16.1.9 Documentation of Statistical Methods

A copy of version 1.0 of the SAP, dated 16 Mar 2020 is provided.

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2a, Open-label, Multiple Dose, Safety, Pharmacokinetic and Biomarker Study of PTI-125 in Mild-to-moderate Alzheimer's Disease Subjects
Study Number:	PTI-125-03
Investigational Drug:	PTl-125
Indication:	Treatment of Alzheimer's disease
Investigators:	Multicenter
IND Number:	
EudraCT Number:	
Sponsor:	Cassava Sciences, Inc. 7801 N. Capital of Texas Hwy, Ste. 260 Austin, TX 78731
Plan Version:	16 March 2020 (1.0)
Plan Prepared by:	Inka Leprince, MS Statistical Consultant PharmaStat, LLC

CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

Study PTI-125-03

Final 1.0

A Phase 2a, Open-label, Multiple Dose, Safety, Pharmacokinetic and Biomarker Study of PTI-125 in Mild-to-moderate Alzheimer's Disease Subjects

Approval:

Michael R Marsman — Digitally signed by Michael R Marsman Date: 2020.03.17 10:32:40 -05'00'

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
Aβ	amyloid beta
AD	Alzheimer's disease
AE	adverse event
ANOVA	analysis of variance
ATC	anatomical/therapeutic/chemical
AUC	area under the curve
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BID	twice daily
BLQ	below the lower limit of quantification
BMI	body mass index
$C_{1/F}$	apparent oral clearance
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CM	concomitant medication
C_{last}	concentration of the last quantifiable drug concentration
C_{max}	maximum plasma concentration
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	percent coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
GLSMR	geometric least squares mean ratio
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL-1β	interleukin 1 beta
IL-6	interleukin 6
IQR	interquartile range
LS	least squares
λ_Z	elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination

Abbreviation	Description
mTOR	mammalian target of rapamycin
PK	pharmacokinetic(s)
PTI-125	small molecule drug candidate to treat AD
PTI-125DX	blood-based diagnostic/biomarker
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SOC	system organ class
TEAE	treatment-emergent adverse event
TLFs	tables, listings and figures
$T_{1/2}$	terminal elimination half-life
T_{last}	time to the last quantifiable concentration
T_{max}	time to C_{max}
TNFα	tumor necrosis factor alpha
Vz/F	apparent volume of distribution
YKL40	chitinase-like protein 1

2 REVISION HISTORY

Version	Date	Document Owner	Revision Summary
1.0	16Mar2020	Inka Leprince	First version

3 RELEVANT DOCUMENTS: PROTOCOL, AMENDMENTS AND CASE REPORT FORMS

Original Protocol (30 October 2018)
Amendment #1 (31 October 2018)
Amendment #2 (05 February 2019)

Case Report Form Version 1.0 (29 November 2018)
Case Report Form Version 2.0 (11 July 2019)

4 PURPOSE OF THE ANALYSIS PLAN

This statistical analysis plan (SAP) pre-specifies the statistical analysis methods for supporting the completion of the clinical study report (CSR) of Study PTI-125-03 for investigational product PTI-125, a novel drug candidate designed to treat and slow the progression of Alzheimer's disease (AD). This SAP will be used to analyze the safety data collected during the study. Pharmacokinetic (PK) data and biomarker data will be analyzed by third parties. Therefore, the detailed data analysis methods for PK and biomarker will be documented separately from this plan. The planned analyses identified in this SAP may be included in regulatory submissions and/or future manuscripts.

The analysis methods described in this plan are considered *a priori*, in that they have been defined prior to clinical database lock. Exploratory analyses, which are not defined in this SAP, may be performed to support the clinical development program. Any post-hoc or unplanned analyses that are performed for the CSR, but not defined in this SAP, will be documented in the CSR. Changes from the planned analyses stated in the study protocol are described in Section 15. Should the SAP and the protocol be inconsistent with respect to any further planned analyses, the language of the SAP is governing.

5 STUDY OBJECTIVES

The objectives of this study are to investigate the safety, pharmacokinetics and effect on biomarkers of PTI-125 following a 28-day repeat-dose oral administration in mild-to-moderate AD subjects, 50-85 years of age, within a Mini-Mental State Examination (MMSE) range of ≥ 16 and ≤ 24.

