# Clinical Study Protocol

## A Randomized, Double-Blind, Placebo-Controlled Study of COR388 HCl in Subjects with Alzheimer's Disease

**Protocol Number: COR388-010**

**EudraCT Number: 2019-000370-27**

**NCT03823404**

**Date 17 May 2021**

**CORTEXYME, INC.**

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**Original Protocol Date (Version): 18 January 2019 (Version 1.0)**

**Amended Protocol Date (Version): 11 April 2019 (Version 2.0)**

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**Amended Protocol Date (Version): 17 May 2021 (Version 7.0)**

**Cortexyme, Inc.**
**269 East Grand Ave.**
**South San Francisco, CA 94080**

## Contact Information

**Sponsor** Michael J. Detke, MD, PhD
Cortexyme, Inc.
269 East Grand Ave.
South San Francisco, CA 94080
mdetke@cortexyme.com
+1 (317) 902-2002

**Medical Monitor** Stephen Kirzinger, MD
Sr. Medical Director
Worldwide Clinical Trials
1106 Colonel Anderson Parkway
Louisville, KY 40222
Phone: +1 (502) 419-4732
Email: stephen.kirzinger@worldwide.com

## Investigator's Agreement

I have read Protocol COR388-010 and agree to conduct the study according to its terms. I understand that all information supplied to me by Cortexyme, Inc., is confidential.

_____ _____

Principal Investigator Signature Date

**Protocol Signature Sheet**

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**Protocol Date v5.0 Date: 3 August 2020**

**Protocol v6.0 Date: 15 December 2020**

**Protocol v7.0 Date: 17 May 2021**

I approve this Protocol, including appendices.

**Approval Signature**

DocuSigned by:
7BFA336252BF435...

**Sponsor Company** _____ 5/18/2021
Date

Michael J. Detke, MD, PhD
Chief Medical Officer
Cortexyme, Inc.
269 East Grand Ave.
South San Francisco, CA 94080
Phone: +1 (317) 902-2002
Email: mdetke@cortexyme.com

# 1 PROTOCOL SYNOPSIS

**Title** A Randomized, Double-Blind, Placebo-Controlled Study of COR388 HCl in Subjects with Alzheimer's Disease

**Objectives** The objectives of the study are to:

- Assess the efficacy of 2 dose levels of COR388 HCl in Alzheimer's disease (AD) subjects; and
- Assess the safety and tolerability of 2 dose levels of COR388 HCl in AD subjects.

**Study Phase** Phase 2/3

**Study Design** This is a 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 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). The subject 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 measurement of bacterial DNA (*Pg*) using quantitative polymerase chain reaction (qPCR), biomarkers of AD, and gingipain activity. Saliva, and blood will be analyzed for biomarkers of AD and neuroinflammation, and for the presence of bacterial deoxyribonucleic acid (DNA) of *Porphyromonas gingivalis* (*P. gingivalis [Pg])* 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 cell 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.

Following the Data Monitoring Committee (DMC) recommendation after the November 16, 2020 meeting, increased frequency of liver safety monitoring has been implemented, which increased the frequency of safety laboratory analyte collections (see Table 1 and Table 2, Schedule of Evaluations).

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 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 positive either homozygous or heterozygous vs. 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***

The open label extension (OLE), as described below, was implemented in protocol versions 4.0 through 6.0. On 16 February 2021, the Sponsor terminated the OLE portion of the study following notification from the Food and Drug Administration (FDA) of a partial clinical hold. Per this notification, no new patients were enrolled into OLE, and all active participants were discontinued from study treatment with a requirement that a follow-up visit occur 4 weeks after the last dose of COR388.

***Open Label Extension Period***

Subjects who choose to participate in the OLE 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 40 mg or 80 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 OLE, 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.

**Study Population**

The study will enroll approximately 573 generally healthy male and female subjects, ≥55 and ≤80 years of age, with mild to moderate probable AD dementia according to the NIA-AA criteria, who experienced clinical decline in the last year as defined in the study protocol.

**Criteria for Inclusion & Exclusion**

Investigators should contact the Medical Monitor if they have questions about eligibility of specific subjects.

**Inclusion Criteria:**

Subjects will be eligible to participate in this study if they meet all of the following criteria:

1. Subject has provided full written informed consent prior to the performance of any protocol-specified procedure; or if unable to provide informed consent due to cognitive status, subject has provided assent and a legally authorized representative has provided full written informed consent on behalf of the subject.
2. Caregiver has provided full written informed consent, on a separate informed consent form (ICF), on his/her own behalf prior to the performance of any protocol-specified procedure.
3. Male and female subjects must be 55 years to 80 years of age, at the time of consent.
4. Subject has probable AD dementia according to the NIA-AA criteria (McKhann 2011) with clinical evidence of progressive cognitive decline in the last year. Clinical decline will be determined based on serial cognitive test scores, if available, or subject/caregiver report as documented by the Investigator.
5. Subject has an MMSE score between 12 and 24 inclusive at both screening and Visit 2 and a ≤3-point difference between these visits.
6. Subject has a Modified Hachinski score $\leq 4$ at screening.
7. Subject has brain MRI scan consistent with the diagnosis of AD performed during the screening period. Computed Tomography scan can be used only if the subject has an absolute contraindication for MRI.
8. Subject has a primary caregiver willing to accept responsibility for supervising the treatment (e.g., administering study drug), accompanying the study subject to clinic visits and assessing the condition of the subject throughout the study in accordance with all protocol requirements.
9. Subject is not likely to experience a change in living conditions (e.g., institutionalization, moving to a different city, etc.), or change in primary caregiver, during participation in the trial.
10. Subjects with background symptomatic therapy with acetylcholinesterase inhibitors, and/or memantine, are allowed as long as the dose has been stable for 90 days prior to screening and no changes are planned during the study.
11. Subjects who have occasional use of sedative agents are acceptable, but these agents should not be given within 48 hours prior to cognitive assessments.
12. Subjects who have background medications used for stable chronic illnesses that are not prohibited by the protocol are allowed. The dose of psychoactive drugs must be stable for 30 days prior to screening, and no changes must be planned during the study unless for safety reasons.
13. Subject has body mass index $\leq 38$ kg/m$^2$ at Screening.
14. Subject must be able to ingest oral medications and can swallow the study drug without breaking or crushing.

15. Subject must be willing to undergo Apolipoprotein E genotype (ApoE) genetic testing (ApoE results may be disclosed after trial completion).
16. Subjects participating in the study must meet one of the following criteria:
    a. Females: Surgically sterilized (e.g., hysterectomy, bilateral oophorectomy or tubal ligation) for at least 6 months or postmenopausal (postmenopausal females must have no menstrual bleeding for at least 1 year). If not postmenopausal, agree to use a highly effective method of contraception that can achieve a failure rate of less than 1% per year when used consistently and correctly, such as hormonal contraception or a double barrier method (e.g., intrauterine device plus condom or true abstinence defined as in line with the preferred and usual lifestyle of the subject. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods are not acceptable. Declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception) from 30 days prior to dosing until 30 days after last dose and have negative human chorionic gonadotropin (β-hCG) test for pregnancy at screening.
    b. Males who have not had a vasectomy must use appropriate contraception methods (barrier or true abstinence defined as in line with the preferred and usual lifestyle of the subject. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods are not acceptable. Declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception) from 30 days prior to dosing until 90 days after last dose.

**Open Label Extension:** Subjects will be eligible to participate in the open label extension portion of the study if they meet inclusion criteria # 8, 9, 10, 11, 12, 14, and 16 above. Subjects with any change in their medical history that in the Investigator's opinion will increase the subject's risk of participating in the study or confounding study assessment should not continue in the open label extension portion of the study. The Investigator should contact the Sponsor with questions of eligibility for participation.

**NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

**Exclusion Criteria:**

Subjects will not be eligible to participate in this study if they meet any of the following exclusion criteria:

1. Subject has imaging consistent with other differential dementia diagnoses other than the diagnosis of AD. For example, any suggestion of vascular disease including multiple infarction involving large blood vessels or localized single infarction (angular gyrus, thalamus, anterior cerebral artery and posterior cerebral artery region), multiple lacunae of the basal nuclei or white matter or extensive lesions of the periventricular white matter or combination of several lesions are considered exclusionary.

Additionally, any single lacune in an area known to impact cognition such as the hippocampus will also be exclusionary. Finally, Probable CAA with/without supporting pathological evidence according to the modified Boston criteria, if in the opinion of the investigator this may be contributing to symptoms overlapping with those of AD or confound neuropsychological assessments, would be exclusionary. Importantly, should there be any evidence of neurologic symptoms between scanning and baseline visits, rescanning is necessary to ensure proper patient selection.

2. Subject has had an increase or restoration of cognition based on medical history.
3. Subjects who meet the following imaging exclusion criteria will not be included in this study:
    a. Claustrophobia that will result in significant anxiety and difficulty lying still for brain imaging (MRI or CT scan).
    b. Severe motor problems or chronic pain indication that prevents the subject from lying still for brain imaging.
4. Subject with history of cancer requiring systemic therapy in the last 5 years; except for localized cancer of the skin and in-situ cervical cancer successfully treated with surgical excision. Stable (for at least 90 days) prostate cancer is allowed.
5. Subject has a contraindication for LP, such as infected skin over the needle entry site, possible increased intracranial pressure, severe thrombocytopenia or coagulopathy, suspected spinal epidural abscess, or spinal structural abnormalities that would interfere with LP procedures.
6. Subject has evidence of clinically significant unstable cardiovascular, pulmonary, renal, hepatic, gastrointestinal, neurologic or metabolic disease within 6 months prior to Screening.
7. Subject has any of the following cardiovascular conditions:
    a. Unstable angina, uncompensated and/or symptomatic congestive heart failure (Grade 2 or higher on the New York Heart Association scale) or myocardial infarction within 6 months.
    b. Acute or poorly controlled blood pressure >180 mmHg systolic or >100 mmHg diastolic.
    c. Current, or recent history of, any of the following that are clinically significant in the investigator's judgment: arrhythmia, hypotension, heart block ($1^{st}$, $2^{nd}$ or $3^{rd}$ degree AV block), ANY bundle branch block, ventricular pacing, symptomatic ectopy, unstable arrhythmias including atrial fibrillation; stable atrial fibrillation is allowed.
    d. History of prolonged QT or prolonged QT on screening ECG (QTcF $\geq$480 msec).
    e. History of prolonged PR interval or prolonged PR interval on screening ECG (PR >210 msec).

f. History of prolonged QRS interval or prolonged QRS interval on screening ECG (QRS >120 msec).

g. Supraventricular or ventricular ectopy on the screening ECG or Brugada pattern on the ECG.

8. Subject with major stroke, uncontrolled seizure disorder, or other medical illnesses that in the Investigator's opinion will increase the subject's risk of participation in the study or confound study assessments.

9. Subject with history or current evidence of major neurological or psychiatric illness such as schizophrenia, bipolar disorder, Parkinson's Disease, etc. Subjects with major depressive disorder that may interfere with the patient's ability to perform the study and all assessments. NOTE: Mild depression or depressive mood arising in the context of AD are not criteria for exclusion. The use of anti-depressants or the use of anti-epileptic medication for non-seizure-related treatment is allowed if the dose has remained stable for at least 60 days prior to enrollment.

10. Subject with history of violent or aggressive behavior that requires medication to control.

11. Subjects with active suicidal thoughts (Type 4 or 5 on the C-SSRS) in the 6 months preceding screening or at baseline; or have a history of a suicide attempt in the previous 2 years, or more than 1 lifetime suicide attempt; or are at serious suicide risk in the Investigator's clinical judgment.

12. Subject with history of alcohol or drug use disorder within 12 months of screening as defined by the Diagnostic and Statistical Manual of Mental Disorders-5.

13. Subject with previous treatment with investigational vaccine therapy for AD.

14. Subject has participated in another Investigational New Drug (IND) research study involving small molecule drugs within 60 days or biological drugs within 90 days prior to the first dose of study drug or 5 half-lives of the investigational drug, whichever is longer.

15. Subject has a history of epilepsy or seizure disorder requiring ongoing treatment, or any seizure or loss of consciousness within 6 months prior to enrollment.

16. Subject has any of the following laboratory findings at screening:

    a. Alanine aminotransferase >3 x upper limit of normal (ULN), aspartate aminotransferase >3 x ULN, or history of clinically significant liver disease in the Investigator's judgment.
    **NOTE**: Subjects with ALT or AST >2 x ULN at Visit 9/Week 40 will not be eligible to participate in OLE.
    **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

    b. Hemoglobin ≤10 g/dl.

c. International Normalized Ratio (INR) >1.5 or total bilirubin >1.5 x ULN (unless subject has evidence of Gilbert's disease).
d. Creatinine clearance (CL) of <45 ml/min.
e. Poorly controlled diabetes as defined by hemoglobin $A_{1C}$ ($HbA_{1C}$) >8.
f. Positive blood screen for Human Immunodeficiency Virus (HIV 1 and 2), Hepatitis B surface antigen (HBsAg), or Hepatitis C virus antibodies (HCV-Ab) at Screening.
g. Positive urine screen for drugs of abuse that include opiates, cocaine, amphetamines, or barbiturates.

17. Subject has abnormal laboratory tests that suggest an alternate etiology for dementia, such as serum vitamin B12 deficiency, thyroid function abnormality, severe anemia, electrolyte abnormality, or positive syphilis serology. In these cases, the patient should be re-evaluated to determine if these potential causes of dementia have been addressed. Only if these causes have been ruled out as the cause of the dementia can the patient be enrolled.
18. Use of systemic (i.e., oral, intravenous, etc., but not topical) antibiotics in the last 60 days or history of recurrent infection that requires chronic or repeated courses of antibiotics.

**Open Label Extension:** Subjects will not be eligible to participate in open label extension portion of the study if they meet any of the following exclusion criteria # 1, 4, 6, 7, 8-12, 15, 16 a, b, c, d and e. Laboratory testing and ECG results from Visit 9 will be used to evaluate eligibility. Subjects with any change in their medical history that in the Investigator's opinion will increase the subject's risk of participating in the study or confounding study assessment should not continue in the open label extension portion of the study. The Investigator should contact the Sponsor with questions of eligibility for participation.
**NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

**Study Treatments**

Eligible subjects will be randomized 1:1:1 to receive one of the following treatments:

- 80 mg COR388 HCl, twice daily (bid);
- 40 mg COR388 HCl, bid; or
- Placebo, bid

Open Label Extension: Subjects will receive 40 mg or 80 mg COR388 HCl, bid.
**NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

**Drug Supplies**

The study drug will be provided in capsule form for oral administration. All capsules will be identical in appearance.

| | |
|---|---|
| **Duration of Subject Participation** | **Double-blind:** 48 weeks of treatment + up to 6 weeks for screening + 6 weeks Safety follow up for subjects who don't participate in open label extension<br>**Open Label Extension:** 48 weeks of treatment + 6 weeks for Safety follow-up<br>**NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.<br>**Total Duration of Participation:** up to 108 weeks |
| **Efficacy Evaluations** | The two co-primary endpoints are:<br>• Mean change in Alzheimer's Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog 11) from baseline to the end of treatment period.<br>• Mean change in Alzheimer's Disease Cooperative Study Group-Activities of Daily Living (ADCS-ADL) from baseline to the end of treatment period.<br>Secondary endpoints in all subjects include:<br>• Change in Clinical Dementia Rating-Sum of Boxes (CDR-SB).<br>• Change in Mini-Mental State Examination (MMSE)<br>• Change in Neuropsychiatric Inventory (NPI)<br>Exploratory endpoints in all participating subjects include change from screening/baseline and/or Visit 2 to the end of treatment period in the following measures:<br>•<br>• Blood-based biomarkers in serum and peripheral blood mononuclear cells (PBMCs); and<br>• Saliva biomarkers of *P. gingivalis* infection and inflammation.<br>• Cerebrospinal fluid:<br>o CSF Aβ42, total Tau, and phosphorylated Tau;<br>o Bacterial DNA in the CSF based on quantitative polymerase chain reaction (qPCR) and sequencing; and<br>o CSF biomarkers.<br><br>Exploratory endpoints in subjects participating in sub-studies include change from screening/baseline to the end of treatment period in the following measures:<br>• Winterlight Speech Assessment (only in English speaking (primary language) subjects and only in the US and UK);<br>• Magnetic resonance imaging sub-study (subjects who have MRIs done in conjunction with the study):<br>o Hippocampal volume; and<br>o Cortical thickness. |

- Clinical periodontitis sub-study (subjects enrolled at selected sites):
  - Pocket Depth (PD);
  - Clinical Attachment Level (CAL) at 6 sites per tooth (distobuccal [DB], buccal [B], mesiobuccal [MB], distolingual [DL], lingual [L], and mesiolingual [ML]);
  - The percentage of sites with Bleeding on Probing (BOP); and
  - Biomarkers of *P. gingivalis* infection and inflammation in subgingival plaque (SGP) and buccal cell swabs.

