STATISTICAL ANALYSIS PLAN (SAP)

Protocol Number: COR388-010
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study of COR388 HCl in Subjects with Alzheimer's Disease
Product Name or Number: COR388 HCl
Sponsor: Cortexyme, Inc.

NCT03823404

SAP Version Number (Date): Version 5.0 (27 August 2021)

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Sponsor:	Cortexyme, Inc. 269 East Grand Ave. South San Francisco, CA 94080
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TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AD	Alzheimer's Disease
ADAS-Cog 11	Alzheimer's Disease Assessment Scale-Cognitive Subscale 11
ADCS-ADL	Alzheimer's Disease Cooperative Study Group-Activities of Daily Living
ANCOVA	Analysis of Covariance
ApoE	Apolipoprotein E
ATC	Anatomical Therapeutic Chemical
B	Buccal
BMI	Body Mass Index
BOP	Bleeding on Probing
CAL	Clinical Attachment Level
CDC/AAP	Centers for Disease Control/American Academy of Periodontology
CFB	Change from Baseline
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CSF	Cerebrospinal Fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed Tomography
DB	Distobuccal
DL	Distolingual
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECGs	Electrocardiograms
ET	Early Termination
GM	Gingival margin
ID	Identification
IP	Investigational Product
IRS	Interactive Response System
ITT	Intent-to-Treat Population
JCP	Joint Conditional Power
L	Lingual
LPs	Lumbar Punctures
MAR	Missing at Random
MB	Mesiobuccal
MedDRA	Medical Dictionary for Regulatory Activities
ML	Mesiolingual
MMRM	Mixed-Effects Model for Repeated Measures

Abbreviation or Term	Definition
MNAR	Missing Not a Random
MRI	Magnetic Resonance Imaging
MMSE	Mini-Mental State Examination
NIA-AA	National Institute on Aging-Alzheimer's Association
NPI	Neuropsychiatric Inventory
PBMCs	Peripheral Blood Mononuclear Cells
PD	Pocket Depth
Pg	*Porphyromonas gingivalis (P. gingivalis*)
PP	Per Protocol Population
pPCR	Quantitative Polymerase Chain Reaction
SDs	Standard Deviations
SGP	Subgingival Plaque
SOPs	Standard Operating Procedures
TEAEs	Treatment-Emergent Adverse Events
UK	United Kingdom
US	United States
WHODRUG	World Health Organization Drug Dictionary

2 STUDY OVERVIEW

This is a Phase 2/3, multi-site, randomized, double-blind, placebo-controlled study that will assess the efficacy, safety, and tolerability of 2 dose levels of COR388 HCl in subjects with probable Alzheimer's Disease (AD) dementia according to the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria (McKhann 2011).

The study will enroll approximately 573 generally healthy male and female subjects ≥55 and ≤80 years of age. Enrolled subjects must have a documented diagnosis of probable AD dementia with clinical evidence of progressive cognitive decline in the last year. Clinical decline will be defined as the evidence of progressive cognitive decline on sequential evaluations based on information from informants and/or cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations for probable AD dementia (McKhann 2011). Subjects should not have other conditions or brain imaging abnormalities that can explain the symptoms of dementia. All subjects will have lumbar punctures (LPs) performed at baseline (Visit 2) and at end of treatment Week 48 (Visit 10) or early termination visit (ET). Cerebrospinal fluid (CSF) will be tested for evidence of *Porphyromonas gingivalis* (Pg) infection and biomarkers of AD and neuroinflammation. Blood (serum and plasma) will be analyzed for biomarkers of AD and neuroinflammation and antibodies specific for Pg. Saliva collected in the form of an oral rinse will be tested for the measurement of Pg bacterial DNA using qPCR.

A subset of sites will be selected to monitor subjects for clinical evidence of periodontitis in addition to AD. An oral examination will be conducted by a study dentist/hygienist at these sites to assess for the presence of clinical evidence of periodontitis at screening, 24 and 48 weeks.

Subgingival plaque (SGP) and buccal swabs will be collected at these sites and analyzed for measurements of biomarkers associated with *P. gingivalis* DNA, proteins, and inflammation.

Due to the nature of AD, subjects must identify a primary caregiver prior to enrollment in the study who will assist the subject with study participation. The primary caregiver must sign a caregiver informed consent. The safety of study participants will be evaluated throughout the study by repeated physical examinations, vital signs, safety laboratory tests, 12-lead electrocardiograms (ECGs), Columbia-Suicide Severity Rating Scale (C-SSRS), magnetic resonance imaging (MRI), and assessments of treatment-emergent adverse events (TEAEs). Periodic safety reviews will be conducted during the study. The study will consist of 3 periods: a screening period of up to 6 weeks, a treatment period of up to 48 weeks, and a safety follow-up period of 6 weeks. An interim analysis may be conducted to reassess the sample size and evaluate for overwhelming efficacy after 24 weeks of treatment on key outcome measures.

Screening

During the screening period, the eligibility of subjects will be confirmed according to the Schedule of Evaluations in this protocol. The Mini-Mental State Examination (MMSE) will be administered by a trained rater to assess the level of cognitive impairment. MMSE will be assessed as early in the screening period as possible. Subjects with MMSE score of 12-24, inclusive, will have the rest of their screening procedures performed or scheduled. Magnetic resonance imaging (MRI) of the brain will be performed in all subjects at screening, except subjects with an absolute contraindication for MRI, who can have a Computed Tomography

(CT) scan of the brain instead. Screening procedures can be done on multiple days if needed, with more invasive procedures done after less invasive screening procedures are completed. A screen failure is any subject who signs the informed consent but does not qualify for the study or discontinues the study prior to randomization. A subject can be rescreened if the Principal Investigator thinks the subject may qualify for the study upon rescreening, and if the Medical Monitor agrees.

Treatment Period

Subjects who meet all eligibility criteria will enter the treatment period and will be randomized 1:1:1 to receive 40 mg COR388 HCl, 80 mg COR388 HCl, or placebo twice a day. Randomization will be stratified by baseline MMSE (MMSE ≥12 and ≤18, and MMSE ≥19 and ≤24) and Apolipoprotein E [ApoE4 Carries (Positive either Homozygous or Heterozygous) vs. Non-Carriers (ApoE4 All Others)] genotype to assure balanced distribution of mild and moderate AD and a balanced distribution of ApoE4 subjects, across treatment arms. Subjects will receive their assigned blinded study treatment orally twice a day for up to 48 weeks and will come back to the investigative site periodically for scheduled efficacy and safety evaluations. Blood samples for pharmacokinetics levels and biomarkers will be collected during selected visits. Baseline LP will be performed prior to the first dose of study drug, and follow-up LP will be done at the end of the treatment period. Subjects will continue to receive the study drug for 48 weeks, unless the Investigator determines that treatment of a given subject should be stopped or interrupted for safety or tolerability reasons, the subject withdraws consent, or the Sponsor decides to stop the study.

Safety Follow-up Period

After completion of study treatment, subjects will continue to be monitored on the study for 6 weeks and will have a phone call to assess safety at Weeks 49 and 51 and will return for the Safety Follow-up Visit (Week 54). For subjects with early termination, end of study procedures (Week 48) will be performed, and subjects will be encouraged to return to the clinic for the Safety Follow-up Visit after 6 weeks. Phone calls will be performed to assess safety at Week 1 and Week 3 after end of study procedures are performed.

Open Label Extension Period

Subjects who choose to participate in the open label extension portion of the study and meet all eligibility criteria will begin the treatment period after completing the Week 48 Visit. Subjects will receive COR388 HCl 80 mg or 40 mg treatment orally twice a day for up to 48 weeks and will come back to the investigative site periodically for scheduled efficacy and safety evaluations. Subjects will continue to receive the study drug for 48 weeks, unless the Investigator determines that treatment of a given subject should be stopped or interrupted for safety or tolerability reasons, the subject withdraws consent, or the Sponsor decides to stop the study.

Open Label Extension Safety Follow-up Period

After completion of study treatment for the open label extension, subjects will continue to be monitored on the study for 6 weeks and will have 2 phone calls to assess safety at Week 97 and Week 98 and will return for the Safety Follow-up Visit at Week 102.

For subjects with early termination, end of study procedures (Week 96) will be performed, and subjects will be encouraged to participate in the Safety Follow-up phone calls and return to the clinic for Safety Follow-up Visit.

3 STUDY OBJECTIVES, ENDPOINTS, AND ESTIMANDS

This statistical analysis plan (SAP) document is the complete and final statement of the pre-planned assessments for the Double-Blind Phase of Protocol COR388-010. This version supersedes and replaces all such language in the protocol and earlier versions of this document. The SAP for the Open Label Extension Phase will be in a separate document.

This study was designed to assess the efficacy of COR388 HCL in treating Alzheimer's disease. Therefore, a comprehensive set of primary, secondary, and exploratory objectives are pre-specified for these endpoints. However, a sub-study nested within the main study was implemented to explore the efficacy of COR388 HCL in treating periodontitis. Therefore, a second, independent set of objectives are pre-specified for the periodontitis sub-study.

Alzheimer's Disease

The primary objective of this study is to assess the efficacy of COR388 HCl in the treatment of AD. Based on the postulated mechanism of action, an effective treatment is expected to slow or prevent further accumulation of AD pathology, neurodegeneration, cognitive decline, and loss of function in activities of daily living.

The primary endpoints of this study are:

- Mean change in Alzheimer's Disease Assessment Scale-Cognitive Subscale 11 (ADAS Cog 11), from baseline to the end of the double-blind treatment period, defined as the average of the week 40 and week 48 assessments.
- Mean change in Alzheimer's Disease Cooperative Study Group-Activities of Daily Living (ADCS-ADL), from baseline to the end of the double-blind treatment period, defined as the average of the week 40 and week 48 assessments.

The primary estimands for the primary endpoints are based on a hypothetical strategy for dealing with the intercurrent event (ICE) of early study discontinuation to assess what would have been observed if the ICE had not occurred. Supplementary estimands for these endpoints are based on a composite strategy in which subjects with relevant ICEs are ascribed poor outcomes regardless of observed outcomes up to the occurrence of ICEs. See Section 12.2 for more details.

For study success, contrasts with placebo must be statistically significant on both primary endpoints in at least one of the active arms. However, for publication purposes, successful proof of concept will be reported if the ADAS-Cog 11 shows statistical significance for either or both active arms regardless of the outcome on the ADCS-ADL.

The secondary endpoints of this study are:

- Mean change in Clinical Dementia Rating-Sum of Boxes (CDR-SB) from baseline to the end of treatment period.
- Mean change in Mini-Mental State Examination (MMSE) from baseline to the end of treatment period.
- Mean change in Neuropsychiatric Inventory (NPI) Total Score from baseline to the end of treatment period.

Exploratory endpoints assessed in all subjects include change from screening (Visit 1) and/or baseline (Visit 2) to the end of treatment in the following measures:

- NPI Caregiver Distress Score;
- Magnetic resonance imaging:
- Hippocampal volume; and
- Cortical thickness.
- Biomarkers of AD
- Biomarkers of P. gingivalis infection
- Biomarkers of inflammation and neuroinflammation

Exploratory endpoints in subsets of subjects who participated in the various sub-studies include change from screening/baseline to the end of the double-blind treatment period in the following measures:

- Winterlight Speech Assessment (only in English speaking subjects (primary language and only in the US and UK);

Exploratory Population Pharmacokinetics (Pop PK) will also be assessed in this study.