6 STUDY DESIGN

6.1 Overall Study Design

This is a Phase 2a, multi-center, open-label study. A total of thirteen (13) subjects were enrolled in this study to receive 100 mg PTI-125 twice daily (BID). Five (5) study centers participated in this study.

Screening Period: Eligible subjects will be screened within 30 days prior to the first administration of the study drug (PTI-125). Eligible subjects will be enrolled into the study if they: are 50 to 85 years of age; have a clinical diagnosis of dementia due to possible or probable AD; and have a MMSE score of 16 to 24 at screening. The full list of inclusion and exclusion criteria can be found in the PTI-125-03 protocol, Section 5. Once all other inclusion and none of the exclusion criteria are met, a cerebrospinal fluid sample will be collected for pre-dose biomarkers and for the inclusion criterion of a Tau/Aβ Ratio that indicates AD (i.e., ≥ 0.30). Assessments of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD[1]) and Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered during the screening period for cognitive/behavioral data.

Treatment Period: Subjects will receive study drug (PTI-125) on an inpatient basis (i.e., in the clinic) on Days 1 and 2. Subjects will receive study drug on an outpatient basis for the remaining 26 days of the 4-week Treatment Period. The dose of study drug will be fixed for the 4 weeks of the Treatment Period at 100 mg PTI-125 BID, dispensed as coated tablets to be taken orally. During the 4-week Treatment Period, subjects will attend four study (clinic) visits (Days 1, 7, 14, 28) for periodic collection of blood and urine for safety, PK, and biomarker data.

Day 28 will include a CSF draw for biomarker data and assessments of the BEHAVE-AD for cognitive/behavioral data (see Table 1 for the schedule of assessments).

Follow-up Period: Subjects will return to the clinic on Day 29 for a Follow-up visit which will include PK assessment (24 hours after the last dose of study medication), clinical laboratory tests, and other safety assessments.

The maximum duration of Study PTI-125-03 per subject is expected to be 59 days (i.e., a maximum of 30-day Screening Period, a 4-week Treatment Period, and a 1-day Follow-up visit). Assessments and procedures for evaluation of safety, PK, and biomarkers will be conducted per the protocol-specified schedule (see Table 1).

Table 1 Study PTI-125-03 Protocol Schedule of Events (Protocol Version September 18, 2018)

Study Activity	Period	Screening	Treatment					Follow-up
	Visit Name		D1	D2	D7	D14	D28[a]	
	Timing	Days -30 to -1[b]	Day 1	Day 2	Day 7	Day 14	Day 28	Day 29
Informed consent		X						
Demographics and medical history		X						
Prior/concomitant medications		X						
ECG[c]		X	X	X	X	X		X
Vital signs[d]		X	X	X	X	X	X	
Physical examination		X	Brief	X[e]	X[e]	X[e]		X
Clinical laboratory tests (serum chemistry, hematology, urinalysis)		X	X	X	X	X		X
MMSE		X						
HCVm, HBsAg, & HIV screen		X						
Drug administration[f, g]			X	X	X	X	X	
Blood plasma sample collection for PK analysis			X	X	X	X	X	X
Adverse event monitoring			X	X	X	X	X	X
Discharge				X				
Whole blood draw for biomarkers			X			X	X	
BEHAVE-AD		X				X	X	
C-SSRS		X					X	
CSF draw		X					X	

BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; CSF = cerebrospinal fluid; ECG = electrocardiogram, ED = early discontinuation; HBsAg = hepatitis B surface antigen; HCVm = hepatitis C virus; HIV = human immunodeficiency virus; MMSE = Mini-Mental State Examination; PK = pharmacokinetic(s).