**Safety Endpoints**

Safety endpoints include:

- The incidence and severity of TEAEs;
- Vital signs and physical examinations;
- Laboratory values;
- MRI scans;
- 12-lead ECGs; and
- C-SSRS.

**Open Label Extension:**

- The incidence and severity of TEAEs;
- Vital signs and physical examinations;
- Laboratory values;
- 12-lead ECGs; and
- C-SSRS.

  **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

**Statistical Considerations**

The study is designed as an adaptive trial and will allow for stopping early for efficacy, futility and potential adjustment in sample size based on the results of a planned interim analysis. Approximately 573 subjects are planned to be randomized 1:1:1 per treatment group (191 per treatment group) assuming approximately 10% will drop out prior to 48 weeks. This sample size would provide approximately 90% power to detect a 2.5-point difference between active treatment group and placebo with respect to change from baseline ADAS-Cog 11 score at Week 48, assuming a standard deviation of 7.1 at a two-sided significance level of 0.05 using a two-sided test. The ADCS-ADL was added as a co-primary outcome, with assumptions of a 3.9-point difference between the active treatment group compared to placebo with respect to change from baseline on ADCS-ADL, assuming a standard deviation of 10.5, providing approximately 95% power on this outcome measure, with approximately 90% power for the overall co-primary outcomes, depending on their correlation.

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. Overwhelming efficacy, futility and sample size adjustment will be evaluated. The Lan-DeMets spending function will be used to determine the test boundaries. If the 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.
Further details are provided in the statistical analysis plan (SAP).

## Table 1. Schedule of Evaluations – Double-blind study

| Study Period | Screening | Treatment Period | | | | | | | | | | | | | | | Safety Follow-up (if not participating in open label extension portion[12]) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit number | 1 | 2 | 3 | 3a | 4 | 4a | 4b | 5 | 5a | 6 | 6a | 7 | 7a | 8 | 9 | 10/ET[12] | Phone Call | | 11 |
| Week | -6 to -1 | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 15 | 18 | 21 | 24 | 28 | 32 | 40 | 48 | 49 | 51 | 54 |
| Day | -42 to -1 | 0 - 7 | 14 ± 2 | 28 ± 3 | 42 ± 3 | 56 ± 3 | 70 ± 3 | 84 ± 3 | 105 ± 3 | 126 ± 3 | 147 ± 3 | 168 ± 3 | 196 ± 3 | 224 ± 3 | 280 ± 8 | 336 ± 8 | 343 ± 2 | 357 ± 2 | 378 ± 8 |
| **Evaluations** | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | X[13] | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | | | | | | | | | X[14] | | | |
| Medical History and confirmation of cognitive decline in the last 12 months | X | | | | | | | | | | | | | | | | | | |
| Full Physical Examination, Height, and BMI Calculation | X | | | | | | | | | | | | | | | | | | |
| MRI (or CT) of the Brain | X | | | | | | | | | | | | | | | X[1] | | | |
| Modified Hachinski | X | | | | | | | | | | | | | | | | | | |
| MMSE[2] | X | X | | | | | | X | | | | X | | | X | X | | | X |
| Randomization | | X | | | | | | | | | | | | | | | | | |
| ADAS-Cog 11 | X | X | | | | | | X | | | | X | | | X | X | | | X |
| ADCS-ADL | | X | | | | | | X | | | | X | | | X | X | | | X |
| CDR-SB | X | X | | | | | | X | | | | X | | | X | X | | | X |
| NPI | | X | | | | | | | | | | X | | | | X | | | |
| Winterlight Speech Assessment (only in English speaking (primary language) subjects and only in the US and UK) | X | X | | | | | | X | | | | X | | | | X | | | |
| Dispense Study Drug | | X | X | | X | | | X | | | | X | | | X | X[15] | | | |
| Concomitant Medications | X | X | X | | X | | | X | | X | | X | | X | X | X | X | X | X |
| Oral Examination and collection of oral biomarker samples (only at selected sites)[3] | X | | | | | | | | | | | X[4] | | | | X[4,5] | | | |
| Saliva Collection | X | X | | | | | | | | | | X | | | | X | | | X |
| Symptom-Based Physical Examination | | X | X | | X | | | X | | X | | X | | X | X | X | | | X |
| Weight | X | | | | | | | | | | | | | | | X | | | |
| Vital Signs | X | X | X | | X | | | X | | X | | X | | X | X | X | | | X |
| Columbia-Suicide Severity Rating Scale | X | X | X | | X | | | X | | X | | X | | X | X | X | | | X |

Footnotes appear on following page.

## Table 1. Schedule of Evaluations – Double-blind study (Continued)

| **Study Period** | **Screening** | **Treatment Period** | | | | | | | | | | | | | | | **Safety Follow-up (if not participating in open label extension portion[12])** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit number | 1 | 2 | 3 | 3a | 4 | 4a | 4b | 5 | 5a | 6 | 6a | 7 | 7a | 8 | 9 | 10/ET[12] | Phone Call | | 11 |
| Week | -6 to -1 | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 15 | 18 | 21 | 24 | 28 | 32 | 40 | 48 | 49 | 51 | 54 |
| Day | -42 to -1 | 0 - 7 | 14 ± 2 | 28 ± 3 | 42 ± 3 | 56 ± 3 | 70 ± 3 | 84 ± 3 | 105 ± 3 | 126 ± 3 | 147 ± 3 | 168 ± 3 | 196 ± 3 | 224 ± 3 | 280 ± 8 | 336 ± 8 | 343 ± 2 | 357 ± 2 | 378 ± 8 |
| **Evaluations** | | | | | | | | | | | | | | | | | | | |
| Safety Laboratory Tests[16] | X | X | X | | X | | | X | | X | | X | | X | X | X | | | X |
| Liver Safety Monitoring[16] | | | | X | | X | X | | X | | X | | X | | | | | | |
| Lumbar Puncture (LP)[6] | | X | | | | | | | | | | | | | | X | | | |
| Adverse Events | | X | X | | X | | | X | | X | | X | | X | X | X | X | X | X |
| Blood Collection for PK[7] | | X | X | | | | | | | | | X | | | X | X | | | |
| 12-Lead ECG | X | X[8] | X[8,9] | | X | | | X | | | | X[8,9] | | | X[8] | X[8] | | | X |
| ApoE Genotyping | X | | | | | | | | | | | | | | | | | | |
| Urine Collection Pregnancy Test[10] | X | | | | | | | | | | | | | | | X | | | |
| Blood Collection for FSH[11] | X | | | | | | | | | | | | | | | | | | |
| Serum and whole blood (PBMCs) for biomarkers | | X | | | | | | | | | | X | | | | X | | | |
| Blood Collection for Serology (HCV-Ab, HBsAg, HIV 1 and 2) | X | | | | | | | | | | | | | | | | | | |
| Blood Collection for Vit. B12, Thyroid function tests and Syphilis | X | | | | | | | | | | | | | | | | | | |
| Urine Collection for Drug Screen | X | X | | | | | | | | | | | | | | | | | |

1. Visit 10/ET MRI will be done only in subjects who had a screening MRI performed and may be done up to 8 days prior to Visit 10/ET. CT scans of the brain can be used instead of MRIs, only in subjects who have an absolute contraindication for MRI.
2. Administer the first MMSE as early in the screening period as possible. MMSE score should be ≥12 and ≤24 at both screening and Visit 2, and a ≤3-point difference between visits, for inclusion in the study.
3. Oral biomarker samples include subgingival plaque and buccal cell swabs (only at selected sites).
4. Subjects will have follow-up oral examinations at 24 and 48 weeks.
5. Visit 10/ET oral examinations may be completed up to 8 days prior to Visit 10 (or ET) when applicable.
6. Baseline (V2) LP must be done after the baseline MMSE score has been verified and subject's eligibility has been confirmed, and prior to the first dose of study drug. To allow flexibility of scheduling the LP procedure, the MMSE and then the LP may be performed up to 7 days prior to baseline V2. Likewise, the LP at Visit10/ET may be performed up to 7 days prior to the other visit procedures, even if the LP is outside the visit window. The LP procedures must be

performed as per SOC and site specific SOPs, if applicable (including imaging before and/or during the LP, if required).

7. A pre-dose trough sample will be drawn at all visits 2, 3, and 7 immediately prior to the AM dose, and the subject will then take their dose of study drug on-site. The exact times of AM dosing and PK sample collections at the site will be documented. A single post-dose sample will be drawn from each subject while on-site at the clinic per the following schedule: V2 30 minutes - 4 hours; V3 60 minutes ± 30 minutes; V7 2 hours ± 30 minutes; V9 3 hours ± 30 minutes; and V10/ET 4 hours ± 30 minutes.
8. At visits when the subject takes their dose of study drug on-site, ECGs should be measured approximately 1-1.5 hours after dosing.
9. At Visit 3 and Visit 7, ECGs will also be performed at trough (prior to dosing).
10. A urine pregnancy test will be conducted only in women of child bearing potential at screening and End of Treatment or Early Termination Visit 10, and at other visits only if indicated. If the urine pregnancy test is positive, a serum pregnancy test will be performed to confirm pregnancy.
11. Only for peri-menopausal (irregular menstrual periods) or post-menopausal (no menstrual period for >12 months) female subjects.
12. Subjects who want to participate in the open label extension portion of the study will complete the Week 48 visit and then continue with the Schedule of Evaluations in Table 2. **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.
13. Informed consent will be obtained for subjects who agree to participate in the open label extension portion of the study.
14. Inclusion/exclusion will be evaluated to determine eligibility for subjects who want to participate in the open label extension portion of the study. Laboratory testing and ECG results from Visit 9 will be used to evaluate eligibility.
15. If a subject is eligible and agrees to participate in the open label extension, the OLE study drug (40 mg or 80 mg) will be dispensed at V10. The subject should be instructed to take the first dose in the morning of the next day.
16. Liver Safety Monitoring (laboratory analyte testing) must be performed at each study visit within the prespecified visit window OR the study drug dosing must be interrupted until the testing is done.

Abbreviations: 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; AM = morning; ApoE = apolipoprotein E; BMI = body mass index;
CDR-SB = Clinical Dementia Rating-Sum of Boxes; CSF = cerebrospinal fluid; CT = Computed Tomography; DNA = deoxyribonucleic acid;
ECG = electrocardiogram; ET = Early Termination; FSH = Follicle Stimulating Hormone; HBsAg = Hepatitis B surface antigen; HCV-Ab = Hepatitis C virus antibodies; HIV 1 and 2 = Human Immunodeficiency Virus 1 and 2; MMSE = Mini-Mental State Examination;
MRI = magnetic resonance imaging; NPI = Neuropsychiatric Inventory; PBMCs = peripheral blood mononuclear cells; *Pg* = *Porphyromonas gingivalis*;
PK = pharmacokinetics; qPCR = quantitative polymerase chain reaction.

## Table 2. Schedule of Evaluations – Open Label Extension[4]

| **Study Period** | **Treatment Period[4]** | | | | | | | | | | | | | **Safety Follow-up** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit number | OLE-1 | OLE-1a | OLE-2 | OLE-2a | OLE-2b | OLE-3 | OLE-3a | OLE-3b | OLE-3c | OLE-4 | OLE-4a | OLE-5 | OLE-6/ET | OLE-Phone Call | | OLE-9 |
| | | | | | | | | | | | | | | OLE-7 | OLE-8 | |
| Week | 50 | 52 | 54 | 56 | 58 | 60 | 63 | 66 | 69 | 72 | 78 | 84 | 96 | 97 | 98 | 102 |
| Day | 350 ± 3 | 364 ± 3 | 378 ± 3 | 392 ± 3 | 406 ± 3 | 420 ± 3 | 441 ± 3 | 462 ± 3 | 483 ± 3 | 504 ± 3 | 546 ± 6 | 588 ± 6 | 672 ± 8 | 679 ± 2 | 686 ± 2 | 714 ± 8 |
| **Evaluations** | | | | | | | | | | | | | | | | |
| Informed Consent | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | | | | | | | | | | | | | | | | |
| ADAS-Cog 11 | | | | | | X | | | | X | | | X | | | X |
| ADCS-ADL | | | | | | X | | | | X | | | X | | | X |
| CDR-SB | | | | | | X | | | | X | | | X | | | X |
| Dispense Study Drug | X | | X | | | X | | | | X | | X | | | | |
| Concomitant Medications | X | | X | | | X | | | | X | | X | X | X | X | X |
| Saliva Collection | | | | | | | | | | X | | | X | | | X |
| Symptom-Based Physical Examination | X | | X | | | X | | | | X | | X | X | | | X |
| Weight | | | | | | | | | | | | | X | | | |
| Vital Signs | X | | X | | | X | | | | X | | X | X | | | X |
| Columbia-Suicide Severity Rating Scale | X | | X | | | X | | | | X | | X | X | X | X | X |
| Liver Safety Monitoring[3] | | X | | X | X | | X | X | X | | X | | | | | |
| Safety Laboratory Tests | X | | X | | | X | | | | X | | X | X | | | X |
| Urine pregnancy test[1] | | | | | | | | | | | | | X | | | |
| Adverse Events | X | | X | | | X | | | | X | | X | X | X | X | X |
| 12-Lead ECG | X | | X | | | | | | | X | | | X | | | X |
| Oral Examination and collection of oral biomarker samples (only at selected sites)[2] | | | | | | | | | | | | | X | | | |

1. A urine pregnancy test will be conducted only in women of childbearing potential. If the urine pregnancy test is positive, a serum pregnancy test will be performed to confirm pregnancy.
2. Oral biomarker samples include subgingival plaque and buccal cell swabs (only at selected sites). Visit OLE-6/ET oral examinations may be completed up to 8 days prior to OLE-6 Visit (or ET) when applicable.
3. Liver Safety Monitoring (laboratory analyte testing) must be performed at each study visit within the prespecified visit window OR the study drug dosing must be interrupted until the testing is done.
4. **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

## TABLE OF CONTENTS

## List of Tables

## List of Abbreviations

| Abbreviation | Term |
|---|---|
| Abnormal CS | Abnormal Clinically Significant |
| Abnormal NCS | Abnormal Not Clinically Significant |
| 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 |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AL | Attachment level |
| ANCOVA | Analysis of covariance |
| ApoE | Apolipoprotein E |
| B | buccal |
| Bid | Twice daily |
| BMI | Body mass index |
| BOP | Bleeding on Probing |
| CAL | Clinical Attachment Level |
| CDC/AAP | Centers for Disease Control/American Academy of Periodontology |
| CDR-SB | Clinical Dementia Rating-Sum of Boxes |
| CEJ | Cementoenamel junction |
| CFR | Code of Federal Regulations |
| CL | Creatinine clearance |
| CNS | Central Nervous System |
| CRA | Clinical Research Associate |
| CRO | Contract Research Organization |
| CS | Compound symmetry |
| CSF | Cerebrospinal fluid |
| CSH | Heterogeneous compound symmetry |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CT | Computed Tomography |
| CV | Coefficient of variation |
| DB | Distobuccal |
| DL | Distolingual |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic acid |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |

| Abbreviation | Term |
|---|---|
| FDA | Food and Drug Administration |
| FSH | Follicle stimulating hormone |
| GM | Gingival margin |
| β-HCG | Human chorionic gonadotropin |
| $HbA_{1C}$ | Hemoglobin $A_{1C}$ |
| HBsAg | Hepatitis B surface antigen |
| HCV-Ab | Hepatitis C virus antibodies |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| HPMC | Hydroxypropyl methylcellulose |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IRS | Interactive Response System |
| ITT | Intent-to-Treat |
| L | Lingual |
| LP | Lumbar Puncture |
| MAR | Missing at random |
| MB | Mesiobuccal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| ML | Mesiolingual |
| MMRM | Mixed-effects model for repeated measures |
| MMSE | Mini-Mental State Examination |
| MNAR | Missing not at random |
| MRI | Magnetic resonance imaging |
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| NOAEL | No observed adverse effect level |
| NPI | Neuropsychiatric Inventory |
| PBMC | Peripheral blood mononuclear cell |
| PD | Pocket Depth |
| *Pg* | *Porphyromonas gingivalis (P. gingivalis [Pg])* |
| PK | Pharmacokinetics |
| PP | Per Protocol |
| PT | Preferred Term |

| Abbreviation | Term |
|---|---|
| qPCR | Quantitative polymerase chain reaction |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard deviation |
| SGP | Subgingival plaque |
| $t_{½}$ | Half-life |
| TEAE | Treatment-emergent adverse event |
| $T_{max}$ | Time to maximum plasma concentration |
| ULN | Upper limit of normal |

# 2 INTRODUCTION

Alzheimer's disease (AD) continues to cause a tremendous impact on the lives of millions of patients and their caregivers and puts a huge burden on healthcare systems worldwide. In the absence of effective disease modifying treatments, AD continues to represent a major area of unmet medical need. Cortexyme is developing a novel small molecule, COR388 HCl, for the treatment of AD. The development of this compound represents a new paradigm for disease modification in AD that is based on a large body of emerging scientific data from both Cortexyme and independent researchers, as detailed in the Investigator's Brochure (IB) and summarized in the sections below.