- There will be a pre-specified subgroup analysis of subjects with adequate drug exposure on the co-primary outcomes.
- There will also be post-hoc exploratory analyses comparing drug exposures to key efficacy and safety endpoints.

Correlations of biomarkers with clinical endpoints will also be evaluated. The primary biomarker endpoint is bilateral hippocampal volume as measured by MRI. This is the primary biological endpoint of interest due to its inherent role in Alzheimer's disease pathology and its ability to predict "likely clinical benefit" supportive of accelerated approval.

The safety endpoints for this study are:

- The incidence and severity of TEAEs;
- Vital signs and physical examinations;
- Laboratory values;
- MRI scans;

- 12-lead ECGs; and
- C-SSRS

Periodontitis sub-study

For the exploratory clinical periodontitis sub-study, subjects will be enrolled at selected study sites. The primary objective of this sub-study is to assess the efficacy of COR388 HCl in the treatment of periodontitis. The primary endpoint of the sub-study is mean change in Pocket Depth (PD) from baseline to the end of the double-blind treatment period for tooth sites with depth => 4mm at any time during the study. As with the primary endpoints for the AD study, a hypothetical strategy will be used to deal with the ICE of early study discontinuation. Successful proof of concept will be reported if the primary endpoint is statistically significant at the 0.10 level ($p \leq 0.10$).

The secondary endpoints of the clinical periodontitis sub-study are:

- Mean change in Clinical Attachment Level (CAL) from baseline to the end of treatment period for tooth sites with depth => 3mm.
- Mean change in percentage of sites with Bleeding on Probing (BOP) from baseline to the end of treatment period.

4 GENERAL METHODS

4.1 Analysis Populations

Analysis datasets will be defined as follows:

- Intent-To-Treat Population (ITT): The ITT population will include all subjects who are randomized regardless of whether they took study drug. This population will be the primary basis for efficacy analyses. When change from baseline is assessed, subjects will be included in the analysis only if both a baseline and a postbaseline measure are available because both measures are needed to derive change from baseline, the analysis variable.
- The Per Protocol population (PP): The PP population will include all ITT subjects who do not have any major protocol deviations that would affect efficacy (e.g., <80% treatment compliance, taking a prohibited medication). Major protocol deviations will be reviewed and determined prior to unblinding. The PP population will be used for supportive analyses.
- Safety Population: The Safety population will include all subjects who receive at least one dose of study drug. Safety analyses will be performed using the Safety population, and subjects will be analyzed according to the treatment they actually received.

4.2 Summarization of Data

Study results will be summarized by treatment group unless otherwise specified.

Continuous data will be summarized using means, standard deviations (SDs), medians, maximum, minimum, and number of subjects. Categorical data will be summarized by counts and percentages.

4.3 Visit Windows

Although stricter windows were used for scheduling visits, for analysis, the visit windows will be defined as follows:

Double-blind Phase

Scheduled in-clinic Visit	Scheduled Week	Scheduled Day	Time Window (Days) for assessment collected at each in-clinic visit		Time Window (Days) for ECG assessments	
1	Screening		Assigned as collected (if applicable)			
2	Baseline (Week 0)	1	Assigned as collected (if applicable)			
3	Week 2	14	2	28	2	28
4	Week 6	42	29	63	29	63
5	Week 12	84	64	105	64	126

6	Week 18	126	106	147		
7	Week 24	168	148	196	127	224
8	Week 32	224	197	252		
9	Week 40	280	253	308	225	308
10	Week 48#	336	309	343	309	343
11	Follow-up	378	Assigned as collected (if applicable)			

For subjects withdrawing early (prior to Day 309), their Week 48/Early Termination visit will be windowed. Otherwise assigned as collected (Week 48).

The following example illustrates how this visit window will be implemented. Week 6 is scheduled at study day 42. If the assessment occurs within study days 29 through 63 then the assessment will be deemed a Week 6 result. If the assessment occurs before study day 29 then the Week 2 window will be examined. If the assessment occurs after study day 63 then the Week 12 window will be examined. Any assessments that are scheduled at less frequent visits will use the same approach with contiguous visit windows between scheduled visits, and the first post-baseline visit window will start at day 2.

If two assessments are collected during the same visit window, the assessment which is closest to the actual planned study day will be used in the analysis for safety outcomes. For efficacy outcomes with more than one assessment in a visit window, the non-missing assessments will be averaged prior to analysis.

4.4 Randomization

Subjects who meet all eligibility criteria will enter the treatment period and will be randomized 1:1:1 to receive 40 mg COR388 HCl, 80 mg COR388 HCl, or placebo twice a day. Randomization will be stratified by baseline MMSE (MMSE ≥12 and ≤18, and MMSE ≥19 and ≤24) and Apolipoprotein E [ApoE4 Carriers (Positive for ApoE4, either Homozygous or Heterozygous) vs. Non-Carriers (All Others)] genotype to assure balanced distribution of mild and moderate AD and a balanced distribution of ApoE4+ subjects, across treatment arms. All subjects will be centrally assigned to randomized study intervention using an Interactive Response System (IRS).

4.5 Sample Size Justification

The study will have an adaptive design that allows for potential adjustment in sample size based on the results of a planned interim analysis. An unblinded interim analysis will be conducted by a firewalled independent statistician (all clinical trial personnel will remain blinded) when approximately 100 subjects per arm have completed the Week 24 visit. Approximately 573 subjects are planned to be randomized 1:1:1 per treatment group (191 per treatment group) assuming approximately 10% missing data at the primary endpoint. Due to the planned interim analysis, adjustments will be made to the alpha level used in the final analysis to control for overall Type I error. The final criterion for efficacy to be used at the interim and final analysis depends on when the interim analysis occurs. The Lan-DeMets method modified according to Chen et al. (2004) to account for correlation between endpoints used at the interim and final analyses will be used to calculate the level of significance for each analysis.

With 573 subjects randomized (191 per group) and 10% missing data (172 completers per group) this study has approximately 90% power to detect a 2.5-point difference between each active treatment group compared to placebo based on change from baseline in the ADAS-Cog 11, assuming a standard deviation of 7.1 and a significance level (alpha) of 0.05 using a two-sided test. For the co-primary outcome of ADCS-ADL, a 3.9-point difference between the active treatment groups and placebo is assumed for mean change from baseline to the end of treatment, with a standard deviation of 10.5. These assumptions lead to approximately 95% power on this outcome measure, with up to 90% power for the joint success of the co-primary outcomes, depending on their correlation.

These power estimates further assume that 2 sequential sets of analyses, interim and final, will be conducted, with the Lan-DeMets spending function used to determine the test boundaries. Therefore, if an interim analysis is conducted when approximately 300 subjects have completed the Week 24 visit, then a significance level of 0.005 will be used for the interim analysis and a significance level of approximately 0.0456 will be used for the final analysis. See Section 12.5 for more details on multiplicity adjustment.

As discussed by Chen et al 2004, the sample size re-estimation procedure based on the promising zone methodology (i.e., conditional power 50% to 90%) will not inflate the type I error and no statistical adjustment is necessary. However, the adjusted alpha at the end of the study will be based on the updated sample size at the final analysis, thereby causing the level of significance at the final analysis to potentially differ slightly from the 0.0456 quoted above that is based on the currently anticipated sample size.

The actual enrollment for this study was 643 subjects randomized, approximately 12% greater than originally anticipated. The over-enrollment was appropriate to offset the higher rate of missing data anticipated as a result of COVID.

4.6 Output Production and Validation

All analyses will be performed using SAS V 9.3 or higher (SAS Institute, Inc, Cary, North Carolina, USA). Validation and quality control of the tables and listings, which display the results of the statistical analysis of the data from this study, will follow the appropriate Innovative Analytics standard operating procedures (SOPs).

5 PROTOCOL DEVIATIONS

Prior to database lock, a full list of protocol deviations will be compiled and reviewed by the clinical team to identify major versus minor deviations. Major protocol deviations will be displayed for the safety population in subject listing.

6 SUBJECT DISPOSITION

The number of subjects who are enrolled, who are randomized, who are randomized but not dosed, who are in the ITT population, who are in the safety population, who complete the study, and who discontinue from the study, along with reason for study discontinuation, will be summarized in tabular format for all enrolled subjects in the double-blind phase. The number of subjects with early withdrawal will also be summarized for the safety population in tabular format as follows: <2 weeks, 2 to <6, 6 to <12, …, >=48 weeks in the study in the double-blind phase.

Subject disposition information will be displayed for the safety population in a subject listing.

The number of subjects randomized by country and site will be summarized in tabular format for the randomized population.

7 DEMOGRAPHIC CHARACTERISTICS

For quantitative variables (e.g., age, height, weight, body mass index [BMI], MMSE total score at baseline), summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for all subjects in the safety population. For qualitative variables (e.g., sex, race, ethnicity, MMSE stratum, ApoE4 stratum, participated in Alzheimer's Disease study clinical trial previously), results will be summarized for all subjects in the safety population as counts and percentages. Individual demographic information for the safety population will be displayed in subject listings.

8 MEDICAL HISTORY

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (using MedDRA Version stated in Data Management Plan). Frequency tables by System Organ Class and Preferred Term will be present for prior medical history and on-going medical history, separately, for the safety population.

Medical history will be listed for the safety population.

9 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded using World Health Organization Drug Dictionary (WHODRUG, version specified in the Data Management Plan). Prior and concomitant medications will be listed for each subject according to Anatomical Therapeutic Chemical (ATC) Level 4 term, preferred name, and verbatim term.

10 EXTENT OF EXPOSURE

Extent of exposure (number of days of exposure to study drug) will be presented by treatment group for the Safety Population.

11 STUDY DRUG INTERRUPTION

The number of interruption(s) of study medication (e.g., 0, 1, 2, >=3) will be tabulated by treatment group. Duration of study medication interruption (e.g., longest duration within each subject) will be summarized by treatment group the Safety Population.

12 EFFICACY ANALYSES

12.1 Primary Endpoint Analyses

The co-primary endpoints are mean changes from baseline to the end of study (average of the assessments at Weeks 40 and 48, calculated for each patient prior to analysis) in the ADAS-Cog 11 total score and the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) total score. For ADAS-Cog 11, baseline will be defined as the average of the last two non-missing values (either scheduled, unscheduled or repeat evaluations) performed between screening and Week 0 (i.e., before or at the day the subject receives the first dose of study drug). If only one baseline ADAS-Cog 11 assessment is available, it will be used. For ADCS-ADL, baseline will be the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug. For publication purposes, successful proof of concept will be reported if the ADAS-Cog 11 shows statistical significance for either or both active arms regardless of the outcome on the co-primary outcome.

Sites will be pooled for Europe and the US as follows:

For Europe, all sites within a country will be pooled and considered as single site. After pooling sites within a country, all countries are expected to have at least 2 patients in each treatment arm. If this condition is not satisfied, the countries with less than 2 patients per treatment arm will then be pooled with the nearest country. For Great Britain, this will be France, for Spain, this will also be France, for France, it will be pooled with Great Britain. If any 2 of those 3 countries do not have at least 2 patients per arm, only those 2 countries will be pooled. For Netherlands, it will be Poland and for Poland, it will be Netherlands.