Notes: Allowed visit windows are ± 2 days for all study visits during the Treatment. The Follow-up visit will immediately follow the Day 28 visit.

a. Subjects who terminate the study early are required to undergo an Early Discontinuation (ED) Visit with the following procedures to be performed: documentation of the reason for early study discontinuation; full physical examination; clinical laboratory tests (biochemistry, hematology, urinalysis); ECG; adverse event collection; blood draw for biomarkers; BEHAVE-AD; and CSF draw.

b. Screening Visit must occur within 30 days prior to administration of the study medication.

c. Screening visit ECG will be collected with the subject in a supine position.

d. Vital signs include: blood pressure, heart rate, respiratory rate, and temperature.

e. Listen to heart and lungs.

f. Administer the first dose of study drug on the morning of Day 1, 1-2 hours before breakfast. On Days 7, 14, and 28, subjects are instructed to take study drug after blood draws.

g. Subjects are instructed to bring all unused study drug to each visit. Collect all unused study drug at the Day 28 Visit or at the ED Visit.

6.2 Assessments

Table 1 shows the schedule of events for the study.

6.2.1 Safety Measurements

Safety will be assessed by repeated clinical evaluations including adverse events (AEs), serious adverse events (SAEs), vital signs, physical examination, electrocardiograms (ECGs), and clinical laboratory tests (serum chemistry, hematology, and urinalysis).

6.2.2 Pharmacokinetic Measurements

Plasma samples will be collected for evaluation of PTI-125 PK. On Day 1, blood samples for PK assessments will be drawn at 20, 40, and 60 minutes and at 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after the first dose of study medication and prior to the second dose. On Day 2, the blood sample for the 24 hour PK time point will be drawn. On study Days 2, 7, 14, and 28, the PK samples are to be drawn 30 minutes prior to dosing and will be used for estimation of the C_{min} parameter. On Day 28, in addition to the pre-dose sample, post-dose PK samples will be obtained at 20, 40, and 60 minutes and at 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours. The 24-hour PK blood sample will be collected on Day 29. Other PK parameters, such as C_{max} and CSF/plasma ratio, will be calculated from the PK concentration data to provide an estimate of the extent of accumulation between Day 1 and Day 28. Pharmacokinetic measurements will be analyzed, summarized, and listed separately by a third party.

6.2.3 Biomarker Measurements

The cerebrospinal fluid (CSF) samples will be collected at the second Screening visit and post-dose on Day 28 to characterize several biomarker assays including: amyloid beta (Aβ), tau, phosphorylated tau (ptau), YKL40, IL-6, TNFα, and IL-1β. Whole blood will be collected on Day 1 (pre-dose), Day 14, and Day 28 to characterize PTI-125DX lymphocyte assay, PTI-125DX plasma assay, and lymphocyte mTOR assays. Biomarker data will be analyzed separately by a third party, but will be listed in subject listings.

6.2.4 Other Measurements

BEHAVE-AD rating scale will be used to assess the behavioral and psychological symptoms of dementia. BEHAVE-AD will be administered on Screening 2, Day 14, and Day 28.

7 SAMPLE SIZE AND POWER

According to the protocol, the sample size is based on the estimations of intra-subject variability for log-transformed data from previous studies of new chemical entities. No formal statistical power calculations were performed.

8 SAFETY ANALYSIS SETS

The safety analysis set (SAF) is defined as all subjects who received any amount of study drug (PTI-125). The safety analysis set will be used to assess safety, biomarkers, and behavioral and psychological symptoms of AD.

9 GENERAL CONSIDERATIONS

9.1 Data Summarization and Presentation

The safety analysis set will be used for safety analyses as well as analysis for behavioral and psychological symptoms of AD. Subject listings of all analysis data that support summary tables and/or figures will be provided. Extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables unless specified otherwise, but will be included in the subject listings. In general, subject listings will be sorted by subject number and assessment date (time, and parameter, as applicable).

For most summary statistics, data will be analyzed and displayed in tabular format. Unless otherwise specified, descriptive statistics for continuous variables will include the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum, and maximum. The same number of decimal places as in the observed value will be presented when reporting minimum and maximum; 1 additional decimal place than in the observed value will be presented when reporting mean and median; and 2 additional decimal places than in the observed value will be presented when reporting SD.

All categorical/qualitative data will be presented using frequency, counts, and percentages. All percentages will be presented to 1 decimal place, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies. Where individual variable values are missing, categorical data will be summarized based on

reduced denominators (i.e., only subjects with available data will be included in the denominators). For summaries of AEs and concomitant medications (CMs), the percentages will be based on the number of subjects who received study drug.

Results of statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) numbering convention will be used for all TLFs. All analyses and summaries will be produced using SAS® version 9.4.