Cortexyme has discovered evidence of *Porphyromonas gingivalis* (*P. gingivalis [Pg]*) in the brains of a large proportion of Alzheimer's patients compared to controls. *P. gingivalis* is a Gram-negative asaccharolytic pathogen and a keystone bacterium in the development of periodontal disease. Gingipains are cysteine proteases produced by *Pg* that are critical for the survival of the bacteria, host cell toxicity, and immune evasion. *P. gingivalis* infection has been identified as a risk factor for a number of chronic inflammatory disease states including AD, atherosclerosis, and type 2 diabetes. *P. gingivalis* has been isolated from a variety of human tissues indicating systemic translocation beyond the oral cavity. A growing body of epidemiological evidence and prospective observational studies link periodontal disease, the most prevalent age-related chronic infection in humans, to diagnosis and rapid decline of AD. Cortexyme conducted a series of experiments to evaluate the presence of *Pg* and gingipains in the brains of AD patients and control groups, explore the role of *Pg* in the pathogenesis of AD, and evaluate gingipains as a therapeutic target. Based on the data summarized in the IB, Cortexyme believes this compound will slow or prevent further neurodegeneration, cognitive decline, and accumulation of pathology in AD patients.

COR388 HCl is a proprietary small molecule that is a potent and selective irreversible inhibitor of the bacterial protease lysine gingipain (Kgp) that was selected as a lead compound to progress toward human clinical trials based on its selectivity, pharmacokinetics (PK), efficacy, and safety profiles.

A comprehensive program was conducted to assess the PK, safety, and toxicity of COR388 HCl in 2 animal species and humans. COR388 HCl has a favorable PK profile in animals, and is readily bioavailable after oral administration, resulting in sufficient plasma and central nervous system (CNS) exposures for clinical efficacy. COR388 is a chiral molecule whose epimer COR490 is produced in vivo and has a similar potency, efficacy and PK profile. COR388 has a moderate level of plasma protein binding in animal species tested and human subjects. COR388 is cleared rapidly, with a terminal half-life ranging from 2-3.5 hours in different animal species to 4.5-5.0 hours at steady state in humans.

No evidence of genotoxicity was found on either a battery of in vitro studies in bacteria and mammalian cells or in an in vivo micronucleus study. General toxicology studies in mice and dogs showed no change in serum chemistry,

hematology, and urinalysis laboratory parameters. Treatment with large doses of COR388 was associated with transient cardiovascular effects in dogs. Histopathology evaluation with light and fluorescent microscopy, as well as electron microscopy, revealed minimal increase in the size and number of intracytoplasmic lysosomes in the brain in mice and dogs and the kidney in dogs. There was no evidence of cellular injury. These were considered an adaptive response by the neurons and renal tubular cells aiming at clearing excess COR388 and metabolites, that may not be expected to occur with the lower exposure levels planned in human trials. These findings were considered non-adverse in dogs at all doses, and in mice treated with doses ≤100 mg/kg/day. After a 28-day recovery period, a complete reversal of the findings was found in the kidneys in dogs and the stratum radiatum in mice, with partial recovery in other parts of the mouse brain.

Safety pharmacology studies revealed transient, and reversible effects on the cardiovascular and CNS systems. The no observed adverse effect levels (NOAELs) associated with these effects provide large safety margins over the doses used in this trial.

Cortexyme has completed two Phase 1 safety and PK studies. The Phase 1 program included a single ascending dose study in normal healthy volunteers, and a multiple ascending dose study in older healthy volunteers and AD subjects with clinical evidence of periodontitis.

Results from the single ascending dose study showed that COR388 HCl was absorbed rapidly after oral administration and produced plasma concentrations in the presumed therapeutic range and dose proportional increases in exposures with doses ranging from 25 to 150 mg. Clearance was rapid, with a mean half-life (t½) of 2 to 4 hours. Consumption of a high fat meal had a modest effect on COR388 HCl exposure, which is not likely to be of clinical relevance. Single doses of COR388 HCl ranging from 5 to 250 mg were safe and well tolerated when administered to healthy volunteers, although there was only 1 subject in the 250 mg dose cohort. Treatment-emergent adverse events (TEAEs) were infrequent, mostly mild in severity, and transient. There were no deaths, Serious Adverse Events (SAEs), or TEAEs leading to study drug discontinuation during the study. There were no clinically meaningful changes in safety laboratory findings, electrocardiograms (ECGs), vital signs, or physical examinations observed during the study.

The multiple ascending dose study revealed that oral doses of COR388 HCl ranging from 25 to 100 mg every 12 hours were safe and well tolerated when administered to normal healthy volunteers 55 to 70 years of age and Alzheimer's disease (AD) subjects 58 to 83 years of age. Subjects who received COR388 HCl experienced infrequent TEAEs, which were mostly mild in severity and transient. There were no deaths, SAEs, or TEAEs leading to study drug discontinuation during the study. There were no clinically meaningful changes in laboratory parameters, vital signs, ECGs, or physical examination findings observed during the study. COR388 HCl was readily bioavailable after oral administration, with good tissue distribution and

rapid clearance. The results of the Phase 1a/b trials are described in more detail in the IB.

Safety and PK data from the Phase 1 a/b program along with appropriate preclinical chronic toxicology and other studies enabled Cortexyme to select appropriate doses and move forward with the Phase 2/3 program.

# 3 STUDY OBJECTIVES

The objectives of the study are to:

- Assess the efficacy of 2 dose levels of COR388 HCl in Alzheimer's disease (AD) subjects; and
- Assess the safety and tolerability of 2 dose levels of COR388 HCl in AD subjects.

# 4 INVESTIGATIONAL PLAN

## 4.1 Overall Study Design and Plan

This is a 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 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 subsequent 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). The subject should not have other conditions or brain imaging abnormality that can explain the symptoms of dementia. A Lumbar Puncture (LP) will be performed at baseline (Visit 2) and at end of treatment period week 48 (Visit 10) or early termination visit (ET). Cerebrospinal fluid (CSF) will be tested for measurement of bacterial DNA (*Pg*) using quantitative polymerase chain reaction (qPCR), biomarkers of AD, and gingipain activity. Saliva, and blood will be analyzed for measurements of biomarkers of AD and neuroinflammation, and for the presence of bacterial deoxyribonucleic acid (DNA) of *Porphyromonas gingivalis* (*P. gingivalis [Pg])* 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. Subjects will have follow-up oral examinations at 24 and 48 weeks. Subgingival plaque (SGP) and buccal cell swabs will be collected in addition to saliva 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 efficacy after 24 weeks of treatment on key outcome measures.

During the screening period, the eligibility of subjects will be confirmed according to the Schedule of Evaluations (Table 1).

Eligible subjects will be randomized 1:1:1 to receive one of the following treatments:

- 80 mg COR388 HCl, twice daily (bid);
- 40 mg COR388 HCl, bid; or
- Placebo, bid.

The study drug will be provided in capsule form for oral administration. All capsules will be identical in appearance.

### 4.1.1 Scientific Rationale for Study Design

The primary objective of the study is to assess the efficacy of COR388 HCl in the treatment of AD. Based on the postulated mechanism of action of this compound, treatment is expected to slow or prevent further neurodegeneration, cognitive decline, and accumulation of pathology in AD subjects should COR388 HCl be effective. Available data indicate that Alzheimer's Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog 11) score increases by 2-4 points per year on average in subjects with mild to moderate AD (Ito 2013, Wattmo 2016). Therefore, a treatment period of 48 weeks was selected to allow sufficient time to demonstrate at least 2.5 points difference between active treatment and placebo on ADAS-Cog 11 at the end of treatment period. The doses of 40 and 80 mg were selected to provide plasma levels of COR388 above the levels found to be therapeutic in animal models, while maintaining safe exposure levels based on preclinical and clinical data available to date. The objective of the open label extension portion of the study is to evaluate the safety and efficacy of COR388 HCl treatment in all subjects who want to participate and meet eligibility criteria.

The frequency of visits is selected to provide close monitoring of subjects' safety, without putting undue burden on the subjects and their caregivers. Similarly, study assessments are selected to provide the essential data needed to assess the

efficacy and safety of COR388 HCl, without burdening study subjects with unnecessary procedures or lengthy site visits.

### 4.1.2 Efficacy Evaluations

Primary Endpoint

The two co-primary endpoints are:

- Mean change in Alzheimer's Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog 11) from baseline to the end of treatment period; and
- Mean change in Alzheimer's Disease Cooperative Study Group-Activities of Daily Living (ADCS-ADL) from baseline to the end of treatment period.

Secondary Endpoints

Secondary endpoints in all subjects include:

- Change in Clinical Dementia Rating-Sum of Boxes (CDR-SB);
- Change in Mini-Mental State Examination (MMSE); and
- Change in Neuropsychiatric Inventory (NPI).

Exploratory Endpoints

Exploratory endpoints in all participating subjects include change from screening/baseline and/or Visit 2 to the end of treatment period in the following measures:

- Blood-based biomarkers in serum and peripheral blood mononuclear cells (PBMCs); and
- Saliva biomarkers of *P. gingivalis* infection and inflammation.
- Cerebrospinal fluid:
  - CSF Aβ42, total Tau, and phosphorylated Tau;
  - Bacterial DNA in the CSF on quantitative polymerase chain reaction (qPCR); and
  - CSF biomarkers.

Exploratory endpoints in subjects participating in sub-studies include change from screening/baseline to the end of treatment period in the following measures:

- Winterlight Speech Assessment (only in English speaking subjects (primary language and only in the US and UK);
- Magnetic resonance imaging sub-study (subjects who have MRIs done in conjunction with the study):
  - Hippocampal volume; and
  - Cortical thickness.

- Clinical periodontitis sub-study (subjects enrolled at selected sites):
  - Pocket Depth (PD);
  - Clinical Attachment Level (CAL) at 6 sites per tooth (distobuccal [DB], buccal [B], mesiobuccal [MB], distolingual [DL], lingual [L], and mesiolingual [ML]);
  - The percentage of sites with Bleeding on Probing (BOP); and
  - Biomarkers of *P. gingivalis* infection and inflammation in subgingival plaque (SGP) and buccal cell swabs.

Safety Endpoints

Safety endpoints include:

- The incidence and severity of TEAEs;
- Vital signs and physical examinations;
- Laboratory values;
- MRI scans;
- 12-lead ECGs; and
- C-SSRS.

### 4.1.3 End of Study Definition

End of study is Safety Follow-up Visit 11 or Visit OLE-9 (if subject participates in the open label extension portion of the study), 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.

## 5 STUDY DRUG ADMINISTRATION AND MANAGEMENT

### 5.1 Dose Preparation and Administration

Each subject will receive study treatment according to the randomization scheme. The study drug will be provided in capsule form for oral administration. Subjects will be instructed to take the capsules with water twice a day, one capsule after waking in the morning and one before bed, ideally 12 hours apart and no less than 6 hours apart.

### 5.2 Randomization to Treatment Groups

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 positive either homozygous or heterozygous vs. all others) genotype to assure balanced distribution of mild and moderate AD and a balanced distribution of ApoE4 subjects, across treatment arms. All participants will be centrally assigned to randomized

study intervention using an Interactive Response System (IRS). All subjects in the open label extension portion of the study will receive 40 mg or 80 mg COR388 HCl.

## 5.3 Packaging and Labeling

Study drug will be packaged in blister packs and assembled into weekly cards each containing 16 capsules: 2 capsules for each day of the week and 2 additional capsules to be used only if instructed by the Investigator (late visits, damaged or lost capsules, etc.). The capsules will be identical in appearance, but their contents will depend on the subject's treatment assignment. The cards containing the blister packed capsules will be labeled in compliance with country-specific labeling requirements.

## 5.4 Study Drug Supply, Storage, and Handling

### 5.4.1 COR388 HCl

The COR388 HCl capsules are orange, opaque, size 3 hydroxypropyl methylcellulose (HPMC) capsules containing the appropriate dose of COR388 HCl based on the treatment arm. The capsules should be stored at room temperature.

The study drug will be kept in a secure location that is accessible only to study personnel whom the Investigator has authorized to dispense/prepare study drug.

### 5.4.2 Placebo

The placebo capsules are orange, opaque, size 3 HPMC capsules containing microcrystalline cellulose. Placebo capsules must be stored at room temperature.

The placebo capsules will be kept in a secure location that is accessible only to study personnel whom the Investigator has authorized to dispense/prepare study drug.

### 5.4.3 Unblinding of Individual Study Subjects

From Screening (Visit 1) through the Safety Follow-up Visit (Visit 11), the Investigator should not become unblinded unless knowledge of the treatment is required for the subject's safety and medical care.

In the event of an SAE requiring identification of the study drug administered to an individual subject, the Investigator will access the IRS using the emergency unblinding instructions. The IRS will record the name of the Investigator making the request, the date and time of the request, and the subject number and age. The Sponsor will be informed within 24 hours if unblinding occurs.

The Investigator will attempt to consult with the Medical Monitor regarding the need to unblind the treatment assignment for the subject, if time allows. At all times, the safety and well-being of any subject outweighs the need to consult with the Medical Monitor. In any event, the Investigator will contact the Medical Monitor and

Cortexyme within 24 hours of breaking the blind. The Investigator will be responsible for documenting the time, date, and reason for the unblinding and the names of the personnel involved. Every effort should be made to avoid unblinding other study personnel.

### 5.5 Drug Inventory and Accountability

The Investigator must keep an accurate accounting of the number of investigational product units delivered to the site, dispensed to subjects, returned to the Investigator by the subject, and returned to the Sponsor or other disposition during and at the completion of the study. The investigational product must be dispensed to subjects only by an appropriately qualified person. The investigational product is to be used in accordance with the protocol by subjects who are under the direct supervision of the Investigator. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational products received at the site before final disposition. At the end of the study, or as directed, all study drugs, including unused, partially used, and empty containers, will be returned to the Sponsor/designee or will be destroyed.

### 5.6 Treatment Compliance

Investigational product containers must be returned at each visit, as compliance will be assessed by capsule counts. Noncompliance is defined as taking less than 80% or more than 120% of investigational product during any outpatient evaluation period (visit to visit). Discontinuation for noncompliance is at the Investigator’s discretion and is to be noted on the electronic Case Report Form (eCRF).

## 6 SELECTION OF STUDY POPULATION

Investigators should contact the Medical Monitor if they have questions about eligibility of specific subjects.

### 6.1 Inclusion Criteria

Subjects will be eligible to participate in this study if they meet all of the following criteria:

1. Subject has provided full written informed consent prior to the performance of any protocol-specified procedure; or if unable to provide informed consent due to cognitive status, subject has provided assent and a legally authorized representative has provided full written informed consent on behalf of the subject.
2. Caregiver has provided full written informed consent, on a separate informed consent form (ICF), on his/her own behalf prior to the performance of any protocol-specified procedure.