US sites will be pooled within each state with the following exceptions: Each state will be a separate site except KS will be pooled with ID, MS will be pooled with IL, NM will be pooled with AZ, and NY will be 2 sites: Albany and others, and CA will be 2 sites: CT Trials and other, GA will be 2 sites. Florida sites with at least 2 subjects in each treatment arm will be separate sites. Any remaining Florida sites will be put into the pooling algorithm. Any of the above defined sites or state groups that do not meet the requirement of 2 subjects per treatment arm will also be put into the pooling algorithm.

The pooling algorithm will start with the largest site and pool it with the smallest site, then next smallest, continuing until it has at least 2 patients in each treatment arm. The sort order will be by site size and then site name alphabetically. At the end of the pooling process, if the remaining patients do not result in a site with at least 2 patients per arm, the extra sites/patients will be pooled with the last site created in the pooling process.

The adequacy of the pooling mechanism will be evaluated post database lock prior to unblinding and analysis. Any modification will be described in the CSR.

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for each of the co-primary endpoints at each time point for the ITT population, including weeks 40 and 48 separate as well as averaged. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point as listed above.

Each of the co-primary estimands/endpoints will be analyzed using a likelihood-based mixed-effects model for repeated measures (MMRM) with SAS PROC MIXED to compare mean change from baseline for COR388 HCl vs placebo. The primary analysis will be applied to the ITT dataset. The MMRM model will include treatment group, study visit, site/country, ApoE4 status, acetylcholinesterase inhibitor and/or memantine (AD Med) usage at baseline (yes/no), and the interactions of Visit with treatment group, ApoE4 status, and AD Med usage all as categorical fixed effects. Baseline MMSE score and the baseline score for the variable being analyzed, along with their interactions with visit will be included as continuous fixed effects. The analysis will use an unstructured covariance matrix to model the within-subject errors. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

If the model fails to converge, the model will be simplified by excluding the terms for acetylcholinesterase inhibitor and memantine usage and its interaction with visit. If the model still fails to converge, the site term will be replaced with 3 regions in the US (Pacific time zone, Eastern time zone without Florida and other (includes Florida), and Europe will be one region. If this analysis still fails to converge, more parsimonious correlation structures will be implemented in this order: heterogeneous Toeplitz, heterogeneous compound symmetric, and compound symmetric. The first correlation structure to yield convergence will be the primary analysis.

The following SAS code implements the MMRM primary analysis.

```
Proc Mixed;
        Class trtgrp subj Visit site_country APOE4_status acetylcholinesterase_
            inhibitor_memantine_usage;
        Model cfb = trtgrp Visit site_country APOE4_status acetylcholinesterase_
            inhibitor_memantine_usage baselineMMSE baseline_score
            trtgrp*Visit APOE4_status*Visit acetylcholinesterase_inhibitor_memantine_
            usage*Visit baselineMMSE*Visit Baseline_score*Visit
           /CL solution ddfm=kenwardroger residual outp=testresid covb;
        Repeated visit / subject = subj(trtgrp) type=un rcorr;
        Lsmeans trtgrp*visit / pdiff cl slice=Visit;
Run;
```

where cfb is the change from baseline for that endpoint. As for ADAS-Cog 11 and ADCS-ADL, Baseline MMSE will be defined as the average of the last two non-missing values (either scheduled, unscheduled or repeat) before or at the day subject receives the first dose of study drug.

The primary inferences will be drawn from the adjusted treatment differences (LSMEANS) at end of treatment, defined as the average of Weeks 40 and 48 assessments. Treatment differences for each post-baseline visit will also be derived using the MMRM model, which will entail a second (sensitivity) analysis in which outcomes from each visit are included without averaging the Weeks 40 and 48 assessments.

Estimated treatment differences for each visit will be presented along with corresponding 95% confidence intervals and p-values.

12.2 Sensitivity and Supplementary Analyses

Sensitivity to choice of covariates

The analysis specified below is included as a sensitivity analysis because it was used in analysis of interim data and is used for secondary endpoints in the final analysis. It differs from the current primary analysis in that it does not include interactions of covariates with visit, except for the treatment group by visit interaction.

```
Proc Mixed;
        Class trtgrp subj visit site_country APOE4_status acetylcholinesterase_
           inhibitor_memantine_usage;
        Model cfb = trtgrp visit trtgrp*visit site_country APOE4_status
          Acetylcholinesterase_inhibitor_memantine_usage baselineMMSE
          baseline_score /CL solution ddfm=kenwardroger residual outp=testresid
          covb;
        Repeated visit / subject = subj(trtgrp) type=un rcorr;
        Lsmeans trtgrp*visit / pdiff cl slice=visit;
Run;
```

Sensitivity to protocol violations

The influence of lack of adherence to the protocol will be evaluated by repeating the primary analysis on the per-protocol data set.

Sensitivity to missing data assumptions

The primary MMRM analysis assumes that the missing data arise from a missing at random (MAR) mechanism. To assess the robustness of the results to departures from MAR, a sensitivity analysis will be conducted such that the monotone missing data is imputed assuming a missing not at random (MNAR) mechanism that provides a stress test of the MAR assumption and a conservative estimate of the treatment effect.

For this sensitivity analysis, a pattern-mixture model will be implemented using multiple imputation (100 imputed datasets) and inference will be based on the combined estimates using Rubin's rules, the standard multiple imputation technique, in SAS.

The missing data will be imputed using the controlled-based pattern-mixture model approach outlined by Ratitch and O'Kelly (2011). With this approach, subjects who discontinue from the COR388 HCl 80 mg or COR388 HCl 40mg treatment groups, for reasons not related to COVID, will be assumed to follow the outcome trajectory of otherwise similar subjects in the placebo (control) arm. Missing values will be imputed as if subjects had been on placebo throughout the study, thereby ascribing placebo-like outcomes to these subjects. Subjects who discontinued from placebo (control) treatment will have missing values imputed based on the MAR assumption. That is, missing values for reasons not related to COVID will be imputed for the active arms using the imputation model developed for the placebo group, thereby attenuating the treatment effects in the active arms commensurate with the rate of non-COVID related missing data. Missing values

due to COVID will be left as missing in this sensitivity analysis and thereby assumed to be MAR.

Because pattern mixture models overestimate the already very large variability in Alzheimer's disease data, these model results are likely to be much less able to discriminate treatment differences than the primary model. These results will focus on the potential bias in the primary model due to dropout by comparing the estimates from the primary and sensitivity models, not by preservation or loss of statistical significance.

Sensitivity to non-normality

Inspection of blinded data suggested the potential for violation of the assumption of normally distributed residuals in the primary MMRM analysis. Therefore, a non-parametric analysis will be implemented. To account for missing data via MAR as in the primary MMRM analysis, multiple imputation will be implemented using SAS PROC MI, with an imputation model congenial with the MMRM analysis model, and each imputed dataset analyzed via the Wilcoxon rank sum test implemented via SAS PROC NPAR1WAY. The resulting z scores and standard errors of 1 will be combined via Rubin's rules for final inference using SAS PROC MIANALYZE.

Supplementary Estimands and analyses

The supplementary estimand for the co-primary endpoints is based on a composite strategy for dealing with the ICE of early study withdrawal. The outcomes in this analysis are a composite of the observed outcomes and whether the subjects completed the study. Subjects who discontinued early will be assigned poor outcomes regardless of observed outcomes prior to withdrawal. Data will be analyzed using the Wilcoxon rank sum test via SAS NPAR1WAY, with the worst rank assigned to patients who withdrew early.

12.3 Subgroup Analyses

Demographics and Baseline Characteristics Subgroup Analyses

To assess the effects of various demographic and baseline characteristics on treatment outcome, subgroup analyses for the co-primary endpoints, the mean change from baseline in ADAS-Cog 11 at the average of Weeks 40 and 48, and the mean change from baseline in ADCS-ADL at the average of Weeks 40 and 48, will be as follows:

- Baseline MMSE severity (baseline MMSE 12-18 (moderate); Baseline MMSE 19-24 (mild); and
    - *Baseline MMSE severity as a continuous variable
- *ApoE4 status (e.g., ApoE4 Carriers (Positive either Homozygous or Heterozygous); Non-Carriers (All Others)).
- Amyloid positive and negative using Ab42/Ab40 Ratio status at baseline (ratio <=0.095, ratio >0.095) from cerebrospinal fluid (EuroImmun Assay)

- Acetylcholinesterase inhibitor and/or Memantine status at baseline (yes, no)
- Region (US; all other)

Biomarker Subgroup Analyses

The following subgroups will be used to understand the mechanism of action better and inform future trials and biomarker selection:

- *Porphyromonas gingivalis antibody status at baseline (High vs Low)
- *Porphyromonas gingivalis DNA status at baseline (not detected, detected) from oral samples (saliva in oral rinse, buccal swab, or subgingival plague)
- *Evidence of Porphyromonas gingivalis infection (not detected, detected) from cerebrospinal fluid
- *Evidence of target inhibition based on reduction of gingipain activity

These subgroup analyses may also be performed for the secondary and exploratory endpoints. The subgroups marked with an asterisk are the most relevant ones and are expected to show differences.

Two of the subgroup analyses are based on continuous scores that have been classified into 2 groups: baseline MMSE group and Ab42/Ab40 ratio group. For these subgroup analyses, the interaction between treatment and covariate and the 3-way interaction of treatment by covariate by time will be assessed to determine whether any differences between groups are related to an effect on the continuous underlying variable.

Following is the SAS code which will be used for the MMRM analysis of subgroups:

```
Proc Mixed;
        Class trtgrp subj visit subgroup_factor site_country APOE4_status
                        acetylcholinesterase_inhibitor_memantine_usage;
        Model cfb = trtgrp visit subgroup_factor trtgrp*visit
          trtgrp*subgroup_factor trtgrp*visit*subgroup_factor site_country
          APOE_status acetylcholinesterase_inhibitor_memantine_usage
          Baseline_score BaselineMMSE /CL solution ddfm=kenwardroger residual
          outp=testresid covb;
        Repeated visit / subject = subj(trtgrp) type=UN rcorr;
        Lsmeans trtgrp*subgroup_factor / pdiff cl;
Run;
```

where cfb is the change from baseline for that endpoint. Country/site, visit, ApoE4, and acetylcholinesterase inhibitor and/or memantine usage at baseline are categorical terms. Baseline MMSE and baseline score will be treated as continuous variables. Baseline will be defined as the average of the last two non-missing values, or if one is missing, the last non-missing value (either

scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug. The baseline MMSE values will be removed from the model for the MMSE severity subgroups.

Cmax and AUC(0-24 Hours) Subgroup Analyses

Subjects in the 80 mg COR388 HCl group with the highest plasma Cmax exposures, defined as the top 60% of the 80 mg COR388 HCl group, will be compared to the placebo group using the MMRM analysis. This MMRM analysis will be repeated for the highest plasma AUC (0-24 hours) exposures using the top 60% of the 80 mg COR388 HCl group compared to the placebo group.