9.2 Definitions and Derived Variables

9.2.1 Age

Age (years) will be calculated as the number of years between date of birth and date of informed consent, expressed as an integer.

9.2.2 Body Mass Index

Body mass index (BMI, kg/m^2) is derived as weight (kg) / [height (m) × height (m)].

9.2.3 Study Day

Study Day, which follows the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standard, is defined as (Assessment date - date of first study drug dosing + 1), where the assessment date is on or after the date of first study drug dosing; (Assessment date – date of first study drug dosing), where the assessment date is before the date of first study drug dosing.

9.2.4 Multiple Records at a Time Point

For analysis purposes, the mean value of multiple measurements collected at the same position (i.e., supine, etc.) on the same visit day and at the same time point will be summarized for the corresponding protocol-defined time point. All collected measurements and the mean values will be listed.

9.2.5 Baseline Values

Baseline values are defined as the last non-missing assessment prior to the first dose of study drug, unless otherwise specified.

9.2.6 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AEs, regardless of relationship to study drug, that have an onset or worsening in severity on or after the first dose of study drug (see also Section 10.3.1). Related AEs are those reported by investigators as possibly related or probably related to the study drug. Serious TEAEs (SAEs) are defined as described in Section 9.4 of the protocol (and are industry standard definitions).

9.2.7 Concomitant Medications

Prior medications are defined as all prescription and over-the-counter medications that were taken within 30 days (whether continuing or not) prior to the first dose of study drug. Concomitant medications (CM) are defined as all prescription and over-the-counter medications that are used concurrently (from Day 1 to Day 28) with the study drug administration. A CM is considered to be any medication that is continued from Screening and continued after the first study drug dosing (i.e., a prior medication can also be a CM if it continued after the first dose of study drug) or any medication with start dates or stop dates within the Treatment Period.

10 STATISTICAL AND ANALYSIS ISSUES

10.1 Adjustments for Covariates

There will be no adjustments for covariates.

10.2 Handling Dropouts or Missing Data

Missing data will not be imputed, unless otherwise specified. Early termination visits will be mapped to the next scheduled visit for inclusion in summary tables, where appropriate.

Every effort will be made by the Sponsor to ensure completeness of data collection. In the subject listing, all collected and all imputed values will be presented.

10.3 Handling of Safety Data

10.3.1 Adverse Events

All AE verbatim terms reported on the eCRFs will not be mapped based on Medical Dictionary for Regulatory Activities (MedDRA) dictionary. All AEs will be listed in subject listings.

10.3.2 Concomitant Medications

For all prior and concomitant medications (as defined in Section 9.2.6), medication verbatim terms reported on the eCRFs will be listed in subject listings.

If start date is missing, the medication will be considered to have started prior to the study and will be listed as a prior medication; if a stop date is recorded, the stop date will be used to determine whether it is also a CM (and listed accordingly). If the stop date of any medication is missing, then the medication will be treated as ongoing (i.e., a CM). Unless there is complete stop date information sufficient for the determination of "prior" versus "concomitant," medications with incomplete start dates (e.g., missing year, etc.) will be identified as concomitant if:

- Day and month are missing and the year is equal to or after the year of the first date of study drug dosing;
- Day is missing and the year is after the year of the first date of study drug dosing;
- Day is missing and the year is equal to the year of the first date of study drug dosing and the month is equal to or after the month of the first date of study drug dosing; or
- Year is missing.

10.4 Interim Analyses and Data Monitoring

There will be no interim analyses.

10.5 Multicenter Considerations

This trial was conducted at 5 study centers in the United States. Data from all study centers will be pooled for analysis of safety. Because the number of subjects at each center is likely to be small, no analyses will be performed by center.

10.6 Multiple Comparisons, Multiplicity

The analysis results will be presented descriptively. Since this is an open-label Phase 2a study, there is no comparator. Safety data analyses are exploratory in nature without statistical testing. Therefore, there will be no adjustments for multiple comparisons.

10.7 Active-Control Studies

There is no comparator in this study.

10.8 Examination of Subgroups

Due to the small sample size, there will be no subgroup analyses.