3. Male and female subjects must be 55 years to 80 years of age, at the time of consent.
4. Subject has probable AD dementia according to the NIA-AA criteria (McKhann 2011) with clinical evidence of progressive cognitive decline in the last year. Clinical decline will be determined based on serial cognitive test scores, if available, or subject/caregiver report as documented by the Investigator.
5. Subject has an MMSE score between 12 and 24 inclusive at both screening and Visit 2 and a ≤3-point difference between these visits.
6. Subject has a Modified Hachinski score ≤4 at screening.
7. Subject has brain MRI scan consistent with the diagnosis of AD performed during the screening period. Computed Tomography scan can be used only if the subject has an absolute contraindication for MRI.
8. Subject has a primary caregiver willing to accept responsibility for supervising the treatment (e.g., administering study drug), accompanying the study subject to clinic visits and assessing the condition of the subject throughout the study in accordance with all protocol requirements.
9. Subject is not likely to experience a change in living conditions (e.g., institutionalization, moving to a different city, etc.), or change in primary caregiver, during participation in the trial.
10. Subjects with background symptomatic therapy with acetylcholinesterase inhibitors, and/or memantine, are allowed as long as the dose has been stable for 90 days prior to screening and no changes are planned during the study.
11. Subjects who have occasional use of sedative agents are acceptable, but these agents should not be given within 48 hours prior to cognitive assessments.
12. Subjects who have background medications used for stable chronic illnesses that are not prohibited by the protocol are allowed. The dose of psychoactive drugs must be stable for 30 days prior to screening, and no changes must be planned during the study unless for safety reasons.
13. Subject has body mass index $\leq$38 kg/m$^2$ at Screening.
14. Subject must be able to ingest oral medications and can swallow the study drug without breaking or crushing.
15. Subject must be willing to undergo Apolipoprotein E genotype (ApoE) genetic testing (ApoE results may be disclosed after trial completion).
16. Subjects participating in the study must meet one of the following criteria:
    a. Females: Surgically sterilized (e.g., hysterectomy, bilateral oophorectomy or tubal ligation) for at least 6 months or postmenopausal (postmenopausal females must have no menstrual bleeding for at least 1 year). If not postmenopausal, agree to use a highly effective method of contraception that can achieve a failure rate

of less than 1% per year when used consistently and correctly, such as hormonal contraception or a double barrier method (e.g., intrauterine device plus condom or true abstinence defined as in line with the preferred and usual lifestyle of the subject. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods are not acceptable. Declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception) from 30 days prior to dosing until 30 days after last dose and have negative human chorionic gonadotropin (β-hCG) test for pregnancy at screening.

b. Males who have not had a vasectomy must use appropriate contraception methods (barrier or true abstinence defined as in line with the preferred and usual lifestyle of the subject. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods are not acceptable. Declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception) from 30 days prior to dosing until 90 days after last dose.

**Open Label Extension:** Subjects will be eligible to participate in the open label extension portion of the study if they meet inclusion criteria # 8, 9, 10, 11, 12, 14, and 16 above. Subjects with any change in their medical history that in the Investigator's opinion will increase the subject's risk of participating in the study or confounding study assessment should not continue in the open label extension portion of the study. The Investigator should contact the Sponsor with questions of eligibility for participation. **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

## 6.2 Exclusion Criteria

Subjects will not be eligible to participate in this study if they meet any of the following exclusion criteria:

1. Subject has imaging consistent with other differential dementia diagnoses other than the diagnosis of AD. For example, any suggestion of vascular disease including multiple infarction involving large blood vessels or localized single infarction (angular gyrus, thalamus, anterior cerebral artery and posterior cerebral artery region), multiple lacunae of the basal nuclei or white matter or extensive lesions of the periventricular white matter or combination of several lesions are considered exclusionary. Additionally, any single lacune in an area known to impact cognition such as the hippocampus will also be exclusionary. Finally, Probable CAA with/without supporting pathological evidence according to the modified Boston criteria, if in the opinion of the investigator this may be contributing to symptoms overlapping with those of AD or confound neuropsychological assessments, would be exclusionary. Importantly, should there be any evidence of neurologic symptoms between scanning and baseline visits, rescanning is necessary to ensure proper patient selection.

2. Subject has had an increase or restoration of cognition based on medical history.
3. Subjects who meet the following imaging exclusion criteria will not be included in this study:
    a. Claustrophobia that will result in significant anxiety and difficulty lying still for brain imaging (MRI or CT scan).
    b. Severe motor problems or chronic pain indication that prevents the subject from lying still for brain imaging.
4. Subject with history of cancer requiring systemic therapy in the last 5 years; except for localized cancer of the skin and in-situ cervical cancer successfully treated with surgical excision. Stable (for at least 90 days) prostate cancer is allowed.
5. Subject has a contraindication for LP, such as infected skin over the needle entry site, possible increased intracranial pressure, severe thrombocytopenia or coagulopathy, suspected spinal epidural abscess, or spinal structural abnormalities that would interfere with LP procedures.
6. Subject has evidence of clinically significant unstable cardiovascular, pulmonary, renal, hepatic, gastrointestinal, neurologic or metabolic disease within 6 months prior to Screening.
7. Subject has any of the following cardiovascular conditions:
    a. Unstable angina, uncompensated and/or symptomatic congestive heart failure (Grade 2 or higher on the New York Heart Association scale) or, myocardial infarction within 6 months.
    b. Acute or poorly controlled blood pressure >180 mmHg systolic or >100 mmHg diastolic.
    c. Current, or recent history of, any of the following that are clinically significant in the investigator's judgment: arrhythmia, hypotension, heart block (1st, 2nd or 3rd degree AV block), ANY bundle branch block, ventricular pacing, symptomatic ectopy, unstable arrhythmias including atrial fibrillation; stable atrial fibrillation is allowed.
    d. History of prolonged QT or prolonged QT on screening ECG (QTcF $\geq$480 msec).
    e. History of prolonged PR interval or prolonged PR interval on screening ECG (PR >210 msec).
    f. History of prolonged QRS interval or prolonged QRS interval on screening ECG (QRS >120 msec).
    g. Supraventricular or ventricular ectopy on the screening ECG or Brugada pattern on the ECG.

8. Subject with major stroke, uncontrolled seizure disorder, or other medical illnesses that in the Investigator's opinion will increase the subject's risk of participation in the study or confound study assessments.
9. Subject with history or current evidence of major neurological or psychiatric illness such as schizophrenia, bipolar disorder, Parkinson's Disease, etc. Subjects with major depressive disorder that may interfere with the patient's ability to perform the study and all assessments. NOTE: Mild depression or depressive mood arising in the context of AD are not criteria for exclusion. The use of anti-depressants or the use of anti-epileptic medication for non-seizure-related treatment is allowed if the dose has remained stable for at least 60 days prior to enrollment.
10. Subject with history of violent or aggressive behavior that requires medication to control.
11. Subjects with active suicidal thoughts (Type 4 or 5 on the C-SSRS) in the 6 months preceding screening or at baseline; or have a history of a suicide attempt in the previous 2 years, or more than 1 lifetime suicide attempt; or are at serious suicide risk in the Investigator's clinical judgment.
12. Subject with history of alcohol or drug use disorder within 12 months of screening as defined by the Diagnostic and Statistical Manual of Mental Disorders-5.
13. Subject with previous treatment with investigational vaccine therapy for AD.
14. Subject has participated in another Investigational New Drug (IND) research study involving small molecule drugs within 60 days or biological drugs within 90 days prior to the first dose of study drug or 5 half-lives of the investigational drug, whichever is longer.
15. Subject has a history of epilepsy or seizure disorder requiring ongoing treatment, or any seizure or loss of consciousness within 6 months prior to enrollment.
16. Subject has any of the following laboratory findings at screening:
    a. Alanine aminotransferase >3 x upper limit of normal (ULN), aspartate aminotransferase >3 x ULN, or history of clinically significant liver disease in the Investigator's judgment.
       **NOTE**: Subjects with ALT or AST >2 x ULN at Visit 9/Week 40 will not be eligible to participate in OLE.
       **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.
    b. Hemoglobin ≤10 g/dl.
    c. International Normalized Ratio (INR) >1.5 or total bilirubin >1.5 x ULN (unless subject has evidence of Gilbert's disease).
    d. Creatinine clearance (CL) of <45 ml/min.
    e. Poorly controlled diabetes as defined by hemoglobin $A_{1C}$ ($HbA_{1C}$) >8.

f. Positive blood screen for Human Immunodeficiency Virus (HIV 1 and 2), Hepatitis B surface antigen (HBsAg), or Hepatitis C virus antibodies (HCV-Ab) at Screening.
g. Positive urine screen for drugs of abuse that include opiates, cocaine, amphetamines, or barbiturates.

17. Subject has abnormal laboratory tests that suggest an alternate etiology for dementia, such as serum vitamin B12 deficiency, thyroid function abnormality, severe anemia, electrolyte abnormality, or positive syphilis serology. In these cases, the patient should be re-evaluated to determine if these potential causes of dementia have been addressed. Only if these causes have been ruled out as the cause of the dementia can the patient be enrolled.
18. Use of systemic (i.e., oral, intravenous, etc., but not topical) antibiotics in the last 60 days or history of recurrent infection that requires chronic or repeated courses of antibiotics.

**Open Label Extension:** Subjects will not be eligible to participate in open label extension portion of the study if they meet any of the following exclusion criteria # 1, 4, 6, 7, 8-12, 15, 16 a, b, c, d and e. Laboratory testing and ECG results from Visit 9 will be used to evaluate eligibility. Subjects with any change in their medical history that in the Investigator's opinion will increase the subject's risk of participating in the study or confounding study assessment should not continue in the open label extension portion of the study. The Investigator should contact the Sponsor with questions of eligibility for participation. **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

## 6.3 Subject Restrictions

### 6.3.1 Prior and Concomitant Medications

Subjects will not be allowed to use medications or combinations containing medications from prohibited classes during participation in the study (i.e., from Screening (Visit 1) through Safety Follow-up Visit 11 or Visit OLE-9 for subjects participating in OLE. Prohibited concomitant medication classes include: anticholinergics, CNS-penetrant antihistamines, and antipsychotics.

The use of prescribed benzodiazepines and sedatives/hypnotics are allowed during the study but should not be used 48 hours before any study visit with cognitive testing.

The use of prescribed acetyl cholinesterase inhibitors (e.g., donepezil, rivastigmine, etc.) or memantine is allowed during the study as long as the dose has been stable for at least 90 days prior to Screening and there are no plans to modify the dose or stop treatment during the study. Switching to a different drug in the same class is prohibited during the study.

The use of prescribed medication for stable chronic illnesses, including psychoactive drugs, is allowed during the study as long as the medication class is not prohibited,

the dose has been stable for at least 30 days prior to Screening, and there are no plans to modify the dose or stop treatment during the study. Starting new medication during participation in the study should be avoided, unless deemed necessary by the Investigator.

Systemic (i.e., oral, intravenous, etc., but not topical) antibiotics are prohibited in the last 60 days prior to Screening (Visit 1), or history of recurrent infection that requires chronic or repeated courses of antibiotics.

Patients requiring treatment with prophylactic antibiotics in order to undergo minimally invasive oral examination procedures (measurements of pocket depth, gingival margin and bleeding on probing) due to preexisting medical conditions such as artificial heart valve, history of rheumatic fever or recent (within a year) joint replacement surgery, or currently receiving immunosuppressive therapy are eligible to participate in the study; however, they should be excluded from participating in oral examinations.

The use of any over-the-counter medicinal products, including herbal and dietary supplements, are allowed unless, in the opinion of the Investigator, the administration of the over-the-counter medicinal product could affect the subject's safety or the results of the study.

All medications (including drug name, dose, and dose regimen) administered from 30 days prior to Visit 1 through the Safety Follow-up Visit (Visit 11) will be recorded in the source documents and on the Prior and Concomitant Medication electronic Case Report Form (eCRF).

# 7 STUDY VISITS

The study will consist of 3 periods: Screening period up to 6 weeks, treatment period up to 48 weeks, and a safety follow-up period of 6 weeks. When feasible, study visits should be performed at the same time of day for the same subject.

## 7.1 Screening: Visit 1 (Day -42 to Day -1)

During the screening period, the eligibility of subjects will be confirmed according to the Schedule of Evaluations in this protocol (see Table 1). The following evaluations will be performed at Screening in the following order as close as possible when feasible:

1. Obtain informed consent from subject, and caregiver informed consent signed by the primary caregiver;
2. Past medical history and confirmation of cognitive decline in the last 12 months;
3. Concomitant medications;
4. Inclusion/exclusion criteria for eligibility;
5. Modified Hachinski;
6. Columbia-Suicide Severity Rating Scale (C-SSRS);

7. Mini-Mental State Examination (MMSE). Subjects with MMSE score of 12-24, inclusive, will have the rest of their screening procedures performed or scheduled);
8. Alzheimer's Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog 11);
9. Clinical Dementia Rating, Sum of Boxes (CDR-SB);
10. Winterlight Speech Assessment (only in English speaking (primary language subjects and only in the US and UK);
11. 12-lead electrocardiogram (ECG);
12. Weight;
13. Vital signs;
14. Full physical examination, including height and body mass index (BMI) calculation;
15. Urine drug screen;
16. Urine pregnancy test (women of child bearing potential only);
17. Blood/urine sample collection for:
    a. Serology (Hepatitis C virus antibodies [HCV-Ab], Hepatitis B surface antigen [HBsAg], Human Immunodeficiency Virus [HIV] 1 and 2);
    b. Apolipoprotein E (Apo E) genotyping;
    c. Follicle stimulating hormone (FSH) for peri-menopausal (irregular menstrual periods) or post-menopausal (no menstrual period for >12 months) female subjects;
    d. Vitamin B12
    e. Thyroid function tests
    f. Syphilis
    g. Pregnancy test (only if urine pregnancy test is positive); and
    h. Safety laboratory tests;
18. Saliva collection;
19. Oral examination and collection of oral biomarker samples (subgingival plaque [SGP] and buccal cell swabs) (only at selected sites); and
20. Magnetic resonance imaging (MRI) of the brain. Computed Tomography (CT) scans of the brain can used instead of MRIs only in subjects who have an absolute contraindication for MRI.

Screening procedures can be done on multiple days if needed, with more invasive procedures done after other 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.

### 7.2 Study Treatment: Visit 2 (Day 0)

Subjects who meet all of the eligibility criteria will be scheduled for Visit 2.

Note: To accommodate the logistics of performing the baseline LP procedure, a separate visit within 7 days prior to V2/Day 0 may be scheduled. At this visit,

baseline MMSE score will be verified, and the LP procedure will be performed. The remaining V2 assessments must be completed at Day 0, when the first dose of study drug will be administered.

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. MMSE;
2. Lumbar puncture to collect cerebrospinal fluid (CSF) may be conducted up to 7 days prior to other procedures listed below;
3. Inclusion/exclusion criteria to assess for continued eligibility.
4. ADAS-Cog 11;
5. Alzheimer's Disease Cooperative Study Group - Activities of Daily Living (ADCS-ADL);
6. CDR-SB;
7. Randomization;
8. Concomitant medications;
9. Symptom-based physical examination;
10. Vital signs;
11. Neuropsychiatric Inventory (NPI);
12. C-SSRS;
13. Urine drug screen;
14. Blood/urine sample collection:
    a. Pharmacokinetics (PK): A pre-dose trough sample will be drawn immediately prior to the AM dose. The exact times of AM dosing and PK sample collections at the site will be documented.
    b. Serum and whole blood (peripheral blood mononuclear cells [PBMCs]) for biomarkers; and
    c. Safety laboratory tests;
15. Saliva collection;
16. Winterlight Speech Assessment (only in English speaking (primary language) subjects and only in the US and UK);
17. Adverse events;
18. Administer study drug at the site;
19. 12-lead ECG 1-1.5 hours post-dose;
20. Blood sample collection: Second PK blood draw 30 minutes to 4 hours post-dose; and
21. Dispense study drug.

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.

## 7.3 Study Treatment: Visit 3 (Day 14 ± 2)

Note: Please make every effort possible to have the visit scheduled in the morning so the AM dose can be taken in the morning. Ideally, daily doses should be taken 12 hours apart and no less than 6 hours apart.