Following is the SAS code which will be used for the MMRM analysis for the 'highest' Cmax and 'highest' AUC(0-24 hours) subgroups:

```
Proc Mixed;
        Class trtgrp subj visit site_country APOE4-status acetylcholinesterase_
                inhibitor_memantine_usage;
        Model cfb = trtgrp visit trtgrp*visit site_country APOE4_status
                Acetylcholinesterase_inhibitor_memantine_usage
                baseline_score baselineMMSE /CL solution ddfm=kenwardroger
                residual outp=testresid covb;
Repeated visit / subject = subj(trtgrp) type=UN rcorr;
Lsmeans trtgrp*visit / diff pdiff cl slice=visit;
Run;
```

where cfb is the change from baseline for that endpoint. Country/site, visit, ApoE4, and acetylcholinesterase inhibitor and/or memantine usage at baseline are categorical terms. Baseline MMSE and baseline score will be treated as a continuous variable. Baseline will be defined as the average of the last two non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

COVID-19 Subgroup Analyses

The following subgroup analyses will be used to examine the exclusion of subjects with adverse event preferred terms of COVID-19:

- Exclusion of subjects with preferred terms of COVID-19, COVID-19 pneumonia, asymptomatic COVID-19, or exposure to SARS-CoV-2

Following is the SAS code which will be used for the MMRM analysis for COVID-19 subgroup analysis:

```
Proc Mixed;
        Class trtgrp subj visit site_country APOE4-status acetylcholinesterase_
           inhibitor_memantine_usage;

        Model cfb = trtgrp visit trtgrp*visit site_country APOE4_status
                Acetylcholinesterase_inhibitor_memantine_usage
```

```
                baseline_score baselineMMSE /CL solution ddfm=kenwardroger
                residual  outp=testresid covb;
        Repeated visit / subject = subj(trtgrp) type=UN rcorr;
        Lsmeans trtgrp*visit / diff pdiff cl slice=visit;
Run;
```

where cfb is the change from baseline for that endpoint. Country/site, visit, ApoE4, and acetylcholinesterase inhibitor and/or memantine usage at baseline are categorical terms. Baseline MMSE and baseline score will be treated as continuous variables. Baseline will be defined as the average of the last two non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

Additional subgroup analysis may be performed, such as excluding subjects based on the presence of COVID-19 antibodies that indicate recent infection."

12.4 Secondary Endpoint Analyses

Secondary endpoints will be analyzed for the ITT population only.

Clinical Dementia Rating-Sum of Boxes (CDR-SB)

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for the CDR-SB at each time point for the ITT population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point. Baseline will be defined as the average of the last two non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

The change from baseline in CDR-SB at the average of Weeks 40 and 48 will be analyzed using the MMRM model below:

```
        Proc Mixed;
                Class trtgrp subj visit site_country APOE4_status acetylcholinesterase_
                   inhibitor_memantine_usage;
                Model cfb = trtgrp visit trtgrp*visit site_country APOE4_status
                  Acetylcholinesterase_inhibitor_memantine_usage baselineMMSE
                  baseline_score /CL solution ddfm=kenwardroger residual outp=testresid
                  covb;
                Repeated visit / subject = subj(trtgrp) type=un rcorr;
                Lsmeans trtgrp*visit / pdiff cl slice=visit;
        Run;
```

CDR-SB information for the ITT population will be displayed in subject listings.

Mini-Mental State Examination (MMSE)

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for the MMSE total score at each time point for the ITT population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point. Baseline will be defined as the average of the last two non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

The change from baseline in MMSE Total Score at the average of Weeks 40 and 48 will use the same model as for CDR above, except that baseline score is not included because for this outcome baseline score and baseline MMSE are identical.

MMSE information for the ITT population will be displayed in subject listings.

Neuropsychiatric Inventory (NPI) Total Score

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for the NPI Total Score at each time point for the ITT population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

The change from baseline in NPI Total Score at Week 48 will use the same model as for the CDR above

NPI information for the ITT population will be displayed in subject listings.

Correlations of Biomarkers with Co-primary endpoints

The primary biomarker endpoint is bilateral hippocampal volume as measured by MRI. This is the primary biological endpoint of interest due to its inherent role in Alzheimer's disease pathology and its ability to predict "likely clinical benefit" supportive of accelerated approval.

Correlations between bilateral hippocampal volume as measured by MRI with the co-primary clinical endpoints will be assessed using Pearson's and Spearman's correlations via PROC CORR in SAS. Other correlations of interest include correlations between hippocampal volume, measures of gingivalis infection, biomarkers of AD pathology or neurodegeneration, and clinical endpoints.

12.5 Multiplicity

Strong, family-wise protection of Type I error will be maintained at 5% through multiplicity adjustments for multiple looks at the data (interim and final), multiple dose arms, and multiple endpoints.

The Type I error for the interim and final analysis will be adjusted using the Lan-DeMets spending function. If the study does not stop at the interim analysis for overwhelming efficacy or futility, the study will retain its original design and the final analysis will be based

on 48 weeks of treatment with ADAS-Cog and ADCS-ADL as co-primary endpoints (see Figure 1). Because of the changes in co-primary endpoints for the final analysis (i.e., CDR-SB at Week 24 replaced by ADCS-ADL at Week 40/48 and ADAS Cog at Week 24 replaced by ADAS-Cog at Week 40/48), the Lan-DeMets correction for sequential analysis will be further adjusted as described in Chen, et al. (2014). This adjustment will account for the correlation between the outcomes and time points. The correlations used for this adjustment will be 0.56 between ADAS-Cog at Weeks 24 and 48, and -0.30 between CDR-SB at Week 24 and ADCS-ADL at 48-week. These correlations were estimated using pooled data from placebo patients from 3 ADCS studies (i.e., NSAID, Selegiline, and Homocysteine studies) described in Sano, et al. 1997, Aisen, et al. 2003, and Aisen, et al. 2008. The boundaries will be calculated to account for the change in timing of evaluation and endpoint and the more conservative boundary will be used for final analysis at Week 40/48. Using the planned enrollment at interim and final analyses, the final alpha was expected to be 0.0456. Using the actual enrollments, the actual alpha is 0.0455.

At both the interim analysis and the final analysis, the Benjamini-Hochberg multiplicity adjustment procedure (Benjamini and Hochberg, 1995 and Benjamini and Yekutieli, 2001) will be used to adjust for the multiple comparisons between placebo and the two active dose arms. Both treatment comparisons, 40 mg (low dose) and 80 mg COR388 HCl (high dose) vs. placebo are of equal interest. Therefore, the Benjamini-Hochberg adjustment will be applied as follows: $\alpha = i/m*Q$, where α is the appropriate critical p value (actual alpha), Q= 0.0455, i is the rank of the endpoint (1 or 2 in this case) and m = the number of tests (2 in this case). The resulting critical p value for declaring significance of the dose arm with the best outcome = ½*0.0455 = 0.0228, and the appropriate p value for declaring significance of the other dose arm = 2/2*0.0.0455 = 0.0455.

Treatment comparisons of 40 mg and 80 mg COR388 HCl vs. placebo for the secondary endpoints will be performed only if both co-primary endpoints compared to placebo are statistically significant at the respective interim or final analysis. Otherwise, secondary endpoints will be presented using descriptive statistics.

Multiplicity is controlled across the two co-primary endpoints within each dose arm by requiring both endpoints to be statistically significant to conclude that dose was effective.

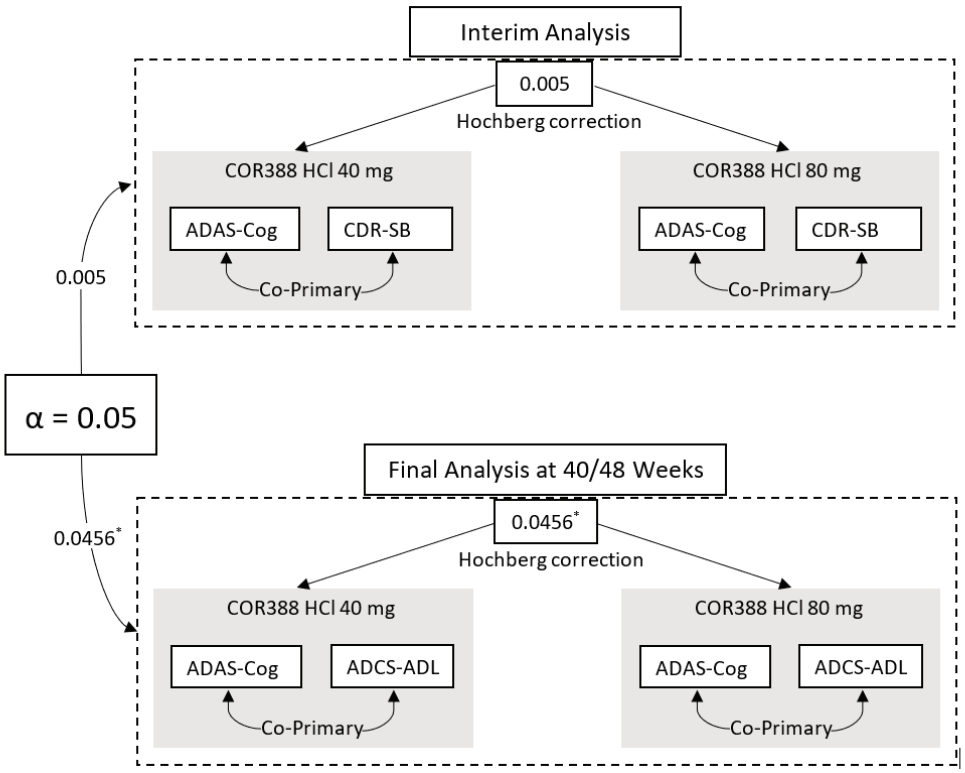


Figure 1: Diagram of alpha spending at interim and final analyses based on planned sample sizes.

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for ADAS-Cog 11, CDR-SB, and ADCS-ADL endpoints at each time point for the ITT population. Summary statistics will also be presented for the change-from-baseline values to each post baseline time point.

ADAS-Cog 11, CDR-SB, and ADCS-ADL information for the ITT population will be displayed, separately, in subject listings.

No adjustment for multiplicity will be done for MMSE and NPI total score.

12.6 Exploratory Endpoint Analyses

NPI Caregiver Distress Total Score

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for the NPI caregiver distress total score at each time point for the ITT population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

The change from baseline in NPI caregiver distress total Score at the Week 48 will use the same methodology as that for the secondary endpoint analysis.

NPI information for the ITT population will be displayed in subject listings.

Winterlight Speech Assessment

The Winterlight speech assessment will only be conducted in English speaking (primary language) subjects and only in the United States and United Kingdom.

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for each of 3 scores from the Winterlight Speech Assessment at each time point for the ITT population. The 3 scores are prepositions, information units, and global coherence. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

The change from baseline in each of 3 scores from the Winterlight Speech Assessment at the Week 48 will use the same methodology as that for secondary endpoint analysis.

Information on the 3 scores above from the Winterlight Speech Assessment for the ITT population will be displayed in subject listings.

For the above exploratory endpoints (i.e., MMSE Total Score, NPI Total Score, and 4 Winterlight Speech Assessment Scores), no adjustment for multiplicity will be done.