11 STUDY SUBJECTS

11.1 Subject Disposition

Enrollment and disposition will be summarized for all subjects. All enrolled subjects are defined as those who received at least one dose of study drug. The subject disposition summary will include:

- Number of subjects who enrolled in the study
- Number (%) of subjects in the SAF analysis set
- Number (%) of subjects who completed the study
- Number (%) of subjects who prematurely discontinued from the study
    - The primary reason for withdrawal from the study

A listing of disposition will be provided for all enrolled subjects.

11.2 Protocol Deviations

Protocol deviations will be listed by category (e.g., eligibility criteria, out-of-window visit or procedure, etc.; see list below). All deviations will be identified prior to database lock and will be summarized and presented in listing(s); listings will include flags for deviation type (important or minor). Important protocol deviations are defined per ICH E3 guidance (https://database.ich.org/sites/default/files/E3_Guideline.pdf). All deviations will be summarized by deviation category and type. Examples of protocol deviation include, but are not limited to:

- Investigational product
- Informed consent
- Key eligibility criteria
- SAE reporting procedure was not followed
- Out-of-window procedure
- Procedure missed or data not interpretable
- Missed or out-of-window visit
- Restricted/prohibited medications
- Other

As of this writing, no protocol deviations were identified by the sponsor.

11.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all subjects. Demographic characteristics will include age, sex, race, and ethnicity. The following baseline characteristics will be summarized: baseline weight, height, and BMI. In addition, the baseline BEHAVE-AD score, screening Mini-Mental State Examination score, number of years since diagnosis of AD, and Tau/Aβ ratio (> 0.30) will be summarized. All of the above information will also be listed by subject.

11.4 Medical History

Medical history will not be mapped, based on MedDRA dictionary, to preferred terms and system organ classes (SOCs). Medical history will be listed for all subjects by subject identification number.

12 STUDY DRUG AND OTHER MEDICATIONS

12.1 Prior and Concomitant Medications

All prior and concomitant medications will not be mapped, according to the World Health Organization Drug Dictionary, to Anatomical/Therapeutic/Chemical class. All medications will be listed by subject identification number.

12.2 Restricted Medications

The concomitant use of restricted medications, as defined in Section 5.3 of the study protocol, if any, will be listed separately by subject identification number.

12.3 Exposure to Study Drug and Study Treatment Compliance

Summaries of study drug exposure and compliance will include the total number of tablets dispensed, total number of tablets taken, total dose (mg) taken, study drug compliance, and duration (days) of exposure during the study treatment period. Total number of tablets dispensed, total number of tablets taken, total number of tablets returned, total number of tablets expected to be taken, and compliance percentage are collected in the eCRF.

The duration of study drug exposure is defined as the number of days on treatment from the first dose of study drug until the last dose of study drug. Study drug exposure will be summarized descriptively.

The study drug exposure and drug accountability information, including reasons or comments for incomplete or missed doses, if available, will be listed in a subject listing.

13 SAFETY ANALYSES

One of the study objectives is to assess the safety of PTI-125. Safety will be evaluated by AEs, clinical laboratory test results, vital signs, ECG findings, and physical examinations. All analyses of the safety data will be performed using the SAF analysis set. All descriptive statistics will be presented as described in Section 9.

13.1 Safety Variables

Safety variables include:

1. AEs, SAEs, and withdrawal of study drug due to an AE
2. Laboratory test results
3. Vital signs
4. Findings from 12-lead ECG
5. Findings from physical examination

13.2 Adverse Events

- TEAEs are defined in Section 9.2.5. All reported AEs (including non-TEAEs) will be listed. An overall summary of TEAEs will include the following:All TEAEs
- TEAEs by worst severity
- Study drug-related TEAEs
- Serious TEAEs
- Study drug-related serious TEAEs
- TEAEs leading to study drug discontinuation (if any)
- TEAEs leading to study drug interruption (if any)
- Deaths (if any)

The AE listing will include start and stop date of events; reported (verbatim) terms; flags for TEAE and SAE; relation to PTI-125; and outcome (resolved, resolved w/sequelae, resolving, not resolved, fatal, unknown).

13.3 Clinical Laboratory Evaluation

Clinical laboratory test results from laboratories (serum chemistry, hematology, and urinalysis [specific gravity and pH]) will be summarized using descriptive statistics at baseline and at each scheduled post-baseline time point, unless otherwise specified. Changes from baseline will also be summarized by time point, where available.