The following evaluations will be performed at this visit:

1. Concomitant medications;
2. Symptom-based physical examination;
3. Vital signs;
4. C-SSRS;
5. Blood/urine sample collection:
    a. Safety laboratory tests; and
    b. PK - A pre-dose trough sample will be drawn. The exact times of AM dosing and PK sample collections at the site will be documented.
6. 12-lead ECG before dosing drug (trough)
7. Administer study drug at the site;
8. Adverse events;
9. 12-lead ECG 1-1.5 hours post-dose;
10. Blood sample collection: Second PK blood draw 60 minutes ± 30 minutes post-dose; and
11. Dispense study drug.

## 7.4 Study Treatment: Visit 4 (Day 42 ± 3)

The following evaluations will be performed at this visit:

1. Concomitant medications;
2. Symptom-based physical examination;
3. Vital signs;
4. C-SSRS;
5. Blood/urine sample collection:
    a. Safety laboratory tests;
6. 12-lead ECG;
7. Adverse events; and
8. Dispense study drug.

## 7.5 Study Treatment: Visit 5 (Day 84 ± 3)

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. ADAS-Cog 11;
2. MMSE;
3. ADCS-ADL;
4. CDR-SB;
5. Concomitant medications;

6. Symptom-based physical examination;
7. Vital signs;
8. C-SSRS;
9. Winterlight Speech Assessment (only in English speaking (primary language subjects and only in the US and UK);
10. Blood/urine sample collection:
    a. Safety laboratory tests;
11. 12-lead ECG;
12. Adverse events; and
13. Dispense study drug.

### 7.6 Study Treatment: Visit 6 (Day 126 ± 3)

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. Concomitant medications;
2. Symptom-based physical examination;
3. Vital signs;
4. C-SSRS;
5. Blood/urine sample collection:
    a. Safety laboratory tests; and
6. Adverse events.

### 7.7 Study Treatment: Visit 7 (Day 168 ± 3)

Note: Please make every effort possible to have the visit scheduled in the morning so the AM dose can be taken in the morning. Ideally, daily doses should be taken 12 hours apart and no less than 6 hours apart.

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. ADAS-Cog 11;
2. MMSE;
3. ADCS-ADL;
4. CDR-SB;
5. NPI;
6. Winterlight Speech Assessment (only in English speaking (primary language subjects and only in the US and UK);
7. Concomitant medications;
8. Oral examination and collection of oral biomarker samples (SGP and buccal cell swabs) (only at selected sites);
9. Saliva collection;
10. Symptom-based physical examination;
11. Vital signs;

12. C-SSRS;
13. Blood/urine sample collection:
    a. Safety laboratory tests;
    b. PK - A pre-dose trough sample will be drawn and the subject will then take their dose of study drug on-site. The exact times of AM dosing and PK sample collections at the site will be documented.
    c. Serum and whole blood (PBMCs) for biomarkers;
14. Adverse events;
15. 12-lead ECG before dosing drug (trough);
16. Administer study drug at the site;
17. 12-lead ECG 1-1.5 hours post-dose;
18. Blood sample collection: Second PK blood draw 2 hours ± 30 minutes post-dose; and
19. Dispense study drug.

### 7.8 Study Treatment: Visit 8 (Day 224 ± 3)

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. Concomitant medications;
2. Symptom-based physical examination;
3. Vital signs;
4. C-SSRS;
5. Blood/urine sample collection:
    a. Safety laboratory tests; and
6. Adverse events.

### 7.9 Study Treatment: Visit 9 (Day 280 ± 8)

Note: Please make every effort possible to have the visit scheduled in the morning so the AM dose can be taken in the morning. Ideally, daily doses should be taken 12 hours apart and no less than 6 hours apart.

The following evaluations will be performed at this visit in the following order as close as possible when feasible:

1. Administer study drug at the site
2. Blood/urine sample collection
    a. Safety laboratory tests;
    b. PK – A single post-dose sample will be drawn from each subject while on-site at the clinic at 3 hours ± 30 minutes post-dose. The exact times of AM dosing and PK sample collection at the site will be documented.
3. Adverse events;
4. 12-lead ECG 1-1.5 hours post-dose;
5. ADAS-Cog 11;
6. MMSE;

7. ADCS-ADL;
8. CDR-SB;
9. Concomitant medications;
10. Symptom-based physical examination;
11. Vital signs;
12. C-SSRS; and
13. Dispense study drug.

## 7.10 Study Treatment: Visit 10/Early Termination (Day 336 ± 8)

Note: To accommodate the logistics of performing the LP procedure, it may be done up to 7 days prior to V10/Day 336. Please make every effort possible to have the visit scheduled in the morning so the AM dose can be taken in the morning. Ideally, daily doses should be taken 12 hours apart and no less than 6 hours apart.

The following evaluations will be performed at this visit or at Early Termination in the following order as close as possible when feasible:

1. Administer last dose of double-blind study drug at the site;
2. Blood/urine sample collection:
    a. Safety laboratory tests;
    b. PK - A single post-dose sample will be drawn from each subject while on-site at the clinic at 4 hours ± 30 minutes post-dose. The exact times of AM dosing and PK sample collections at the site will be documented.
    c. Serum and whole blood (PBMCs) for biomarkers;
    d. Pregnancy test (only if urine pregnancy test is positive);
3. Adverse events;
4. Oral examination and collection of oral biomarker samples (SGP and buccal cell swabs) at selected sites (will be completed within 8 days before Visit 10 [or Early Termination] when applicable).
5. 12-lead ECG 1-1.5 hours post-dose
6. MRI of the brain, only in subjects who had a screening MRI performed, and has to be done within 8 days prior to Visit 10. CT scans of the brain can be used instead of MRIs, only in subjects who have an absolute contraindication for MRI;
7. ADAS-Cog 11;
8. MMSE;
9. ADCS-ADL;
10. CDR-SB;
11. NPI;
12. Winterlight Speech Assessment (only in English speaking (primary language subjects and only in the US and UK);
13. Concomitant medications;
14. Symptom-based physical examination;
15. Saliva collection;

16. Weight;
17. Vital signs;
18. Lumbar puncture to collect CSF;
19. Urine pregnancy test (women of child bearing potential only);
20. C-SSRS;
21. Informed consent will be obtained for subjects who agree to participate in the open label extension portion of the study; and
22. Inclusion/exclusion will be evaluated to determine eligibility for subjects who want to participate in the open label extension portion of the study.
    Dispense OLE study drug – subjects who participate in OLE only. The subject should be instructed to take the first dose of COR388 in the morning of the next day.
    **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

### 7.11 Safety Follow-up Phone Calls: (Days 343 ± 2 and 357 ± 2)

Adverse events and any changes to concomitant medications will be evaluated during these phone calls. The follow-up phone calls will be structured and scripted to ensure completeness and standardization. The general structure of the inquiry will be open ended inquiry about any new symptoms, specific questioning about any reported sign or symptom and then a structured questioning about neurologic and withdrawal sign and symptoms by body system as seen with benzodiazepines and opiates and amphetamines. These will be conducted after either Visit 10 or Early Termination.

**NOTE:** Subjects who choose to participate in the open label extension portion of the study will not complete the safety follow-up phone calls and continue with the Schedule of Evaluations in Table 2.
**NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

### 7.12 Safety Follow-up Visit: Visit 11 (Day 378 ± 8)

After completion of study treatment, subjects will continue to be monitored on the study for 6 weeks 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.

**NOTE:** Subjects who choose to participate in the open label extension portion of the study will not complete the safety follow-up visit and continue with the Schedule of Evaluations in Table 2.
**NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. ADAS-Cog 11;
2. MMSE;
3. ADCS-ADL;
4. CDR-SB;
5. Concomitant medications;
6. Saliva collection;
7. Symptom-based physical examination;
8. Vital signs;
9. C-SSRS;
10. Blood/urine sample collection:
    a. Safety laboratory tests
11. 12-lead ECG; and
12. Adverse events.

### 7.13 Increased Safety Laboratory Monitoring (Liver Safety Monitoring)

Per DMC recommendation (following the November 16, 2020 meeting) the following increased laboratory analyte testing is being implemented:

- Every 2 weeks for the initial 12 weeks
- Every 3 weeks as of Week 12 through Week 24
- Every 4 weeks as of Week 24 through Week 32

Liver Safety Monitoring (laboratory analyte testing) must be performed at each study visit within the prespecified visit window (see Table 1, Schedule of Evaluations) OR the study drug dosing must be interrupted until the testing is done.

## 7.14 Open Label Extension (OLE)

**NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

Subjects who complete Visit 10 may be eligible to participate in the open label extension portion of the study. If subjects meet inclusion and none of the exclusion criteria, and sign the informed consent, they will continue in the open label extension portion and not complete the Safety Follow-up Phone Calls or the Safety Follow-up Visit: Visit 11 (Day 378 ± 8). Laboratory testing and ECG results from Visit 9 will be used to evaluate eligibility.

Subjects who are not eligible or do not consent to the open label extension will proceed to the Safety Follow-up Phone Calls (Days 343 ± 2 and 357 ± 2) and the Safety Follow-up Visit: Visit 11 (Day 378 ± 8).

## 7.15 OLE Study Treatment: Visit OLE-1 (Day 350 ± 3)

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. Concomitant medications;
2. Symptom-based physical examination;
3. Vital signs;
4. C-SSRS;
5. 12-lead ECG;
6. Blood/urine sample collection:
    a. Safety laboratory tests;
7. Adverse events; and
8. Dispense study drug.

## 7.16 OLE Study Treatment: Visit OLE-2 (Day 378 ± 3)

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. Concomitant medications;
2. Symptom-based physical examination;
3. Vital signs;
4. C-SSRS;
5. 12-lead ECG;
6. Blood sample collection:
    a. Safety laboratory tests;
7. Adverse events; and
8. Dispense study drug.

### 7.17 OLE Study Treatment: Visit OLE-3 (Day 420 ± 3)

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. ADAS-Cog 11;
2. ADCS-ADL;
3. CDR-SB;
4. Concomitant medications;
5. Symptom-based physical examination;
6. Vital signs;
7. C-SSRS;
8. Blood/urine sample collection:
    a. Safety laboratory tests;
9. Adverse events; and
10. Dispense study drug.

### 7.18 OLE Study Treatment: Visit OLE-4 (Day 504 ± 3)

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. ADAS-Cog 11;
2. ADCS-ADL;
3. CDR-SB;
4. Concomitant medications;
5. Saliva collection;
6. Symptom-based physical examination;
7. Vital signs;
8. C-SSRS;
9. 12-lead ECG;
10. Blood sample collection:
    a. Safety laboratory tests;
11. Adverse events; and
12. Dispense study drug.

### 7.19 OLE Study Treatment: Visit OLE-5 (Day 588 ± 6)

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. Concomitant medications;
2. Symptom-based physical examination;
3. Vital signs;
4. C-SSRS;
5. Blood/urine sample collection:
    a. Safety laboratory tests;

6. Adverse events; and
7. Dispense study drug.

## 7.20 OLE Study Treatment: Visit OLE-6/Early Termination (Day 672 ± 8)

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. ADAS-Cog 11;
2. ADCS-ADL;
3. CDR-SB;
4. Concomitant medications;
5. Saliva collection;
6. Symptom-based physical examination;
7. Weight
8. Vital signs;
9. C-SSRS;
10. 12-lead ECG;
11. Urine pregnancy test (women of child bearing potential only);
12. Blood sample collection:
    a. Safety laboratory tests;
    b. Pregnancy test (only if urine pregnancy test is positive);
13. Adverse events.
14. Oral examination and collection of oral biomarker samples (SGP and buccal cell swabs) at selected sites (will be completed within 8 days before Visit OLE-6 [or Early Termination] when applicable).

## 7.21 OLE Safety Follow-up Phone Calls: Visits OLE-7 and OLE-8 (Days 679 ± 2 and 686 ± 2)

Adverse events, the C-SSRS, and any changes to concomitant medications will be reviewed and evaluated during these phone calls. The follow-up phone calls will be structured and scripted to ensure completeness and standardization. The general structure of the inquiry will be open ended inquiry about any new symptoms, specific questioning about any reported sign or symptom and then a structured questioning about neurologic and withdrawal sign and symptoms by body system as seen with benzodiazepines and opiates and amphetamines. These will be conducted after either Visit OLE-6 or Early Termination.

OLE Safety Follow-up Visit: Visit OLE-9 (Day 714 ± 8)

The following evaluations will be performed at this visit in the following order or as close as possible when feasible:

1. ADAS-Cog 11;
2. ADCS-ADL;
3. CDR-SB;
4. Concomitant medications;

5. Saliva collection;
6. Symptom-based physical examination;
7. Vital signs;
8. C-SSRS;
9. 12-lead ECG;
10. Blood sample collection:
    a. Safety laboratory tests;
11. Adverse events.

Increased Safety Laboratory Monitoring (Liver Safety Monitoring)

Per DMC recommendation (following the November 16, 2020 meeting), the following increased laboratory analyte testing is being implemented:

- Every 2 weeks for the initial 12 weeks
- Every 3 weeks as of Week 60 through Week 72
- Every 6 weeks as of Week 72 through Week 84

Liver Safety Monitoring (laboratory analyte testing) must be performed at each study visit within the prespecified visit window (see Table 2, Schedule of Evaluations) OR the study drug dosing must be interrupted until the testing is done.

## 7.22 Unscheduled Visit(s)

Subjects may return for an unscheduled visit at any time and evaluations will be performed, as necessary in the judgment of the Investigator.

## 7.23 Allowances in the Circumstance of a Public Health Emergency

If an investigative site or the patients associated with that site experience a public health emergency, such as a pandemic, then throughout that time, the following changes to what is written elsewhere in this protocol are permissible at the discretion of the PI:

- **At-home and/or virtual visits:** Even when an investigative site remains open to clinical trial patients coming on site, social distancing strategies may result in some patients being unwilling or unable to attend protocol-specific clinic visits. For such reasons, scheduled clinic visits may be replaced by at-home or virtual visits. This may include visits by Study Site staff (or home healthcare providers, if applicable) or virtual visits by videoconference or telephone.
- **Safety assessments:** Every effort should be made to continue performing safety assessments on schedule. This may require visits by Study Site staff (or home healthcare providers, if applicable).

- **Transport of investigational product to support study drug administration:** It is permissible for study drug to be shipped directly to the patient and/or caregiver's home. It is also permissible for patients or caregivers to ship used study drug back to the site.
- **Visit windows:** For safety assessments, the visit windows will remain as given in Table 1 and Table 2, Schedule of Evaluations.
- **Testing at local laboratories:** If it is not practical to conduct testing on site using kits from the central laboratory, then it is permissible to use a local laboratory instead.

All instances when the above listed allowances are applied to the study conduct and its participants will be documented within the study source documents and reflected within the visit specific case report forms and protocol deviations log.

# 8 STUDY PROCEDURES

## 8.1 Informed Consent

For each trial subject, a written ICF will be obtained before any protocol-related activities at Screening (Visit 1). An additional informed consent will be obtained at Visit 10 for subjects who qualify and want to participate in the open label extension portion of the study (**NOTE:** effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor). As part of this procedure, the Investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the investigational product in such a manner that the subject and (if applicable) subject's legal representative are aware of the potential risks, inconveniences, or adverse effects that may occur. Subjects, or the subject's legally authorized representative, must be given ample time to decide about the study participation and opportunity to inquire about details of the study. Subjects should be informed that they may withdraw from the study at any time. They will receive all information that is required by local regulations and International Conference on Harmonisation (ICH) guidelines. The Principal Investigator or a designated representative will provide the Sponsor or its representative with a copy of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF before the start of the study.

The subject or subject's legally authorized representative must be given a copy of the signed ICF, and the original is to be maintained in the designated location at the site. A separate consent may be considered for subjects from sites participating in the dental portion of the study.

The subject's caregiver must also indicate their understanding of the study and their role as a caregiver to the subject during the study. The subject's caregiver must provide written agreement to their role as caregiver.

To be eligible for the study, subjects must provide an IRB/IEC-approved written informed consent, if mentally competent according to IRB/IEC and local guidelines for consenting vulnerable populations. If the subject is not able to provide written informed consent, written informed consent must be obtained from a legally authorized representative on the subject's behalf, and written assent must be obtained from the subject.