Magnetic Resonance Imaging (MRI) Volumetric Measures of the Brain

MRI volumetric measures (right, left, and total hippocampal volume and cortical thickness) of the brain will be performed in all subjects at Screening. Subjects who have an absolute contraindication for MRI can have a CT scan of the brain instead. A follow-up MRI or CT will be performed within 8 days prior to Visit 10 (or Early Termination) in subjects who had a baseline MRI performed at screening.

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for each of 4 scores, the right, left and total hippocampal volume and the Mayo cortical thickness, at each time point for the ITT population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

For each of these 4 MRI scores, the change from baseline at the Week 48 will be analyzed using ANCOVA with fixed effects of treatment group, ApoE4 status, acetylcholinesterase inhibitor and/or memantine usage, site_country and baseline score as a covariate for the ITT population. Right hippocampal volume is historically more sensitive to change than left hippocampal volume and will be the primary region of interest for this analysis, with left and total hippocampal volume and cortical thickness providing additional evidence for a treatment effect.

Following is the SAS code which will be used for the ANCOVA analysis:

```
Proc GLM;
```

```
        Class trtgrp site_country APOE4_status
          acetylcholinesterase_inhibitor_memantine_usage;
        Model cfb = trtgrp site_country APOE4_status acetylcholinesterase_
          inhibitor_memantine_usage baseline_score;
        Lsmeans trtgrp / pdiff cl;
Run;
```

where cfb is the change from baseline for that endpoint. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

Right, left, and total hippocampal volume and the Mayo cortical thickness information will be displayed in subject listings for the ITT population.

For the above exploratory endpoints, no adjustment for multiplicity will be done, but the listed order will be considered an informal hierarchy.

Oral Examination to Determine Presence of Periodontitis

Oral examinations were done in subjects at selected sites. The examination included tooth count, identification of any hard or soft tissue lesions, assessment for presence of severe dental disease, determination of Pocket Depth (PD) and Clinical Attachment Level (CAL) at 6 sites per tooth (distobuccal [DB], buccal [B], mesiobuccal [MB], distolingual [DL], lingual [L], mesiolingual [ML]), gingival margin (GM) position, and assessment of Bleeding on Probing (BOP). CAL is defined as PD minus GM. Subjects enrolled in the study who did not have at least 8 teeth were exempt from the oral examination sub-study.

Measurements of PD and gingival margin GM and calculated attachment levels (AL) will be used to determine the presence of periodontitis according to the Centers for Disease Control/American Academy of Periodontology (CDC/AAP) criteria:

No periodontitis	No evidence of mild, moderate or severe periodontitis
Mild periodontitis	≥ 2 interproximal sites with clinical attachment level (CAL) ≥ 3 mm, and ≥ 2 interproximal sites with pocket depth (PD) ≥ 4 mm (not on same tooth), Or one site with PD ≥ 5 mm
Moderate Periodontitis	≥ 2 interproximal sites with CAL ≥ 4 mm (not on same tooth), **Or** ≥ 2 interproximal sites with PD ≥ 5 mm (not on same tooth)
Severe Periodontitis	≥ 2 interproximal sites with CAL ≥ 6 mm (not on same tooth), **And** ≥ 1 interproximal site with PD ≥ 5 mm

The severity of periodontitis (none, mild, moderate, and severe) will be summarized (n, %) by treatment group at each visit for the ITT population.

Pocket Depths

For all pocket depth analyses only sites with depth => 4mm at any time in the study will be included.

For each subject at each visit, the mean pocket depth will be calculated for all 4 interproximal sites (e.g., DB, MB, DL, and ML).

For mean pocket depth within each subject, summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values at each time point by treatment group for the ITT population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

Mean pocket depth will be analyzed using a mixed-effects model for repeated measures (MMRM) with SAS PROC MIXED to compare change from baseline for COR388 HCl vs placebo. The MMRM model will include treatment group, visit, site_country, treatment group by visit interaction as fixed effects, with baseline mean pocket depth as a covariate using the ITT population. The analysis will be based on an unstructured covariance matrix to model the within-subject errors. A Kenward-Roger approximation will be used for the denominator degrees of freedom.

Following is the SAS code which will be used for the MMRM analysis:

```
Proc Mixed;
Class trtgrp subj visit site_country;
Model cfb = trtgrp visit trtgrp*visit site_country baseline_score /CL solution
  ddfm=kenwardroger residual outp=testresid covb;
Repeated visit / subject = subj(trtgrp) type=UN rcorr;
Lsmeans trtgrp*visit / pdiff cl slice=visit;
Run;
```

where cfb is the change from baseline for that endpoint. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

The same teeth will be used in the above analyses (i.e., if any tooth is missing after the first dose of study drug, all data for this tooth will be excluded from the analyses).

No adjustment for multiplicity will be done.

Shifts from baseline based on predefined categories will be tabulated (n, %) by treatment group at each post-baseline visit for the mean pocket depth. The predefined categories will be <=3mm, 4-6mm, and >=7mm.

Clinical Attachment Level

For all clinical attachment level (CAL) analyses only sites with depth => 3mm at any time in the study and for only subjects with a detectable *Porphyromonas gingivalis* DNA concentration at baseline will be included.

For each subject at each visit, the clinical attachment score will be calculated for all 4 interproximal sites (e.g., DB, MB, DL, and ML).

For mean clinical attachment score within each subject, summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values at each time point by treatment group for the ITT population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

The change from baseline in mean clinical attachment score at Week 48 will use the same methodology as that for the mean pocket depth endpoint analysis but adjusting for corresponding baseline value as a covariate for the ITT population.

The same teeth will be used in the above analyses (i.e., if any tooth is missing after the first dose of study drug, all data from this tooth will be excluded from the analyses). No adjustment for multiplicity will be done.

Shifts from baseline based on predefined categories will be tabulated (n, %) by treatment group at each post-baseline visit for the mean clinical attachment. The predefined categories will be <=2mm, 3-5mm, and >=6mm.

Bleeding on Probing

For each subject at each visit, the percentage of sites with bleeding on probing will be calculated for all 6 sites (e.g., DB, MB, DL, B, L, and ML) across all teeth present.

For percentage of sites with bleeding on probing, summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values at each time point by treatment group for the ITT population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

The change from baseline in percentage of bleeding on probing at Week 48 will use the same methodology as that for the mean pocket depth endpoint analysis but adjusting for corresponding baseline value as a covariate for the ITT population.

The same teeth will be used in the above analyses (i.e., if any tooth is missing after the first dose of study drug, this tooth will be excluded from the analyses).

No adjustment for multiplicity will be done.

Subgroup Analyses

To assess the effect of *Porphyromonas gingivalis* DNA status at baseline (not detected, detected) from oral samples (saliva in oral rinse, buccal swab, or subgingival plague) on treatment outcome, subgroup analyses for the mean change from baseline in pocket depths, clinical attachment levels and percentage of sites with bleeding on probing will be analyzed using the MMRM.

Following is the SAS code which will be used for the MMRM analysis of subgroups:

```
Proc Mixed;
        Class trtgrp subj visit subgroup_factor site_country;
```

```
Model cfb = trtgrp visit subgroup_factor trtgrp*visit
   subgroup_factor*trtgroup trtgrp*visit*subgroup_factor
   site_country baseline_score/CL solution ddfm=kenwardroger residual outp=testresid
   covb;
 Repeated visit / subject = subj(trtgrp) type=UN rcorr;
 Lsmeans trtgrp *subgroup_factor / diff pdiff cl
Run;
```

where cfb is the change from baseline for that endpoint. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

The oral examination information for the ITT population will be displayed in subject listings.

***Porphyromonas Gingivalis DNA* Concentrations from Saliva in Oral Rinse**

Saliva will be collected in an oral rinse with a preservative.

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for *Porphyromonas gingivalis* DNA concentrations at each time point for the ITT population for only subjects with a detectable *Porphyromonas gingivalis* DNA concentration at any point in the study. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point for only patients with a detectable *Porphyromonas gingivalis* DNA concentration at any point in the study. Baseline will be defined as the average of the last two non-missing values (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

Porphyromonas gingivalis DNA concentration will be analyzed using a mixed-effects model for repeated measures (MMRM) with SAS PROC MIXED to compare change from baseline for COR388 HCl vs placebo for only subjects with a detectable *Porphyromonas gingivalis* DNA concentration at any point in the study. The MMRM model will include treatment group, visit, site_country, treatment group by visit interaction as fixed effects, with baseline mean *Porphyromonas gingivalis* DNA concentration as a covariate. The analysis will be based on an unstructured covariance matrix to model the within-subject errors. A Kenward-Roger approximation will be used for the denominator degrees of freedom.

Following is the SAS code which will be used for the MMRM analysis:

```
Proc Mixed;
Class trtgrp subj visit site_country;
Model cfb = trtgrp visit trtgrp*visit site_country baseline_score/CL solution
  ddfm=kenwardroger residual outp=testresid covb;
Repeated visit / subject = subj(trtgrp) type=UN rcorr;
Lsmeans trtgrp*visit / pdiff cl slice=visit;
Run;
```

where cfb is the change from baseline for that endpoint. Baseline will be defined as the average of the last two non-missing values (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

Correlation analyses of Porphyromonas gingivalis concentrations at Week 48 and ADAS-Cog 11 at average of Weeks 40 and 48 will be conducted for only subjects with a detectable Porphyromonas gingivalis DNA concentration at any point of the study.

Porphyromonas gingivalis concentrations for the ITT population will be displayed in subject listings.

***Porphyromonas Gingivalis* DNA Concentrations from Buccal Swab**

Porphyromonas gingivalis concentrations will be collected from buccal cells at selected sites.

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for *Porphyromonas gingivalis* concentrations at each time point for the ITT population for only subjects with a detectable *Porphyromonas gingivalis* DNA concentration at any point in the study. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point for only subjects with a detectable *Porphyromonas gingivalis* DNA concentration at any point in the study. Baseline will be defined as the last non-missing values (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

Porphyromonas gingivalis DNA concentration will be analyzed using a mixed-effects model for repeated measures (MMRM) with SAS PROC MIXED to compare change from baseline for COR388 HCl vs placebo for only subjects with a detectable *Porphyromonas gingivalis* DNA concentration at any point in the study. The MMRM model will include treatment group, visit, site_country, treatment group by visit interaction as fixed effects, with baseline mean *Porphyromonas gingivalis* DNA concentration as a covariate. The analysis will be based on an unstructured covariance matrix to model the within-subject errors. A Kenward-Roger approximation will be used for the denominator degrees of freedom. Following is the SAS code which will be used for the MMRM analysis:

```
Proc Mixed;
        Class trtgrp subj visit site_country;
        Model cfb = trtgrp visit trtgrp*visit site_country baseline_score /CL solution
          ddfm=kenwardroger residual outp=testresid covb;
        Repeated visit / subject = subj(trtgrp) type=UN rcorr;
        Lsmeans trtgrp*visit / pdiff cl slice=visit;
Run;
```

where cfb is the change from baseline for that endpoint. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

Correlation analyses of *Porphyromonas gingivalis* concentrations at Week 48 and ADAS-Cog 11 at average of Weeks 40 and 48 will be conducted for only subjects with a detectable *Porphyromonas gingivalis* DNA concentration at any point in the study.

Porphyromonas gingivalis concentrations for the ITT population will be displayed in subject listings.

