10:01:20 GMT
Signature meaning: Approved