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 meet specific criteria set by the protocol and be willing to sign a caregiver informed consent.

## 8.2 Medical and Medication History

A complete medical history will be obtained from each subject at Screening (Visit 1). The medical history will assess the subject for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history will include all currently relevant history. When possible, only diagnoses and surgeries will be recorded. It is not necessary to collect history for remote, resolved conditions such as past pediatric illnesses or surgeries, which probably do not affect suitability of the subject, unless the examining physician deems these conditions relevant to the subject's current health status. Medication history should include prescription and over the counter medications, herbs, vitamins, and minerals.

Concomitant medications will be recorded at Screening and at all subsequent study visits.

Open Label Extension: Concomitant medications will be recorded at all visits and phone calls. **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

## 8.3 Mini-Mental State Examination (MMSE)

The Mini-Mental State Examination (MMSE) (Folstein 1975) is a widely used and validated assessment to be used to evaluate inclusion eligibility as well as an exploratory measure. The 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. The MMSE will be administered at Screening (Visit 1), Visit 2, Visit 5, Visit 7, Visit 9, Visit 10 (or Early Termination), and Visit 11 (Safety Follow-up Visit). The MMSE score should be $\geq$12 and $\leq$24 at both Screening (Visit 1) and Visit 2, and a $\leq$3-point difference between these visits, for inclusion in the study. The MMSE takes approximately 20 minutes to complete.

## 8.4 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 at Visit 2. Randomization will be stratified by baseline MMSE (MMSE ≥12 and ≤18, and MMSE ≥19 and ≤24) and Apolipoprotein E (ApoE4 positive either homozygous or heterozygous vs all others) genotype to assure balanced distribution of mild and moderate AD and a balanced distribution of ApoE4 subjects, across treatment arms. All participants will be centrally assigned to randomized study intervention using an Interactive Response System (IRS).

## 8.5 Dispense Study Drug

Study drug will be dispensed to eligible subjects at Visit 2, Visit 3, Visit 4, Visit 5, Visit 7, and Visit 9.

Open Label Extension: Study drug will be dispensed to eligible subjects at Visits 10, OLE-1, OLE-2, OLE-3, OLE-4 and OLE-5. Approximately the same number of subjects will be assigned to 80 mg and 40 mg, per the Sponsor's instructions.
**NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

## 8.6 Alzheimer's Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog 11)

The Alzheimer's Disease Assessment Scale-Cognitive items (ADAS-Cog) is an 11-item scale which has been widely used in AD therapeutic research to assess memory, other cognitive functions and praxis (Mohs 1988). The ADAS-Cog 11 will be performed by an experienced and trained clinician as the primary endpoint to measure cognitive ability and to evaluate change from Baseline. The ADAS-Cog 11 is to be administered at Screening (Visit 1), Visit 2, Visit 5, Visit 7, Visit 9, Visit 10 (or Early Termination), and Visit 11 (Safety Follow-up Visit). The ADAS-Cog 11 takes approximately 30 minutes to complete.

Open Label Extension: The ADAS-Cog 11 is to be administered at Visits OLE-3, OLE-4, OLE-6 (or Early Termination) and OLE-9 (OLE Safety Follow-up Visit).
**NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

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

The Clinical Dementia Rating Scale (Hughes 1982) is a global rating of the function of AD subjects assessed in six categories: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. It is based on a semi-structured interview conducted with the subject and identified primary caregiver. The Clinical Dementia Rating-Sum of Boxes (CDR-SB) tool will be administered by a certified clinician and will be used to assess disease progression with cognitive and functional changes. The CDR-SB will be administered at Screening (Visit 1), Visit 2, Visit 5, Visit 7, Visit 9, Visit 10 (or Early Termination), and Visit 11 (Safety Follow-up Visit). The CDR-SB takes approximately 45 minutes to 1 hour to complete.

Open Label Extension: The CDR-SB will be administered at Visits OLE-3, OLE-4, OLE-6 (or Early Termination) and OLE-9 (OLE Safety Follow-up Visit). **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

### 8.8 Alzheimer's Disease Cooperative Study Group-Activities of Daily Living (ADCS-ADL)

The Alzheimer's Disease Cooperative Study Group-Activities of Daily Living (ADCS-ADL) will be performed to assess the subject's ability to perform activities of daily living and will be administered at Visit 2, Visit 5, Visit 7, Visit 9, Visit 10 (or Early Termination), and Visit 11 (Safety Follow-up Visit). The ADCS-ADL takes approximately 20 to 25 minutes to complete.

Open Label Extension: The ADCS-ADL will be administered at Visits OLE-3, OLE-4, OLE-6 (or Early Termination) and OLE-9 (OLE Safety Follow-up Visit). **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

### 8.9 Neuropsychiatric Inventory (NPI)

The Neuropsychiatric Inventory (NPI) is a 12-item scale which assesses behavioral disturbances commonly occurring in dementia subjects. Through a structured interview with the identified primary caregiver 12 behavioral domains are assessed. The NPI will be administered by a trained clinician at Visit 2, Visit 7, and Visit 10 (or Early Termination). The NPI takes approximately 15 minutes to complete, depending on psychopathology.

### 8.10 Winterlight Speech Assessment

The Winterlight Speech Assessment is an analysis of spontaneous speech detecting cognitive impairment to be administered by a trained clinician at Screening (Visit 1), Visit 2, Visit 5, Visit 7, and Visit 10 (or Early Termination). The Winterlight Speech Assessment will be administered to English speaking (primary language) subjects and only in the US and UK. The assessment takes approximately up to 10 minutes to complete.

### 8.11 Saliva Collection

Saliva will be collected at the investigative sites at Screening (Visit 1), Visit 2, Visit 7, Visit 10 (or Early Termination), and Visit 11 (Safety Follow-up Visit). Saliva will be collected using provided kits following the procedure described in the Laboratory Manual.

Saliva samples collected at sites, and other oral fluids (SGP and buccal swabs) collected by the dentist, will be processed and shipped to the central laboratory according to the Laboratory Manual, for analysis of bacterial DNA and biomarkers.

Open Label Extension: Saliva will be collected at Visits OLE-4, OLE-6 (or Early Termination) and OLE-9 (OLE Safety Follow-Up Visit). **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

## 8.12 Oral Examination

An oral examination will be conducted at selected sites by a study dentist or trained dental hygienist, to assess for the presence of periodontitis during Screening (Visit 1). Subjects will have follow-up oral examinations at Visit 7, Visit 10 and Visit OLE-6 or Early Termination.

Visit 10/ET and Visit OLE6/ET oral examinations may be completed up to 8 days prior to Visit 10 (or ET), when applicable.

### 8.12.1 Oral Examination Procedures

#### 8.12.1.1 Oral Examination

The screening examination includes 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]), and assessment of Bleeding on Probing (BOP). All examination findings will be entered into the scoring tool, which will assist in the determination of the presence or absence of periodontitis. Please note that subjects who are otherwise eligible for this GAIN trial, but do not have at least 8 teeth, can still enroll in the study, but they are exempt from the oral examination component of the study.

#### 8.12.1.2 Measurement of Pocket Depths

Pocket depths will be measured for each tooth present with a periodontal probe with 1 mm gradations on 6 tooth surface sites (MB, B, DB, ML, L, DL) and will be rounded down to the nearest millimeter.

#### 8.12.1.3 Assessment of Bleeding on Probing

Bleeding on Probing on all 6 sites of each tooth will be recorded as present (“1”) or absent (“0”) immediately following the PD measures for each of the 4 probed sections of the dentition.

#### 8.12.1.4 Measurement of Gingival Margin Position

The distance of the gingival margin (GM) to the cementoenamel junction (CEJ) on each of the 6 sites on the examined teeth will be measured with a periodontal probe and rounded down to the nearest millimeter.

Clinical attachment levels will be calculated as a derived variable at the time of statistical analysis from the recorded measures of PDs and GM to the CEJ.

#### 8.12.1.5 Determination of the Presence of Moderate to Severe Periodontitis

Measurements of pocket depth (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 AL ≥ 3 mm, and ≥ 2 interproximal sites with PD ≥ 4 mm (not on same tooth)<br>Or<br>one site with PD ≥ 5 mm |
| Moderate Periodontitis | ≥ 2 interproximal sites with AL ≥ 4 mm (not on same tooth),<br>**Or**<br>≥ 2 interproximal sites with PD ≥ 5 mm (not on same tooth) |
| Severe Periodontitis | ≥ 2 interproximal sites with AL ≥ 6 mm (not on same tooth)<br>**And**<br>≥ 1 interproximal site with PD ≥ 5 mm |

AL will be calculated as algebraic sum of PD - GM (PD minus GM).

### 8.12.2 Oral Samples Collection

The following samples will be collected by the study dentist or dental hygienist or other appropriately trained site staff at Screening (Visit 1), Visit 7, Visit 10 and Visit OLE-6 or Early Termination (see Section 8.12.1.5). Oral samples will be sent to the central laboratory to be distributed to a specialty laboratory for biomarker analysis.

#### 8.12.2.1 Collection of Buccal Cells

The subject will be instructed to refrain from drinking or eating 30 minutes prior to sample collection. Sterile cytology brushes will be used to collect 4 samples by twirling the crush on the inner cheek away from the teeth and gum in the oral quadrants. The brushes will be sent to the clinical site laboratory for processing. The details of sample collection and processing procedures will be provided in the Laboratory Manual. Buccal cell collection may take place at the dental office or main research clinic.

#### 8.12.2.2 Collection of Subgingival Plaque (SGP)

The examiner will collect SGP samples using sterile endodontic paper point from teeth identified to have the maximum pocket depth by the study dentist. Multiple teeth can be used for sampling, and the same teeth used during the Screening visit will be used at the Follow-up visit in subjects with evidence of periodontitis. The

details of sample collection and processing procedures will be provided in the Laboratory Manual.

### 8.13 Physical Examination

A full physical examination will be performed at Screening (Visit 1). A full physical examination includes assessment of the following: head, neck and thyroid; eyes; ears; nose; throat; chest; lungs; heart; cervical lymph nodes; abdomen; skin; and the musculoskeletal and neurological systems. A symptom-based physical examination will be performed at all clinic visits after the Screening visit. Symptom-based physical examination of other organs and systems (e.g., breast, rectal, and genitourinary/pelvic exams) will be conducted only when clinically indicated and consented to by the subject. It is not necessary to collect information regarding well-healed surgical scars or tattoos.

### 8.14 Brain Imaging

Magnetic resonance imaging of the brain will be performed in all subjects at Screening (Visit 1). Subjects who have an absolute contraindication for MRI can have a Computed Tomography (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. Technical details of the MRI and CT scans will be provided in the Imaging Manual for the study.

### 8.15 Modified Hachinski

The Modified Hachinski ischemic scale will be utilized to differentiate Alzheimer's type dementia from multi-infarct dementia and will be administered at Screening (Visit 1). The Modified Hachinski will be administered by a trained clinician with a medical background.

### 8.16 Height, Weight, and Body Mass Index (BMI)

Height (cm) and weight (kg) will be measured and BMI will be calculated only at Screening (Visit 1). Only weight will be measured at Visit 10 (or Early Termination).

### 8.17 Vital Signs

Vital signs will include systolic and diastolic blood pressure, pulse, respiratory rate, and temperature. Blood pressure and pulse will be recorded first after the subject has been in a supine position for at least 5 minutes.

Vital signs will be recorded once at Screening (Visit 1), and once at each clinic visit; vital signs should be recorded at approximately the same time of day on each visit.

### 8.18 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be administered by a certified rater trained by the Research Foundation for Mental Health at all visits except at the Safety Follow-up Phone Calls after Visit 10 or Early Termination. Subjects will be assessed for both suicidal

behavior and suicidal ideation using the C-SSRS in order to confirm the absence of suicidal behavior or ideation with at least some intent to act on it (Folstein 1975; Columbia University Medical Center 2017).

In the event a subject has suicidal ideation or clinically significant depression, appropriate action will be initiated at the discretion of the Investigator and/or Medical Monitor.

Open Label Extension: The C-SSRS will be administered at all visits. **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

### 8.19 Laboratory Assessments

Follicle stimulating hormone will be measured at Screening (Visit 1) for peri-menopausal (irregular menstrual periods) or post-menopausal (no menstrual period for >12 months) female subjects. A urine pregnancy test will be conducted only in women of child bearing potential at Screening (Visit 1) and the End of Treatment or Early Termination Visit (Visit 10), and at other visits only if indicated. If the urine pregnancy test is positive, a serum pregnancy test will be performed to confirm pregnancy.

Open Label Extension: A urine pregnancy test will be conducted only in women of child bearing potential at the OLE End of Treatment or Early Termination Visit (OLE-6), and at any other visits only if indicated. **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

Serology will be performed at Screening (Visit 1). Serology will include HCV-Ab, HBsAg, and HIV 1 and 2.

Blood will be collected at Screening (Visit 1) to assess ApoE genotype.

Serum and whole blood will be collected to measure PBMCs and biomarkers at Visit 2, Visit 7, and Visit 10 (or Early Termination).

Safety laboratory tests will be performed at Screening (Visit 1), Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, and Visit 10 (or Early Termination) and the Safety Follow-up Visit (Visit 11). Safety laboratory tests will include chemistry, hematology, and urinalysis. See Appendix A: Clinical Laboratory Analytes for a complete list of analytes.

Open Label Extension: Safety laboratory tests will be performed at Visits OLE-1, OLE-2, OLE-3, OLE-4, OLE-5, OLE-6 (or Early Termination) and OLE-9 (OLE Safety Follow-Up Visit). **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

For more detail refer to the Laboratory Manual.

Per DMC recommendation (following the November 16, 2020 meeting), the following increased laboratory analyte testing (liver safety monitoring) is being implemented:

- Every 2 weeks for the initial 12 weeks

- Every 3 weeks as of Week 12 through Week 24
- Every 4 weeks as of Week 24 through Week 32
- Every 2 weeks for the initial 12 weeks (OLE)
- Every 3 weeks as of Week 60 through Week 72 (OLE)
- Every 6 weeks as of Week 72 through Week 84 (OLE)
  **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor

### 8.19.1 Monitoring of Laboratory Abnormalities

All laboratory values will be assessed by the Investigator to determine clinical significance. All abnormal laboratory values considered clinically significant by the Investigator will be recorded in the adverse event page of the eCRF. Abnormal laboratory values may be considered clinically significant if they are accompanied by signs/symptoms and/or require medical intervention. Abnormal laboratory values occurring during the clinical study are to be followed until repeat test results return to normal (or baseline), stabilize, or the subject is lost to follow-up.

## 8.20 Urine Drug Screen

A urine drug screen will be performed at Screening (Visit 1) and at Visit 2. The analytes will include opiates, cocaine, amphetamines, and barbiturates.

## 8.21 Blood Pharmacokinetic (PK) Evaluations

At Visit 2 a pre-dose trough sample will be drawn immediately prior to the AM dose. The subject will take their first dose at the site with the dose time and date recorded in the eCRF. A PK blood draw will be collected within the first 4 hours after the dose (at any time between 30 minutes to 4 hours post-dose).

At Visit 3, Visit 7, Visit 9, and Visit 10 (or Early Termination), subjects will return to the clinic prior to taking their AM dose. A pre-dose trough sample will be drawn at Visit 3 and Visit 7 immediately prior to the AM dose. The subjects will then take their dose of study drug on-site and the exact time of the dose ingestion will be recorded. A single post-dose sample will be drawn from each subject while on-site at the clinic at 60 minutes ± 30 minutes, and at 2 hours ± 30 minutes, respectively.

At Visit 9 and Visit 10 single post dose sample will be drawn from each subject while on-site at the clinic at 3 hours ± 30 min and at 4 hours ± 30 min, respectively. The exact time of the last dose of study drug will be recorded.

In all cases, the exact clock time of each PK sample will be recorded.

Plasma samples will be quantified for COR388 (and potential metabolites of interest). Data will be analyzed by a population pharmacokinetic approach to derive COR388 (and potential metabolites of interest) systemic exposure metrics. A

detailed population PK analysis plan will be generated and finalized prior to the PK analysis being initiated.