Porphyromonas Gingivalis DNA Concentrations from Subgingival Plague

Porphyromonas gingivalis DNA copy number concentrations were collected from subgingival plague at selected sites.

Porphyromonas gingivalis concentrations for the ITT population will be displayed in subject listings.

Porphyromonas Gingivalis Antibody Levels from Serum

Porphyromonas gingivalis antibody levels will be analyzed from serum.

Porphyromonas gingivalis antibody levels for the ITT population will be displayed in subject listings.

Evidence of *Porphyromonas Gingivalis* Infection in CSF Samples

Evidence of *anti-Porphyromonas gingivalis* antibody levels will be analyzed in CSF and normalized to albumin levels using an exploratory assay.

Results for the ITT population will be displayed in subject listings.

Ab40, Ab42, and Ab42/Ab40 Ratio Concentrations from Cerebrospinal Fluid (CSF)

Ab40 and Ab42 will be analyzed in CSF.

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for Ab42/Ab40 ratio concentrations at each time point for the ITT population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

For Ab42/Ab40 ratio, the change from baseline at the Week 48 will be analyzed using ANCOVA with fixed effects of treatment group, APOE4 status, acetylcholinesterase inhibitor and/or memantine usage, site_country, and baseline Ab42/Ab40 ratio as a covariate for the ITT population.

Following is the SAS code which will be used for the ANCOVA analysis:

```
Proc GLM;
        Class trtgrp site_country APOE4_status
          acetylcholinesterase_inhibitor_memantine_usage;
        Model cfb = trtgrp site_country APOE4_status acetylcholinesterase
          inhibitor_memantine_usage baseline_score;
        Lsmeans trtgrp / pdiff cl;
Run;
```

where cfb is the change from baseline for that endpoint. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

Ab42 and Ab42/Ab40 ratio concentrations for the ITT population will be displayed in subject listings.

Total Tau and p181 Tau from Cerebrospinal Fluid (CSF)

Total Tau and p181 Tau will be analyzed in CSF.

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for total Tau and p181 Tau at each time point for the ITT population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

For total Tau and p181 Tau, the change from baseline at the Week 48 will be analyzed separately using ANCOVA with fixed effects of treatment group, ApoE4 status, acetylcholinesterase inhibitor and/or memantine usage, and site_country and the corresponding baseline value as a covariate for the ITT population.

Following is the SAS code which will be used for the ANCOVA analysis:

```
Proc GLM;
        Class trtgrp site_country APOE4_status
          acetylcholinesterase_inhibitor_memantine_usage;
        Model cfb = trtgrp site_country APOE4_status acetylcholinesterase_
           inhibitor_memantine_usage baseline_score;
        Lsmeans trtgrp / pdiff cl;
Run;
```

where cfb is the change from baseline for that endpoint. Baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

Total Tau and p181 Tau for the ITT population will be displayed in subject listings.

Biomarkers from Serum and Plasma

Available biomarkers of inflammation and neuroinflammation, in serum and plasma, will be analyzed.

13 SAFETY ANALYSES

13.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (using MedDRA Version stated in Data Management Plan). An overall summary table will be presented to summarize all treatment-emergent adverse events, all treatment-emergent study drug-related adverse events, deaths, all serious treatment-emergent adverse events, all treatment-related serious treatment-emergent adverse events, all treatment-emergent adverse events leading to study drug withdrawal, and all treatment-emergent adverse events leading to study drug interruption by treatment group for the safety population. In addition, frequency tables will present all treatment-emergent adverse events by System Organ Class and Preferred Term, treatment-related treatment-emergent adverse events by System Organ Class and Preferred Term, all serious treatment-emergent adverse events by System Organ Class and Preferred Term, all treatment-related serious treatment-emergent adverse events by System Organ Class and Preferred Term, all treatment-emergent adverse events leading to study drug withdrawal by System Organ Class and Preferred Term, all treatment-emergent adverse events leading to study drug interruption by System Organ Class and Preferred Term, all treatment-emergent adverse events by System Organ Class, Preferred Term and maximum severity, and all treatment-emergent adverse events by System Organ Class, Preferred Term and relationship by treatment group for the safety population.

Any adverse events occurring before the start of treatment (i.e., before the first dose of the investigational product) will be recorded in the medical history.

In all displays, adverse events will be displayed by MedDRA System Organ Class and Preferred Term, with subjects who have the same adverse event counted only once for that event and subjects who have more than one adverse event within a System Organ Class counted only once in that System Organ Class.

Treatment-emergent adverse events, fatal treatment-emergent adverse events, and serious treatment-emergent events will be displayed in subject listings.

13.2 Laboratory Tests (Hematology, Serum Chemistry, Coagulation, and Urinalysis)

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for hematology, serum chemistry, coagulations, and urinalysis at each time point by treatment group for the safety population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point by treatment group. In these displays, baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug.

Out of range values at any time post-baseline will tabulated (n, %) by treatment group for the hematology, serum chemistry, coagulations, and urinalysis. Shifts from baseline based on normal reference ranges will be tabulated (n, %) by treatment group at each post-baseline visit for the hematology, serum chemistry, coagulations, and urinalysis.

Liver function test with values satisfying Hy’s Law at any time post-baseline will be tabulated by treatment group.

Hematology, chemistry, coagulation, and urinalysis results will be listed, with values falling outside the laboratory reference range flagged. Choriogonadotropin beta results will also be listed.

Laboratory reference ranges will be provided by the laboratory site(s) and will be included in the clinical study report.

13.3 Vital Signs

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for systolic and diastolic blood pressures, pulse rate, respiration rate, and temperature at each time point by treatment group for the safety population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point by treatment group. In these displays, baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug.

Potential vital sign values of concern at any time post-baseline will be tabulated (n, %) by treatment group for the following vital sign parameters:

- Systolic blood pressure
    - Increase from baseline of ≥ 20 mm Hg
    - Post-baseline value > 160mm Hg
    - Post-baseline value > 160mm and Increase ≥ 20 mm Hg
    - Decrease from Baseline of ≥ 20 mm Hg
    - Post-baseline value <60 mm Hg
    - Post-baseline value < 60mm Hg and Decrease ≥ 20 mm Hg
- Diastolic blood pressure
    - Increase from baseline of ≥ 20mm Hg
    - Post-baseline value > 100mm Hg
    - Post-baseline value > 100mm Hg and Increase ≥ 20mm Hg
    - Decrease from Baseline of ≥ 10 mm Hg
    - Post-baseline value < 50 mm Hg
    - Post-baseline value < 50 mm Hg and Decrease ≥ 10 mm Hg
- Pulse
    - ≥ 30 beats/min increase or decrease from baseline and outside the range of 50-100 beats/min

Vital sign results will be displayed in subject listings for the safety population. In addition, vital sign results where at least one value is a potential value of concern will be listed.

13.4 Physical Examinations

Physical examination findings (e.g., normal; abnormal, not clinically significant; or abnormal, clinically significant) within each body system for each subject will be assessed at each visit. For each body system, the most severe (worst case) any time post-baseline will be tabulated (n, %) by treatment group for the safety population. For each body system, shifts from baseline to each post-baseline visit will be tabulated (n, %) by treatment group for the safety population. In these displays, baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug.

Physical examination abnormalities will be listed for the safety population.

13.5 Electrocardiograms

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for each ECG interval (e.g., PR, QRS, QT, QTcB, QTcF, and RR) and heart rate, at each time point, by treatment group, for the safety population. Summary statistics will also be presented for the change-from-baseline values to each postbaseline time point by treatment group. In these displays, baseline will be defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug.

The following results will be tabulated (n, %) by treatment group:

- Abnormal ECG findings at any time post-baseline for subjects who had a normal ECG at baseline.
- Abnormal ECG findings at each post-baseline visit for subjects who had a normal ECG at baseline.
- Worse case (e.g., Not evaluable<Normal<Abnormal) based on ECG interpretability at any time post-baseline.
- For ECG Overall Interpretation, shifts from baseline to each post-baseline visit will be tabulated (n, %) by treatment group for the safety population.
- Potential ECG values of concern at any time post-baseline for each of the following ECG parameters:
- QTcF and QTcB
    - Post-baseline value ≥ 500 msec
    - Increase from baseline ≥ 60 msec
    - Post-baseline value ≥ 500 msec and increase ≥ 60 msec
- PR interval
    - Post-baseline value > 250 msec
    - Increase from baseline > 50 msec
- QRS duration
    - Post-baseline value > 120 msec
    - Increase from baseline > 25 msec
- Heart Rate
    - Post-baseline value < 50 bpm
    - Post-baseline value > 100 bpm

ECG results will be displayed in subject listings for the safety population. In addition, ECG results where at least one value is a potential value of concern will be listed.

13.6 Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS is composed of questions related to 1) suicidal ideation, 2) suicidal behavior, and 3) suicidal behavior and self-injurious behavior without suicidal intent.

Suicidal ideation will have the following questions with binary responses (yes/no):

- Wish to be Dead
- Non-specific active suicidal thoughts
- Active suicidal ideation with any methods (Not Plan) without Intent to Act
- Active suicidal ideation with some intent, without Specific Plan
- Active suicidal ideation with Specific Plan and Intent

Each of the above questions will be tabulated (n, %) by treatment group. In addition, the number (%) of subjects which answered one or more of the 5 above suicidal ideation items as 'yes' by treatment group.

Suicidal behavior will have the following questions with binary responses (yes/no):

- Preparatory acts or behavior
- Aborted Attempt
- Interrupted Attempt
- Actual attempt (Non-fatal)
- Completed Suicide

Each of the above questions will be tabulated (n, %) by treatment group. In addition, the number (%) of subjects which answered one or more of the 5 above suicidal behavior items as 'yes' by treatment group.

The number (%) of subjects which answered one or more of the 10 above suicidal ideation or suicidal behavior items as 'yes' will be summarized by treatment group. In addition, the number of 'yes' responses from Self-injurious Behavior without suicidal intent will be tabulated (n, %) by treatment group.

C-SSRS events will be displayed in subject listings for the safety population.

13.7 MRI Safety Readings from the Brain

MRI safety readings from the brain collected the following: modality, presence and severity of vasogenic edema, microhemorrhages information, presence of white matter, and presence of other clinically significant MRI/CT abnormalities.

The results from the MRI safety readings from the brain for the safety population will be displayed in subject listings.

14 PHARMACOKINETIC ANALYSES

Population PK will be analyzed as part of a separate pharmacokinetic analysis plan.

15 SUBJECT LISTINGS

Data that are collected and entered into the study database but not displayed in the summary tables that are specified in the preceding sections will be presented in subject listings. These will include (but will not be limited to) data from the following modules:

- Inclusion/Exclusion Criteria
- Pregnancy Report
- Obstetric History
- Pregnancy Exposure
- Pregnancy Illnesses and/or Medication During Pregnancy
- Pregnancy Outcome
- Condition of Neonates(s)
- Neonate Medications

16 INTERIM ANALYSES

16.1 Interim Analysis for Efficacy

An unblinded interim analysis of mean change from baseline in ADAS-Cog 11 and the mean change from baseline in the CDR-SB is planned for when approximately 300 subjects have completed 24 weeks of treatment (Week-24 endpoint). Only an independent statistician and the independent Data Monitoring Committee (DMC) will be unblinded. No study personnel will have access to unblinded data. For further details, refer to the DMC charter.