The number and percentage of subjects with any out-of-range chemistry and hematology values (i.e., above the laboratory-specified upper limit of normal or below the lower limit of normal) will be summarized by time point, where available.

All laboratory results will be listed with reference ranges and range indicator (Low, High, or Clinically Significantly Abnormal).

13.4 Vital Signs

Descriptive statistics for blood pressure, heart rate, respiratory rate, and temperature, including baseline values and change from baseline values, will be summarized by time point. All vital signs parameters will be listed. Abnormal clinically significant findings from vital signs evaluations will be listed.

13.5 Physical Examination

Abnormal clinically significant findings from physical examinations are to be reported as Medical History or Adverse Events depending on the date of onset. Abnormal clinically significant findings from physical examinations will be listed.

13.6 12-Lead Electrocardiogram

Electrocardiogram (ECG) data, such as clinical interpretation of ECGs, heart rate (HR) values, and interval assessments of PR, QRS, RR, QT, and the corrected value of the interval between the Q and T waves on the ECG tracing will be listed. For HR and ECG intervals, descriptive statistics for observed values and change from baseline will be presented by time point.

13.7 Safety Monitoring

The Medical Monitor will review safety data on an ongoing basis to identify potential adverse safety trends. The Data Safety Monitoring Board/Data Monitoring Committee will review safety

data periodically and determine if dosing may continue. Details of the Committee safety data review can be found in the Data Safety Monitoring Committee charter.

14 EXPLORATORY ANALYSES

14.1 Exploratory Pharmacokinetic Analysis

All analyses of PK parameters will be performed by a third party vendor, Worldwide Clinical Trials Early Phase Services/Bioanalytical Sciences, LLC. Plasma samples will be collected on Day 1, Day 7, Day 14, Day 28 and Day 29.

14.2 Exploratory Biomarker Analyses

All analyses of biomarker variables will be performed by a third party vendor. Biomarkers will be obtained from CSF samples and whole blood samples. The biomarkers are identified in the study protocol for the following assays.

- CSF samples collected on Screening 2 (pre-dose) and Day 28
  - Tau/Aβ ratio
  - ptau/tau ratio
  - YKL40
  - IL-6, TNFα, and IL-1β
- Whole blood samples collected Day 1 (pre-dose), Day 14 and Day 28
  - PTI-125DX lymphocyte assay
  - PTI-125DX plasma assay
  - Lymphocyte mTOR assays

The biomarker data including the above, as well as those that are not identified in the protocol, will be listed in subject listings.

14.3 Exploratory Cognitive/Behavioral Endpoint

The cognitive and behavioral endpoint scores of the BEHAVE-AD are used to assess whether the behavioral and psychological symptoms of dementia change over time. The BEHAVE-AD will be assessed once at screening and post-baseline on Days 14 and 28. Reported scores will be summarized descriptively by time point. In addition, mean, SD, 95% CI of mean, and median

will be provided by time point for the change from baseline scores. All data will be listed in a subject listing.

15 CHANGES RELATIVE TO THE PROTOCOL-SPECIFIED ANALYSIS

The protocol specified the use of repeated measures ANOVA for cognitive/behavioral endpoint BEHAVE-AD. This method will not be used for two reasons: First, there is only one group (active treatment group). Second, the data may not be normally distributed. Therefore, descriptive statistics and 95% CI of the mean will be provided instead.

The protocol specified that adverse events reported on case report forms will be mapped to preferred terms and organ systems using the MedDRA mapping system. The medication coding was not done, due to very small number of events were reported.

Uric acid was not performed per protocol Section 7.2.1 Clinical Laboratory Test. Site 04 did not collect Uric Acid. Therefore, uric acid values will be included in the subject listings where available. Additionally, Site 01, Site 03, and Site 05 did not collect In-Patient Day 2 uric acid results. Therefore, uric acid will not be summarized at the In-Patient Day 2 time point.

16 References

1. Reisberg et al., “Behavioral symptoms in Alzheimer’s disease: Phenomenology and treatment.” *J. Clin. Psychology*. 1987;48: 9-15.