## 8.22 Cerebrospinal Fluid (CSF) Evaluations

The LP procedures, and medical care of the subject, will be administered as per clinical site standards including imaging prior to procedure, if applicable. Cerebrospinal fluid will be tested for measurement of bacterial DNA (*Pg*) using qPCR, biomarkers of AD, and gingipain activity. The details of sample collection and processing procedures will be provided in the Laboratory Manual. CSF samples will be sent to the central laboratory to be distributed to a specialty laboratory for biomarker analysis.

Assessments will be performed up to 7 days prior to study drug dosing at Baseline (Visit 2) and Visit 10 (or Early Termination).

## 8.23 Electrocardiograms (ECGs)

Standard 12-lead electrocardiograms (ECGs) will be performed at Screening (Visit 1), Visit 2, Visit 3, Visit 4, Visit 5, Visit 7, Visit 9, Visit 10 (or Early Termination), and Visit 11 (Safety Follow-up Visit). The Investigator will review ECGs for any changes from baseline. At Visit 2, Visit 3, Visit 7, Visit 9, and Visit 10 (or Early Termination), subjects will take their dose on-site and the exact time of the dose ingestion will be recorded. The time to maximum plasma concentration of COR388 ($T_{max}$) is approximately 1-1.5 hours. At visits when the subject takes their dose of study drug on-site, ECGs should be measured approximately 1-1.5 hours after dosing. At Visit 3 and Visit 7, ECGs will also be performed at trough (prior to dosing). ECGs will be reviewed by a cardiologist at the central ECG laboratory to identify any abnormalities and verify automatically calculated values of RR, PR, QRS, and QTc intervals. Clinically significant ECG events and abnormalities will be recorded as adverse events.

Open Label Extension: Standard 12-lead ECGs will be performed at Visits OLE-1, OLE-2, OLE-4, OLE-6 (or Early Termination) and OLE-9 (OLE Safety Follow-Up Visit). **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

## 8.24 Safety Monitoring Plan for Potential Drug Induced Liver Injury

This study is being conducted in compliance with FDA Guidance for Industry on Drug-Induced Liver Injury (DILI), which can be accessed at: https://www.fda.gov/media/116737/download.

If a study patient experiences any signs or symptoms of hepatic illness including loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin and eyes, light colored bowel movements or dark colored urine, or AST or ALT elevation at any time during subject's

participation in COR388-010 study, the following safety measures will be implemented:

1. Verify previous liver enzymes (ALT, AST) as well as any other liver-related lab parameters (e.g., INR, alkaline phosphatase, bilirubin (total, direct, indirect), etc.)
2. Perform detailed review of medical history, especially prior evidence of viral hepatitis, cholestasis and other associated conditions and ensure complete and accurate data entry in EDC.
3. Perform detailed review of concomitant medications including OTC or herbal products and ensure complete and accurate data entry in EDC.
4. Contact the Study Medical Monitor and report on the clinical subject status.
5. Arrange a confirmatory testing within 48-72 hours and repeat until the abnormality is stabilized or resolved.
6. Between V4/Week 6 – V8/Week 32 and OLE-2/Week 54 – OLE-5/Week 84 subject must have LFT testing performed at each per protocol required visit. If such testing is not performed at any of the visits, the IP administration must be halted until the testing is done.
7. If a patient reports any gastrointestinal symptoms at any time during the study, safety laboratory testing must be performed promptly (stat labs).

**If AST or ALT is >2x ULN – perform weekly testing until the abnormality resolves.**

**If AST or ALT is >3x ULN, please continue as follows:**

1. Ensure repeat testing (ALT, AST, ALP, GGT, bilirubin, eosinophils (differential count) 2-3 times weekly until baseline levels are re-established or another frequency is agreed upon with the medical monitor.
2. Rule out acute viral hepatitis (A, B, C, D, and E) and arrange for an abdominal ultrasound/MRI/CT.
3. Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin, auto-antibodies, bile salts/acids).
4. Tests for infection with cytomegalovirus, Epstein-Barr virus, and herpes simplex virus, if fever, rash or lymphadenopathy occur.
5. Serum anti-nuclear antibody, anti-smooth muscle antibody, and IgG concentrations.
6. Consider gastroenterology or hepatology consultations.
7. Please ask the patient to:
   - *Give detailed history of any symptoms and prior or concurrent diseases (please ask with same frequency as repeated blood tests are performed).*
   - *Confirm concomitant drug use (incl. non-prescription drugs, herbal supplements, etc.)*
   - *Provide information about any alcohol use*

- *Provide information about any exposure to environmental chemical agents.*

**Treatment should be stopped if:**

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia

**Rechallenge should not be attempted if:**

- ALT or AST >5xULN
- ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia

# 9 ADVERSE EVENT REPORTING

Throughout the course of the study, all adverse events (AEs) will be monitored and recorded on an AE eCRF, including the AE's description, start and end date, seriousness, severity, action taken, and relationship to the investigational product. If AEs occur, the first concern will be the safety of the study subjects. All AEs will be followed until resolved or stable and the outcome documented on the eCRF.

Open Label Extension: Adverse events will be monitored at all visits and phone calls. **NOTE:** Effective 16 February 2021, the OLE portion of the study was terminated by the Sponsor.

## 9.1 Definitions and Criteria

### 9.1.1 Adverse Events

Per ICH E2A: An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They should be recorded as treatment of the AEs.

### 9.1.2 Serious Adverse Events

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse; malignancy tumors [histologically different from primary tumor])

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

In this study, hospitalization is defined to be at least 24-hours in duration.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as “serious,” which is based on the outcome or action associated with events, as described above. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

### 9.1.3 Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction (ADR) is a reaction for which the nature or severity is not consistent with the applicable product information (IB, Package Insert for marketed products). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant

information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the IB would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Guidance on reporting AEs and SAEs is described in Section 9.2.

### 9.1.4 Abnormal Laboratory Values

Any abnormality in a laboratory value that is new in onset or which has worsened in severity or frequency from the baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the eCRF:

- Requires therapeutic intervention or diagnostic tests;
- Leads to discontinuation of investigational product;
- Has accompanying or inducing symptoms or signs; and/or
- Is judged by the Investigator as clinically significant.

### 9.1.5 Assessing Intensity and Relationship

All AEs will be assessed on 2 descriptive parameters: intensity and relationship to the investigational product:

- Intensity refers to the severity of an event and references impact on a subject's functioning.
- Relationship refers to the likelihood that the event being assessed was caused by the investigational product.

**Intensity**

Each AE will be classified according to the following criteria:

| | |
|---|---|
| Mild: | The AE does not interfere in a significant manner with the subject's normal level of functioning. |
| Moderate: | The AE produces some impairment of functioning but is not hazardous to the subject's health. |
| Severe: | The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health. |

**Relationship**

Each AE will be assessed as to its relationship to the investigational product, based on the following criteria. Although the attribution by the Investigator will be collected for reported events, for analytic purposes a temporal association with the use of the investigational product will be assumed sufficient for at least plausible association.

| | |
|---|---|
| Not related: | No causal relationship exists between the investigational product and the AE, but an obvious alternative cause exists, e.g., the subject's underlying medical condition or concomitant therapy. |
| Possibly related: | A connection with the administration of the investigational product appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the investigational product; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the investigational product. |
| Related: | There is a reasonable/plausible possibility that the AE may have been caused by the investigational product. |

When assessing the relationship to the investigational product, the following criteria will be considered:

- Positive re-challenge (restart of IP dosing following dosing interruption);

  Note: In this study re-challenge of IP will not be allowed if IP dosing was discontinued for IP-related safety reasons e.g. when a DILI protocol is triggered and/or due to an AE that was assessed as possibly or probably related to the IP.

- Positive de-challenge (resolution upon stopping suspect the investigational product, in absence of other intervention or treatment);
- Known class effect;
- Biological plausibility; and
- Lack of alternative explanation—concomitant drug or disease.

## 9.2 Reporting Procedures and Requirements

### 9.2.1 Adverse Events

Adverse events (AEs) occurring from when the subject signs the ICF until the last study event will be recorded. Any AEs occurring before the start of treatment (i.e., before the first dose of the investigational product) will be recorded in the medical

history. Also, the sign, symptom, or disease present before starting the treatment period are only considered AEs if they worsen after starting the treatment period.

If the Investigator detects an AE in a study subject after the last scheduled follow-up visit and considers the event possibly related or related to prior study treatment, the Investigator should report it to the Sponsor/ Contract Research Organization (CRO).

The Investigator should report all AEs on the AE page(s) of the eCRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (e.g., “common cold” or “upper respiratory infection” rather than “runny nose, cough, mild fever”) and should be described with the attributes described in Section 9.1.5.

### 9.2.2 Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 9.1.2). If the AE is considered serious, the Investigator should report this event to the Sponsor and CRO as outlined below and also to the IRB/IEC according to its standard operating procedures.

If the Investigator detects an SAE in a study subject after the last scheduled follow-up visit, and considers the SAE related or possibly related to prior study treatment, the Investigator should report it to the Sponsor and CRO.

All information about SAEs will be collected and reported via the SAE form and sent by e-mail message or facsimile (contact information will be contained in the Investigator site file). The Investigator should send the initial report within 24 hours of becoming aware of the SAE. At minimum, the initial report should include the following information:

- Event;
- Study code;
- Subject number, initials, and date of birth;
- Investigational product; and
- Reporter name and contact information.

In the case of a “minimum report” (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available, but no later than 7 calendar days after the date of the initial report. Each SAE should be followed up until resolution or stabilization and for reported deaths, the Investigator should supply Sponsor/ CRO and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

The original SAE form should be kept at the study site. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

Serious adverse events that are ongoing at Safety Follow-up Visit 11 of OLE-9 should be followed until resolved or stabilized.

## 9.3 Procedures for Documenting Pregnancy During Study

If a female subject becomes pregnant during the study, the Investigator will notify Sponsor/CRO immediately following 9.1.5 confirmation. The Investigator will also: (1) notify the subject's physician that the subject may have been treated with COR388 HCl and (2) follow the progress of the pregnancy to term and document the outcome of the pregnancy. Subjects who become pregnant during the study will not be eligible for any further study treatments. Pregnancy outcome information should be forwarded to Sponsor/CRO when available. The Investigator and Cortexyme will determine, on a case-by-case basis, whether the subject will continue in the study and, if so, which study measures will be collected.

## 9.4 Treatment of Investigational Product Overdose

There is currently no information available regarding potential overdosing of COR388 HCl. Based on the effects observed in preclinical safety and toxicology studies, adverse effects that could be anticipated from exposure to overdoses of COR388 HCl are cardiovascular, CNS, and respiratory effects.

As there are no data available with regard to overdose of COR388 HCl in humans, there is no specific treatment to be used in the event of an overdose. Investigators should use their clinical judgment in treating cases of overdose as dictated by the subject's clinical status.

In the event of a suspected overdose, and if in the opinion of the Investigator the patient does not require emergency clinical treatment, the Investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Have the subject come to the clinic as soon as possible to draw blood for clinical laboratory testing.
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities and ensure appropriate clinical management. Overdose in the absence of other AEs will not be reported as an AE in its own right.
- Document the quantity of the excess dose, as well as the time of administration of the overdose, in the eCRF.
- Subjects should be observed closely in a medical facility where appropriate supportive care is available, if required.

# 10 QUALITY CONTROL AND QUALITY ASSURANCE

## 10.1 Bioanalytic Method Validation

Bioanalytic methods employed in this study have been validated according to existing standard operating procedures of the Sponsor and of the laboratory performing the analysis, in compliance with relevant regulation.

# 11 STATISTICAL AND ANALYTICAL PLANS

## 11.1 General Considerations

The statistical analyses are described in this section. Further details will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to database lock and unblinding for the interim analysis. Any deviations from the analyses described below will be included in the SAP.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations (SDs), medians, maximum, minimum, and number of subjects. Categorical data will be summarized by counts and percentages.

## 11.2 Determination of Sample Size

The study will have an adaptive design that allows for potential adjustment in sample size and evaluation of efficacy 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% will drop out prior to 48 weeks. 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. As originally planned, with 573 subjects randomized, an expected 10% discontinuation rate, and a single primary outcome, a total of 172 subjects per treatment group would provide approximately 90% power to detect a 2.5-point difference between the active treatment group compared to placebo with respect to change from baseline on the ADAS-Cog 11, assuming a standard deviation of 7.1, respectively at a significance level (alpha) of 0.05 using a two-sided test. The ADCS-ADL was added as a co-primary outcome, with assumptions of a 3.9-point difference between the active treatment group compared to placebo with respect to change from baseline on ADCS-ADL, assuming a standard deviation of 10.5, providing approximately 95% power on this outcome

measure, with approximately 90% power for the overall co-primary outcomes, depending on their correlation.
These results assume that 2 sequential tests will be made using the Lan-DeMets spending function 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. As discussed by Chen et al 2004, the sample size re-estimation procedure based on promising zone 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.

## 11.3 Final Analysis

### 11.3.1 Analysis Populations

- Intent-To-Treat Population (ITT): The ITT population will include all subjects who are randomized regardless of whether or not they took study drug. This population will serve as the basis for all 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.

- 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 sensitivity 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 receive.

### 11.3.2 Efficacy Analysis

#### 11.3.2.1 Primary Efficacy Analysis

The co-primary endpoints are the mean change from baseline in ADAS-Cog 11 at the end of the study (average of Weeks 40 and 48), and the mean change from baseline in the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) at the end of the study (average of Weeks 40 and 48).

Each of the coprimary endpoints 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, study visit, site/country, treatment group by study visit interaction as fixed effects, and baseline MMSE (average of the last two non-missing assessments

collected prior to or at the day of first dose of the IP), ApoE4 status, and acetylcholinesterase inhibitor and/or memantine usage at baseline as factors with baseline score as a covariate using the ITT population. The analysis will be based on unstructured covariance matrix to model the within-subject errors. A Kenward-Roger approximation will be used for the denominator degrees of freedom.

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the observed values for each of the coprimary 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.

The Type I error for the interim and final analysis will be adjusted using the Lan-DeMets spending function. Detailed of the adjustment is presented in Section 11.3.2.3 and in the SAP.

Treatment comparisons of 40 mg and 80 mg COR388 HCl to placebo will be adjusted using Benjamini-Hochberg multiplicity adjustment procedure (Benjamini and Hochberg, 1995 and Benjamini and Yekutieli, 2001). Both treatment comparisons, 40 mg (low dose) and 80 mg COR388 HCl (high dose) to placebo are considered of equal interest.

#### 11.3.2.1.1 Sensitivity Analyses

The following sensitivity analyses will be performed on each of the co-primary endpoints:

- Repeat above analysis using the PP population.
- Impute missing values using a last z-score carried forward method (converted back to the original scale) and analyze the primary endpoint (Average of Weeks 40 and 48 only) using analysis of covariance (ANCOVA) with fixed effects of treatment group, ApoE4 status, acetylcholinesterase inhibitor and/or memantine usage, site/country and baseline MMSE with baseline score as a covariate.

- Pattern mixture model:
  The pattern-mixture model approach uses a control-based pattern imputation (Ratitch and O'Kelly, 2011). With this approach, subjects who discontinued from the COR388 HCl 80 mg or COR388 HCl 40mg treatment group will be assumed to follow a similar outcome trajectory as subjects from the placebo (control) arm and subjects who discontinued from placebo (control) treatment are modeled as completers within their own arm (MAR within control arm). That is, the imputation model for the missing observations in the active treatment groups are constructed not from the observed data in the corresponding active treatment group but rather from the observed data in the placebo treatment group. This model is also the imputation model that will be used to impute missing observations in the placebo treatment group. This will

be implemented by utilizing the MONOTONE REG statement of SAS® PROC MI with the option nimpute=5.

Pattern mixture model tends to 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. The results of this imputation method will primarily be used to assess the potential bias of the main model estimates due to dropout by comparing the estimates between the primary and sensitivity models.

Additional subgroups including gender, demographic, and other baseline characteristics may be performed. Further details will be given in the SAP.

#### 11.3.2.2 Secondary Endpoint Analyses

Secondary endpoints will be analyzed for the ITT population only.