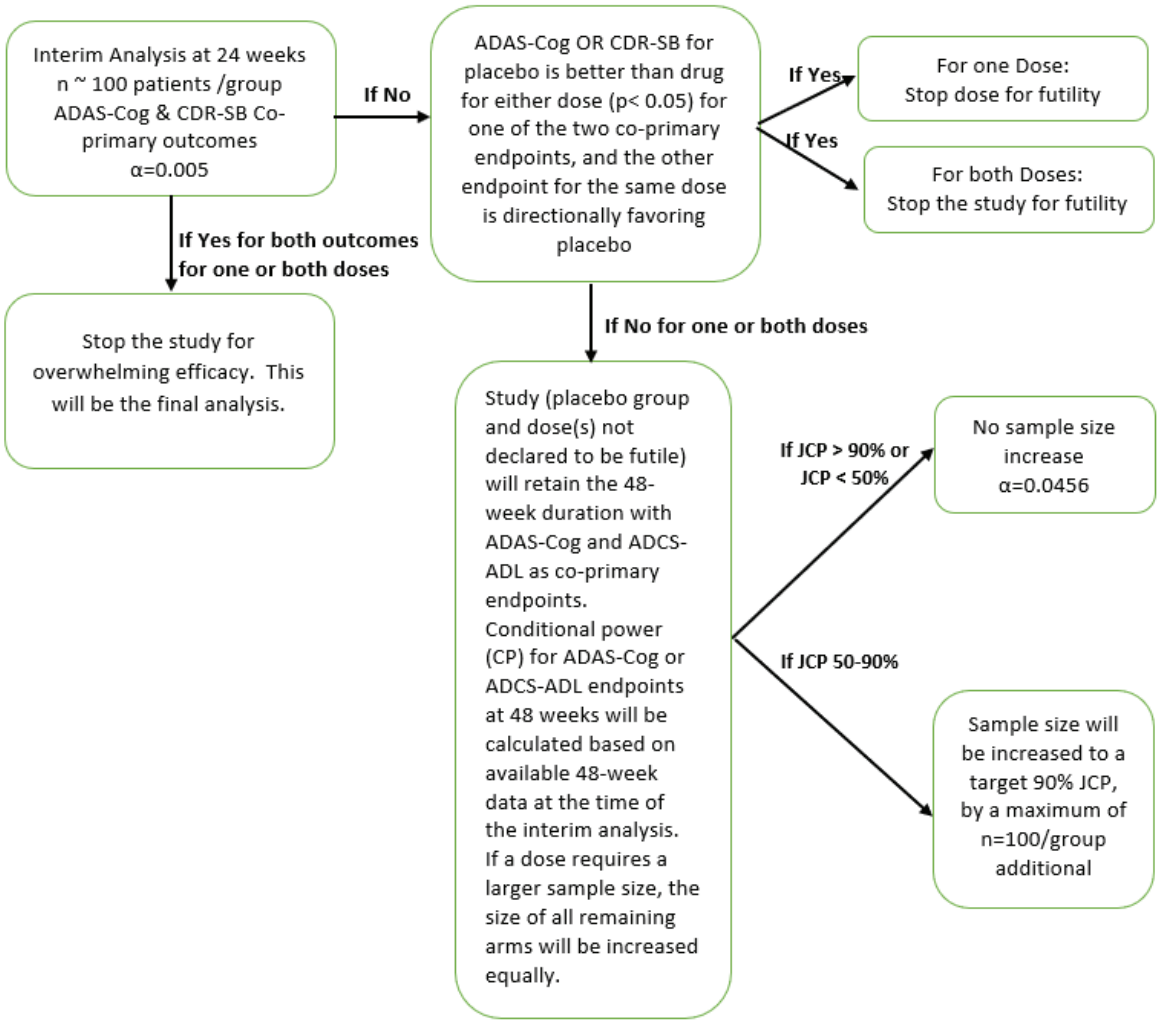
Both treatment comparisons will be assessed at the interim analysis: 40 mg COR388 HCl and 80 mg COR388 HCl vs. placebo for the co-primary endpoints mean change from baseline in ADAS-Cog 11 and mean change from baseline in CDR-SB at Week 24.

These co-primary endpoints will be analyzed using MMRM to compare COR388 HCl at 40 mg vs. placebo and COR388 HCl at 80 mg vs placebo. The MMRM model is similar to the MMRM presented in section 12.1 "Final Analysis" and will include treatment group, visit, treatment group by visit interaction, ApoE4 status, baseline MMSE (collected within 7 days prior to the first dose of the IP), and country/site, and baseline co-primary endpoint (i.e., ADAS-Cog 11 score or CDR-SB) as covariates. Analysis will be performed, including in the population all subjects randomized (i.e., ITT subject population) that had the opportunity to complete the 24 weeks of treatment. When change from baseline is assessed, subjects will be included in the ITT analysis population only if both a baseline and a postbaseline measure are available.

Baseline will be defined as the average of the last two non-missing values (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug. All data available for up to visit 7 (i.e., week 24) will be used for the analysis.

The Lan-DeMets method, adjusted according to Chen et al (2004) as described earlier, will be used to determine the criterion of efficacy to be used at the interim analysis and final analysis. The two-sided significance level at the interim analysis is currently planned to be 0.005 for both doses. P-values to compare each dose with placebo will be adjusted using the Benjamini-Hochberg multiplicity adjustment procedure. If significance is achieved for both ADAS-Cog 11 and CDR-SB for one of the two doses, then the study may be stopped early for overwhelming efficacy. Also, the study, or one of the two doses may be stopped for futility if the Placebo is superior to one or both doses (i.e., 40 or 80 mg) for either ADAS-Cog 11 or CDR-SB at the p-value < 0.05 (see Figure 2) and the other endpoint is directionally favoring placebo.

Figure 2: Decision Tree for Interim Analysis and Sample Size Re-estimation. JCP is the joint conditional power for ADAS-Cog and ADCS-ADL at 48 Weeks.



If the study is not stopped for overwhelming efficacy or futility, as described above, the study will retain its original design and the final analysis will be based on 48-week of treatment for ADAS-Cog 11 and ADCS-ADL. Because of the changes in co-primary endpoint at 48 weeks (i.e., CDR-SB 24 weeks replaced by ADCS-ADL at 48 weeks and ADAS-Cog 11 at 24 weeks replaced by ADAS-Cog 11 at 48 weeks), the Lan-DeMets correction for sequential analysis will be further adjusted as described in Chen et al. (2014). This adjustment will account for the correlation between the outcomes and time points. The correlations used for this adjustment were 0.56 between ADAS-Cog 11 at 24 and 48 weeks, and -0.30 between CDR-SB at 24 weeks and ADCS-ADL at 48 weeks. These correlations were estimated using a pooled data from placebo patients form 3 ADCS studies (i.e., NSAID, Selegiline, and Homocysteine studies) described in Sano et al., 1997, Aisen et al., 2003, and Aisen et al., 2008.

Boundaries will be calculated to account for the change in timing of evaluation and endpoint and the more conservative boundary will be used. Accounting for the above correlations, the final alpha will be 0.0456. If both doses continue to the 48 weeks, p-values to compare each dose with Placebo will be adjusted using the Benjamini-Hochberg procedure.

16.2 Sample Size Re-estimation

Sample size re-estimation will be based on joint conditional power calculated using the 48-week ADAS-Cog 11 and ADCS-ADL co-primary endpoints for one or both doses. The conditional power for each endpoint will be calculated using the formula from Jennison and Turnbull (2000) as quoted in the PASS manual in the section about conditional power for a two-sample t-test:

$$P_k(\theta) = \Phi\left(\frac{Z_k\sqrt{I_k} - z_{1-\alpha/2}\sqrt{I_K} + \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right) + \Phi\left(\frac{-Z_k\sqrt{I_k} - z_{1-\alpha/2}\sqrt{I_K} - \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right)$$

where

θ = the parameter being tested by the hypothesis

k = an interim stage at which the conditional power is computed ($k = 1,\ldots, K-1$)

K = the stage at which the study is terminated and the final test computed

Z_k = the test statistic calculated from the observed data that has been collected up to stage k

I_k = the information level at stage k

I_K = the information level at the end of the study

$z_{1-\alpha}$ = the standard normal value for the test with a type I error rate of α.

The joint conditional probability for ADAS-Cog 11 and ADCS-ADL will be calculated as follows:

$$P(A \cap B) = P_A P_B + \rho_{AB}\sqrt{P_A(1-P_A)P_B(1-P_B)}$$

Where

A = ADAS-Cog 11 endpoint at 48 weeks

B = ADCS-ADL endpoint at 48 weeks

ρ = correlation between ADAS-Cog 11 and ADCS-ADL at the time of analysis

Examples of conditional power boundaries for each endpoint for the joint conditional power to lie between 50% and 90% are presented in Table 1.

Table 1. Required individual conditional power to reach joint conditional power of 50% and 90% assuming no correlation between endpoints. The sample size increase will also take into consideration the correlation between outcomes present at the interim analysis.

	JCP = 50%	JCP = 90%
Outcome 1	Outcome2	Outcome 2
99%	51%	91%
98%	51%	92%
97%	52%	93%

96%	52%	94%
95%	53%	95%
94%	53%	96%
93%	54%	97%
92%	54%	98%
91%	55%	99%
90%	56%	--
89%	56%	--
88%	57%	--
87%	57%	--
86%	58%	--
85%	59%	--
84%	60%	--
83%	60%	--
82%	61%	--
81%	62%	--
80%	62%	--
79%	63%	--
78%	64%	--
77%	65%	--
76%	66%	--
75%	67%	--
74%	68%	--
73%	68%	--
72%	69%	--
71%	70%	--
70%	71%	--