The analysis of secondary endpoints will use the same methodology as that for the primary endpoint analysis but adjusting for corresponding baseline value as a covariate. Treatment comparisons of 40 mg and 80 mg COR388 HCl to placebo for the secondary endpoints at 24-week or 48-week will be performed only if both co-primary endpoints compared to placebo are statistically significant. Otherwise, secondary endpoints will be presented using descriptive statistics

#### 11.3.2.3 Multiplicity

To control for 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 (i.e., 24 weeks ADAS-Cog and CDR-SB as co-primary endpoints) 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. Because of the changes in co-primary endpoint at 48 weeks (i.e., CDR-SB 24-week replaced by ADCS-ADL at 48-week and ADAS-Cog 24-week replaced by ADAS-Cog 48-week), 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 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 48-week.

At both the interim analysis at 24 weeks and final analysis at 48 weeks, to adjust for comparison between placebo and each of the two doses, Benjamini-Hochberg multiplicity adjustment procedure (Benjamini and Hochberg, 1995 and Benjamini and Yekutieli, 2001) will be used. Both treatment comparisons, 40 mg (low dose) and 80 mg COR388 HCl (high dose) to placebo are considered of equal interest.

Treatment comparisons of 40 mg and 80 mg COR388 HCl to placebo for the secondary endpoints at 24-week or 48-week will be performed only if both co-

primary endpoints compared to placebo are statistically significant at the level of approximately 0.005 or 0.0456 for the interim analysis and final analysis, respectively. Otherwise, secondary endpoints will be presented using descriptive statistics.

#### 11.3.2.4 Exploratory Endpoints

Exploratory endpoints will be analyzed for the ITT population only. No adjustment for multiplicity will be done.

Further details of the analyses to be performed will be provided in the SAP.

### 11.3.3 Safety Analysis

#### 11.3.3.1 Adverse Events

Adverse events will be coded by Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) classification.

A treatment-emergent adverse event (TEAE) is defined as any AE that has an onset on or after the first dose of study drug, or any pre-existing condition that has worsened on or after the first dose of study drug. The incidence of TEAEs, treatment-related TEAEs, SAEs including deaths, TEAEs that lead to discontinuation of investigational product, and TEAEs by maximum severity and relationship to study drug will be summarized by MedDRA system organ class, PT, and treatment group.

To assess the potential for abuse associated with the administration of COR388 HCl, a systematic review of TEAE terms suggestive of the potential for abuse will be conducted for all clinical studies in subjects who received at least 1 dose of COR388 HCl and a summary of this information will be included in the regulatory submission. As a general framework for data collection and analysis we will use the overall abuse flag terms in the FDA Guidance (2017).

Since the target patient population are elderly, have substantial comorbidity and are often on other medications, a careful assessment and documentation of adverse event causality will be made in order to ensure that false positive TEAE signals for abuse are not generated. For example, dizziness and sedation or sleepiness are common clinical events in elderly patients with Alzheimer's disease.

Since to date no abuse related TEAE attributable to COR388 HCl have occurred, focus will be on a restricted set of index events for which narratives will only be prepared where the causality relationship to COR388 HCl is probable or definite. Information included in the narratives will consist of time to onset/offset, time course of severity, all concurrent events, concurrent medications, and time of onset of events relative to ingestion of COR388 HCl.

The index TEAEs will include:
• Any reports of altered perception or hallucinations
• Dizziness
• Euphoric mood
• Feeling drunk
• Feeling of relaxation
• Sedation
• Somnolence

#### 11.3.3.2 Laboratory Data

Laboratory data (hematology, blood chemistry, and urinalysis parameters) will be presented for each treatment group using descriptive statistics, including mean and mean change from baseline values at each scheduled time point. Shift tables will display numbers of subjects with normal/abnormal values at baseline versus post-treatment. The frequency of laboratory abnormalities will be tabulated. By-subject data listings will flag laboratory values that are outside normal reference ranges or markedly abnormal findings.

#### 11.3.3.3 Vital Signs

Descriptive statistics for observed values and change from baseline in vital sign parameters [blood pressure (systolic and diastolic), body temperature, pulse, and respiratory rate] will be presented by visit and treatment group.

#### 11.3.3.4 Electrocardiograms

Descriptive statistics for observed values and change from baseline in (continuous) ECG parameters (e.g., RR, PR, QTc) will be presented by visit and treatment group. Shift tables in relation to overall interpretation (Normal, Abnormal Not Clinically Significant [NCS] and Abnormal Clinically Significant [CS]) from baseline to each post-baseline visit will be presented.

#### 11.3.3.5 Other Safety Assessments

The C-SSRS will be summarized at each visit by treatment using descriptive statistics.

Abnormal physical examinations and MRI results will be summarized descriptively by visit and treatment group.

### 11.3.4 Demographic and Baseline Characteristics

Treatment groups will be compared with respect to subject demographics, and baseline characteristics will be summarized using descriptive statistics. No formal statistical analysis tests will be performed.

### 11.3.5 Interim Analysis

The purpose of the interim analysis is to determine if COR388 HCl is efficacious and conduct a sample size re-estimation. One unblinded interim analysis will be performed after approximately 300 subjects have completed 24 weeks of treatment. The DMC will review unblinded data for the mean change from baseline in ADAS-Cog 11 and the mean change from baseline in the CDR-SB post 24 weeks of treatment. Both treatment comparisons will be assessed at the interim analysis: 40 mg COR388 HCl and 80 mg COR388 HCl vs. placebo for the two co-primary endpoints (i.e., mean change from baseline in ADAS-Cog 11 and mean change from baseline in CDR-SB at Week 24). Analyses will be performed as specified in the approved final study SAP.

The DMC should return to the Sponsor one of four recommendations as follows:

1. Stop the study 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;

2. Stop 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;

3. Continue with no sample size adjustment; or

4. Continue with an appropriate sample size adjustment

Interim comparative data will be most securely protected from inadvertent or inappropriate access by the Sponsor. Sponsor will remain blinded to all information except the DMC recommendations.

### 11.3.6 Pharmacokinetic Analysis

Plasma levels of COR388 will be determined from blood samples collected at Visit 2, Visit 3, Visit 7, Visit 9, and Visit 10 (or Early Termination).

Descriptive statistics (sample size, mean, SD, minimum, median, and maximum) will be calculated for all results. Geometric mean and geometric coefficient of variation (CV)% will also be calculated for PK parameters.

## 12 STUDY MANAGEMENT

### 12.1 Regulations and Guidelines

The study will be performed in accordance with this protocol, United States IND regulations (21 Code of Federal Regulations [CFR] 312) or local national laws (as applicable), ICH guidelines for Good Clinical Practice, and the most recent

guidelines of the Declaration of Helsinki. These guidelines are on file at the Sponsor and/or CRO.

## 12.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IRB or IEC. Approval is required for the study protocol, investigational drug brochure, protocol amendments, ICFs, subject information sheets, and advertising materials. No investigational product will be shipped to a site until written IRB/IEC authorization has been received by the Sponsor or its representative.

## 12.3 Discontinuation of the Study by the Sponsor

The Sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation and investigational product pertaining to the study must be returned to the Sponsor or its representative.

## 12.4 Study Documentation

By signing a copy of Form FDA 1572 or other country-specific regulatory forms, the Principal Investigator acknowledges that he/she has received a copy of the IB on COR388 HCl and assures the Sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572 and other country-specific forms. No changes in this protocol can be made without the Sponsor’s written approval.

## 12.5 Study Monitoring and Auditing

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the Sponsor or its representative. Monitoring will include remote (virtual) data reviews, personal visits, and telephone communication to assure that the investigation is conducted according to the protocol, standard operating procedures, Guidelines of Good Clinical Practice, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. On-site and remote review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject. Note that a variety of original documents, data, and records will be considered as source documents in this trial. Procedures for handling source documents remotely will be described in the Clinical Monitoring Plan. The eCRF itself is not to be used as a source document under any circumstances.

Medical advisors and Clinical Research Associates (CRAs) or assistants may request to witness subject evaluations occurring as part of this protocol. The Investigator and appropriate personnel will be periodically requested to attend

meetings/workshops organized by the Sponsor to assure acceptable protocol execution. The study may be subject to audit by the Sponsor or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities, for remote and on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

## 12.6 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established to review accumulating study data to monitor the safety of subjects enrolled in COR388-010 on an ongoing basis and review the interim analysis (see Section 11.3.5). All members will be independent of the study (e.g., not a participating site employee, Cortexyme employee, etc.).

The DMC will review data on a regular basis. After reviewing the safety data, the DMC may make a recommendation to continue the study with or without modification or terminate the study. The DMC Charter defines all DMC responsibilities, functions, membership, meeting structure, communications, DMC SAP, and rules for decision making.

## 12.7 Retention of Records

The Investigator must arrange for retention of study records at the site. The nature of the records and the duration of the retention period must meet the requirements of the relevant regulatory authority. In addition, because this is an international study, the retention period must meet the requirements of the most stringent authority. The Investigator should take measures to prevent accidental or premature destruction of these documents.

## 12.8 Use of Study Findings

By signing the study protocol, the Investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the Sponsor or its representative.

## 12.9 Publications

As a multicenter trial, the Sponsor intends to publish clinical data from all centers participating in the investigation. A publication committee selected by the Sponsor will submit draft manuscripts to all participating investigators for their comments. In conformity with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published by the International Committee of Medical Journal Editors (see

discussion in Kassirer & Angell, 1991), investigators whose contribution consists solely in the collection of data will not be named individually as authors. Rather, those investigators will receive a collective authorship as the “COR388 Study Group” and will be identified in a note.

Individual investigators and/or their associates subsequently may publish additional findings of this study in scientific journals or present them at scientific meetings, provided that the Sponsor is given ample opportunity to review any proposed abstract, manuscript, or slide presentation before its submission. This review is required to ensure that the Sponsor is aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use.

### 12.10 Subject Privacy

To maintain subject confidentiality, all eCRFs, study reports, and communications relating to the study will identify subjects by initials and assigned subject numbers. As required by federal regulations, the Investigator will allow Cortexyme and/or the CRO CRA access to all pertinent medical records in order to allow for the verification of data gathered in the eCRFs and for the review of the data collection process. The FDA (or other regulatory authority) may also request access to all study records, including source documentation for inspection.

As applicable, in accordance with Health Insurance Portability and Accountability Act (HIPAA) and associated privacy regulations, a subject authorization to use personally identifiable health information may be required from each subject prior to research activities. This authorization document must clearly specify what parties will have access to a subject’s personal health information, for what purpose, and for how long.

### 12.11 Amendments to the Protocol

Any amendments to the study protocol will be communicated to the investigators by the CRO or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, and, where appropriate, competent regulatory authority approval prior to implementation, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days and in the countries outside of the United States according to the national regulation.

Any departures from protocol must be fully documented in the source documentation and in a protocol deviation log.

### 12.12 Case Report Form Completion

Electronic CRFs (eCRFs) will be employed for this study. Completed eCRFs for this study will be forwarded to the Sponsor or its representative, where editing and

construction of a quality-assured database will occur. Data will be quality checked, double-entered, and electronically verified before entry into the database. Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties. The statistical analysis of these data will be performed by the Sponsor or its representative. All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary. Data management details will be outlined in a separate data management plan.

## 12.13 Removal of Subjects from Therapy or Assessment

Liver Safety Monitoring (laboratory analyte testing) must be performed at each study visit within the prespecified visit window (see Table 1 and Table 2, Schedule of Evaluations) OR the study drug dosing must be temporarily halted until the testing is done.

Subjects who discontinue IP dosing for IP-related safety reasons will not be permitted to resume IP treatment and must be followed until the safety concern (e.g. transaminase elevations) or an existing AE has stabilized or resolved/returned to baseline. At that time subject's participation in the study must be terminated early and V10/ET procedures must be performed. Subjects should remain in the study through final 6-weeks safety follow up period which ends with a final study visit.

A subject will be considered to have completed the study when he or she completes Visit 11. If a subject is discontinued at any time after randomization into the study, the Investigator will make every effort to follow the subject and complete the Visit 10/Early Termination assessments.

A termination electronic case report form (eCRF) page should be completed for every subject who receives investigational product, whether or not the subject completes the study. The reason for any early discontinuation should be indicated on this form. The primary reason for a subject discontinuing early should be selected from the following standard categories of early termination:

- *Adverse Event (Adverse Reaction)*: Clinical or laboratory events occurred that, in the medical judgment of the Investigator for the best interest of the subject, are grounds for discontinuation. This includes serious and nonserious adverse events (AEs) regardless of relation to the investigational product.

- *Death:* The subject died.

- *Withdrawal of Consent*: The subject desired to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. If the subject gave a reason for withdrawing, it should be recorded in the eCRF.

- *Protocol Violation*: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits). The violation necessitated early discontinuation from the study.

- *Lost to Follow-Up*: The subject stopped coming for visits and study personnel were unable to contact the subject.

- *Other*: The subject was discontinued for a reason other than those listed above, such as theft, loss of investigational product, or termination of study by Sponsor.

## 12.14 End of the Study

For regulatory purposes, the definition of the end of the study is database lock.

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# APPENDIX A: CLINICAL LABORATORY ANALYTES

## Safety Chemistry Panel

| | |
|---|---|
| Alanine transaminase | Albumin |
| Alkaline phosphatase | Amylase |
| Aspartate transaminase | Bicarbonate |
| Gamma-glutamyl transferase | Calcium |
| Blood urea nitrogen | Creatinine kinase |
| Chloride | Estimated glomerular filtration rate |
| Creatinine | Glucose |
| Inorganic phosphorus | HbA1c |
| Lipase | Lactate dehydrogenase |
| Sodium | Potassium |
| Total protein | Total bilirubin |
| Uric acid | Direct bilirubin |
| Magnesium | Indirect bilirubin |

## Hematology

| | |
|---|---|
| White blood cell count and differential [1] | Hemoglobin |
| Red blood cell count | Mean corpuscular volume |
| Platelets | Mean corpuscular hemoglobin |
| Hematocrit | Mean corpuscular hemoglobin concentration |
| Prothrombin time | Partial thromboplastin time |
| | Vitamin B12 |

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

## Immunochemistry

Thyroid Function [T4, T4 (Free), T3, T3 (Free), TSH]
Syphilis

## Endocrinology

Follicle-stimulating hormone [1]

1. Follicle-stimulating hormone in in peri-menopausal (irregular menstrual periods) or post-menopausal (no menstrual period for >12 months) female subjects at screening.

## Serology

| | |
|---|---|
| Hepatitis B surface antigen | Hepatitis C virus antibodies |
| Human immunodeficiency virus 1 and 2 antibodies | |

## Urinalysis

| | |
|---|---|
| Bilirubin | Blood |
| Glucose | Ketones |
| Leukocyte esterase | Microscopy [1] |
| Nitrite | pH |
| Protein | Specific gravity |
| Urobilinogen | |

1. Microscopy will be performed only as needed based on positive dipstick test results.

## APPENDIX A: CLINICAL LABORATORY ANALYTES (CONTINUED)

### Drug Screen

| | |
|---|---|
| Opiates | Amphetamines |
| Cocaine | Barbiturates |

### Cerebrospinal Fluid Biomarkers

| | |
|---|---|
| *Porphyromonas gingivalis* DNA qPCR | Total tau protein |
| Neuroinflammation panel | Phosphorylated tau protein |
| Amyloid beta peptides | Exploratory AD biomarkers |

DNA = deoxyribonucleic acid; qPCR = quantitative polymerase chain reaction.

### Saliva/Oral Fluids Biomarkers-

*Porphyromonas gingivalis* and oral microbiome
DNA qPCR and biomarkers

DNA = deoxyribonucleic acid; qPCR = quantitative polymerase chain reaction.

### Blood Biomarkers

*Porphyromonas gingivalis* biomarkers in serum and PBMCs
Neuroinflammatory markers

PBMCs = Peripheral blood mononuclear cells.

### Liver Safety Monitoring

| | |
|---|---|
| Alanine transaminase | Direct bilirubin |
| Aspartate transaminase | Indirect bilirubin |
| Gamma-glutamyl transferase | Eosinophils (% and Abs) |
| Alkaline Phosphatase | Prothrombin Time as INR |
| Total Bilirubin | |

### Extended Liver Safety Testing for AST or ALT >3x ULN

INR
Direct bilirubin
Auto-antibodies
Bile salts/acids
Cytomegalovirus
Epstein-Barr virus
Herpes simplex virus
Anti-nuclear antibodies
Anti-smooth muscle antibodies
Immunoglobulin G

See liver safety monitoring procedures in Section 8.24