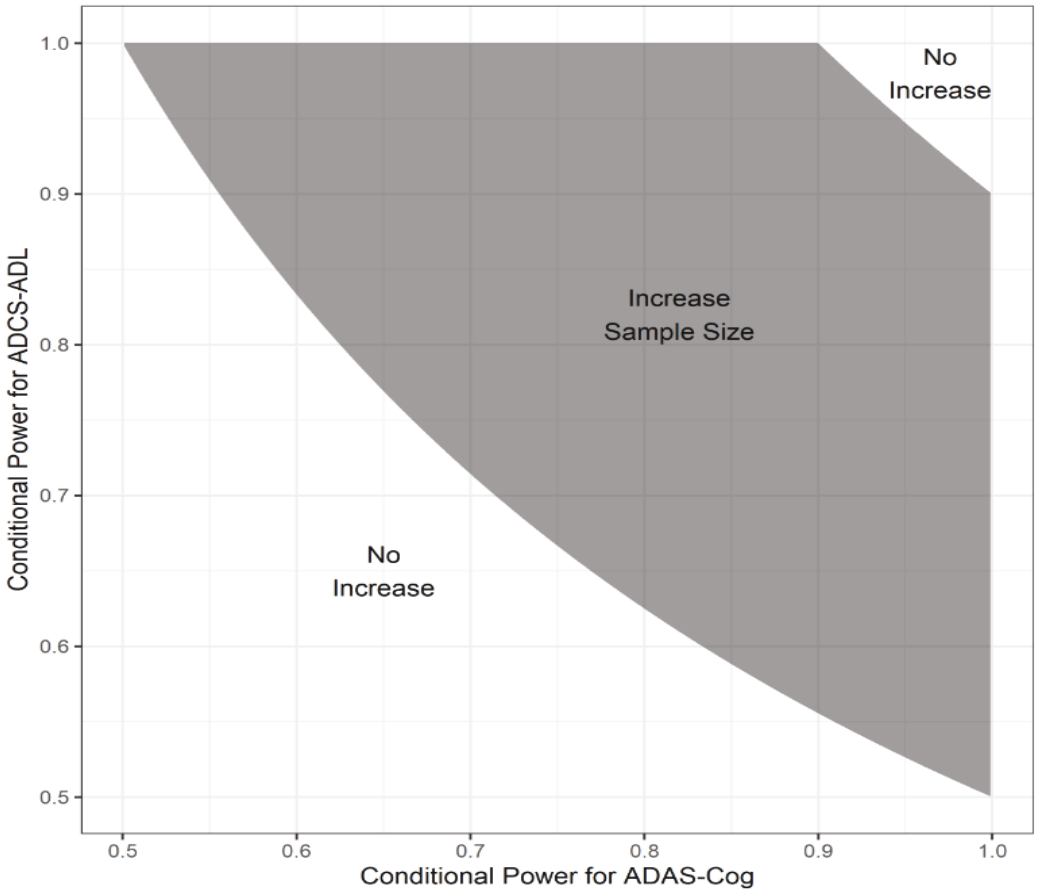


Figure 3: Combination of Conditional Power for ADAS-Cog 11 and ADCS-ADL and Requirement for Sample Size Adjustment

As shown in Figure 3, if the joint conditional power for ADAS-Cog 11 and ADCS-ADL is between 50-90% for at least one dose level, the sample size will be increased from the originally planned approximately 573 (i.e., approximately 191 subjects per group) by a maximum of 100 additional patients per group (i.e., approximately 291 patients per group) to target a joint conditional probability of 90%. The sample size for all remaining arms will be increased by the largest calculated sample size increase across the 2 doses. If joint conditional power is >90% or <50% for all remaining doses the sample size will not be increased.

If the joint conditional power for ADAS-Cog 11 and ADCS-ADL for the final analysis is 90% or higher or 50% or lower for a doses, the study will continue with the planned sample size until all patients have reached the final analysis time point of 48 weeks. Also, as shown in Figure 3, if the joint conditional power for ADAS-Cog 11 and ADCS-ADL is between 50-90% for at least one dose level, the sample size will be increased by a maximum of 100 additional patients per group to target a joint conditional probability of 90%. The sample size for all remaining arms will be increased by the largest calculated sample size increase across the 2 doses.

As described by Chen et al 2004, this sample size re-estimation procedure based on conditional power in the promising zone (i.e., 50 to 95%) will not inflate the type I error and no statistical

adjustment is necessary. However, the adjusted alpha at the end of the study will be based on the new sample size at the final analysis.

The DMC may recommend increasing or not increasing sample size for each active arm, using the guidelines above, based on an overall assessment of ADAS-Cog 11 and ADCS-ADL 48-weeks and safety at each dose.

To maintain data integrity during the unblinded interim analysis, the Data Monitoring Committee (DMC) will be used to provide recommendations on prespecified study adaptations related to sample size estimation and early study discontinuation due to efficacy.

The following recommendations at the interim are possible:

- Stopping early for overwhelming efficacy defined as $p<0.005$ adjusted for multiplicity using the Benjamini-Hochberg procedure for both ADAS-Cog 11 and CDR-SB in favor of either 40 mg COR388 or 80 mg COR388 HCl over placebo;
- Stopping either or both arms (stopping both arms would mean stopping the study) early for futility defined as $p<0.05$ on either ADAS-Cog 11 or CDR-SB in favor of placebo over active dose(s), and the other endpoint for the same dose is directionally favoring placebo;
- Continue with no sample size adjustment; or
- Continue with an appropriate sample size adjustment

All personnel directly involved with the trial, will remain blinded. The Sponsor will not be unblinded to the data and will be notified of the DMC recommendations only, as above. The Sponsor will make the final decision regarding continuation with or without adjustment to sample size after carefully evaluating various factors including safety and enrollment rate.

If the study is stopped early for overwhelming efficacy, the interim analysis for the co-primary endpoints will be considered the final primary outcome for the study, and the primary duration of the study will be 24 weeks.

All study subjects that were not included in the interim analysis will be allowed to complete 24 weeks of double-blinded randomized treatment, and if eligible, to enroll in the OLE. This independent cohort of subjects will be analyzed separately for efficacy on the co-primary endpoints.

If both doses are stopped early for futility, the entirety of the COR388-010 trial, including the OLE will be immediately concluded, and data analyzed based on the current SAP. If a dose is stopped for futility, that dose will be terminated, and all eligible subjects will have the option to move to the OLE.

17 REFERENCES

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18 FINAL SIGN-OFF FOR CORTEXYME, INC, PROTOCOL COR388-010 STATISTICAL ANALYSIS PLAN

DocuSigned by:
Sarah Horine

Signer Name: Sarah Horine
Signing Reason: I approve this document
Signing Time: 8/30/2021 | 3:48:53 PM PDT
847E2336F48D411EB6E61D59D5936B9D

8/30/2021

Sarah Horine, PhD
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Craig Mallinckrodt

Signer Name: Craig Mallinckrodt
Signing Reason: I am the author of this document
Signing Time: 8/30/2021 | 4:14:41 PM PDT
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Signer Name: mike detke
Signing Reason: I approve this document
Signing Time: 8/30/2021 | 4:06:56 PM PDT
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8/30/2021

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Date

19 REVISIONS TO STATISTICAL ANALYSIS PLAN

Date	Revision	Statistician's Signature
October 09, 2020	Version 2	
October 30, 2020	Version 3	•
April 27, 2021	Version 4	•
August 27, 2021	Version 5	•

20 APPENDIX

20.1 Conventions for Statistical Tables and Subject Listings

The following conventions are used in the mockups for the statistical tables and subject listings:

[Sponsor] = [Cortexyme, Inc.]

[Protocol] = [COR388-010]

Calculation of "Day" in Data Listings

Study day will be calculated as the number of days from first dose of study drug. For analysis, study day is relative to first dose of study drug and will be deemed "Day 1", note this differs from the time and events in the Protocol where the first dose of study drug is given on Day 0.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose.

Baseline Determination

Baseline is defined as average of the last two non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug for ADAS-Cog 11, CDR-SB, ADCS-ADL, and MMSE. For all other assessments, baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before or at the day the subject receives the first dose of study drug.

Missing/Partial Start/Stop Date of Adverse Events and Concomitant Medications

Missing and partial start and stop date will be imputed for analysis purposes as follows:

1. Partial or missing stop date will be imputed as follows:
   If the stop date is completely missing and the event has resolved or the subject has stopped taking the concomitant medication, the stop date will be imputed as the date of the subject's last clinic visit in the study.
   - If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the subject's last clinic visit in the study if in the same year.
   - If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the subject's last clinic visit in which case the date of subject's last clinic visit in the study will be used instead.
2. Missing start date will be imputed as follows:
   - If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.
   - If the stop date occurs before the start of study drug, the start date of the event/concomitant medication will be imputed as the subject's screening date.
3. Partial start date (year present, but month and day missing)
   - If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, and the year is the same as the year of first dosing then the

start date will be imputed as the date of the first dose of study drug. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event/concomitant medication will be imputed as the "01-Jan" of the same year.

4. Partial start date (month and year present, but day missing)
   - If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in the same month as the first dose of study drug in which case the date of first dose of study drug will be used.
   - If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

If the start time is missing, it will be imputed only in the case where the start date of the concomitant medication/event corresponds to the date of the first dose of study drug. The time will be imputed as the same time as the first dose of study drug. In all other cases the time will not be imputed.

Missing Values for ADAS-Cog 11 Total Score

For ADAS-Cog11, if <30% (<4 of a total of 11) of the items are missing, the total score (maximum = 70) will be imputed as follows: The total from remaining items will be multiplied by a factor that includes the maximum score for the missing items. For example, if the first item, "Word-Recall Task," which ranges from a score of 0 through 10 (maximum = 10), is missing, and the second item "Commands," which ranges from a score of 0 to 5 (maximum = 5), is missing, then the multiplication factor = 70/(70 - [10 + 5]) = 70/55 = 1.27. Thus, the total score for this example, will be the sum of the remaining 9 items multiplied by 1.27. The imputed number will be rounded up to the nearest integer. If more than 3 items are missing, the total score for ADAS-Cog11 at that visit will be considered missing.

Missing Values for ADCS-ADL Total Score

For the ADCS-ADL, if <4 of the 24 items are missing, the total score will be imputed. The sum of the non-missing items will be prorated to the sum of total items. The imputed number will
be rounded up to the nearest integer. If the nearest integer is greater than the maximum possible score, the imputed score will be equal to the maximum score. If more than 3 of the items are missing, the total score for ADCS-ADL at that visit will be considered missing.

Missing Values for CDR-SB Total Score

The same imputation technique will be applied to the Clinical Dementia Rating-Sum of Boxes (CDR-SB) as outlined above for the ADCS-ADL. If only 1 box (of 6) of the CDR is missing, the sum of the boxes will be imputed by prorating the sum from the other 5 boxes. If the score from more than 1 box is not available, the CDR-SB at that visit will be considered missing.

Exposure to Study Drug

Exposure to study drug will be calculated as the date of last dosing minus the date of first dosing + 1. The exposure calculation will not take into account breaks in therapy.

Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

Adverse Events

- If the relationship to study medication is missing for an adverse event, it will be assumed to be related to study medication for analysis purposes.

Programming Specifications

- In general, font size will be at least 9-point and all margins will be 1 inch.
- Tables and listings will be internally paginated (i.e., page numbers will appear sequentially within each display). All output will have the SAS program name in footer at the lower left margin.
- In general, data listings will be sorted by subject identification (ID) number and visit/assessment/collection/start dates, unless specified otherwise.
- Dates will be displayed in SDTM (Study Data Tabulation Model) format (YYYY-MM-DD) on listings.
- Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.
- Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the subject population unless otherwise specified. For each variable, all categories will be shown.
- Unless otherwise noted (see below), the mean and median (standard deviation) of a set of values should be printed out to 1 (2) more decimal place(s) than the raw value for demographic and safety assessments.

eg,	raw:	xx
	mean and median	xx.x
	standard deviation and standard error:	xx.xx
	range (minimum and maximum):	xx, xx

In cases in which the raw data are reported to 2 or 3 decimal places, the mean, median, standard deviation, and standard error will be displayed to 1 more decimal place than the raw data (eg, in tables summarizing changes from baseline in laboratory parameters).

- All percentages in tables will be reported to the precision of tenths (i.e., 0.1) unless otherwise noted.
- The following specifications apply to tables that summarize categorical data unless otherwise noted:
    - If the categories of a parameter are ordered, then all categories between the maximum possible category and the minimum category will be included, even if n=0 for a given

category between the minimum and maximum level for that parameter unless specified.

- If the categories are not ordered, then only categories for which there is at least one subject represented will be included.