Statistical Analysis Plan: TB006AD2102

Study Title:	A Seamless Phase 1b/2a Double-blind, Randomized, Multiple dose, Multi-center, Sequential Dose-escalation Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of TB006 in Patients with Mild to Severe Alzheimer's Disease
Study Number:	TB006AD2102
Study Phase:	Phase 1b/2a
Sponsor:	TrueBinding, Inc. 300 Lincoln Center Drive Suite 200 Foster City, CA 94404
Version:	Final 2.0
NCT Number:	NCT05074498
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Study Number:	TB006AD2102

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACR	Assessment/Collection/Result
AD	Alzheimer's Disease
ADA	Anti-Drug Antibody
ADL	Activities of Daily Living
AE	Adverse Events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti-HBc	IgM Hepatitis B Core Antibody
Anti-HCV	Hepatitis C Antibody
ApoE4	Apolipoprotein E4
AR(1)	Auto-regressive
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{0-6}	Area under the concentration time curve from time zero to the 6-hour post end of infusion timepoint
AUC_{0-last}	Area Under the Concentration-Time Curve from Zero Time to the Last Measurable Time Point
AUC_{tau}	Area Under the Concentration-Time Curve over a Dosing Interval
[redacted]	[redacted]
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CDER	Center for Drug Evaluation and Research
CDR	Cognitive Drug Research
CDRS	Clinical Dementia Rating Scale
CFB	Change from Baseline
CI	Confidence Interval
CL	Total Clearance
cm	Centimeter
C_{max}	Maximum Observed Plasma Concentration

CMH	Cochran Mantel-Haenszel
COVID	Coronavirus Disease
CPK	Creatine Phosphokinase
CSF	Cerebrospinal Fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Concentration at the End of a Dosing Interval
D	Day
DBP	Diastolic Blood Pressure
DSM 5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
E/D	Early Discontinuation
EAS2	Part 2 – Efficacy Analysis Set
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
[redacted]	[redacted]
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic-Gonatropin
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
IgM anti HBc	Immunoglobulin M Antibody to Hepatitis B Core Antibody
IV	Intravenously
Kg	Kilogram
KR	Kenward-Roger
LDL	Low-Density Lipoprotein
LS	Least Square

MAD	Multiple Ascending Dose
MAR	Missing at random
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MMSE	Mini-Mental State Examination
[redacted]	[redacted]
NCA	Non-Compartmental Analysis
[redacted]	[redacted]
[redacted]	[redacted]
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
PCI	Potentially Clinically Important
PCS	Potentially Clinically Significant
PD	Pharmacodynamics
PDS	Pharmacodynamic Analysis Set
[redacted]	[redacted]
PK	Pharmacokinetic
PKS	Pharmacokinetic Analysis Set
PT	Preferred Term
QTcB	QT Corrected Interval Using Bazett equation
QTcF	QT Corrected Interval Using Fridericia's Formula
qw	Weekly
RBC	Red Blood Cell
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set

SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SRC	Safety Review Committee
$t_{½}$	Terminal Elimination Phase Half Life
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time at Which Maximum Plasma Concentration Occurs
TOEPH	Heterogeneous Toeplitz
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
UN	Unstructured
V_z	Volume of Distribution
WHO DD	World Health Organization-Drug Dictionary

4. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the framework for the reporting, summarization and statistical analysis methodology of the safety, tolerability, pharmacokinetic (PK), pharmacodynamics (PD) and efficacy endpoints measured throughout the study. It is based on Protocol TB006AD2102 Amendment 2.0 dated 15 October 2021.

5. TRIAL OBJECTIVES

5.1. PRIMARY OBJECTIVES

The study is planned to conduct in two different parts, and primary objectives for Part 1 are as listed:

- To determine the safety and tolerability of multiple doses of TB006
- To determine the PK profile of multiple doses of TB006
- To determine the maximum tolerated dose of multiple doses of TB006
- To assess the immunogenicity of TB006 (production of anti-TB006 antibody)

The primary objective for Part 2 is as follows:

- To determine the clinical efficacy of TB006 in patients with mild to severe Alzheimer's disease (AD)

5.2. SECONDARY OBJECTIVES

There is no secondary objective planned for Part 1 of the study.

The following are the secondary objectives for the Part 2 of the study:

- To determine the clinical efficacy of TB006 in patients with mild to severe AD
- To determine the safety and tolerability of multiple doses of TB006
- To determine the PK following multiple doses of TB006

6. STUDY DESIGN CONSIDERATIONS

6.1. STUDY DESIGN

This is a seamless, two-part Phase 1b/Phase 2a, multi-center, randomized, double-blind, placebo-controlled study. Part 1 is a multiple ascending dose (MAD) escalation study to evaluate the safety, tolerability, PK, PD, and efficacy of TB006 in patients with AD. Part 2 is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy of TB006 after 1 month of treatment. The total study duration for each patient will be up to approximately 19 weeks.

Patients will receive a total of 5 doses, given in qw intervals. In Part 1, the planned starting dose in Group 1 will be 140 mg qw for 5 weeks. Subsequent planned doses are 420 and 1,000 mg qw for Groups 2 and 3, respectively. The planned dose in Part 2 will be the highest safe and well-tolerated dose from Part 1. All doses are infused IV over 1 hour. Part 1 will interleave with the single ascending dose (SAD) study (Study TB006HV1101). Each group in Part 1 will commence after the safety, tolerability, and PK of the single dose equivalent to the combined total of 5 qw doses planned in this study has been established. Explicitly, dosing in Group 1 (140 mg qw) will commence when the safety and tolerability of the 700 mg single dose in the SAD study has been established. Groups 2 (420 mg qw) and 3 (1000 mg qw) will begin after a review of the available safety, tolerability, and PK data from the previous group; and after the 2,100 and 5,000 mg single dose, respectively, has been administered. Dose levels may be adjusted depending on the safety, tolerability, and available PK of doses in the SAD study and previous groups in this study. Patients will be enrolled across all active centers into each dose group sequentially.

In Part 1, 8 patients will be enrolled into each dose group; 6 patients in each group will be randomized to active TB006 treatment, and 2 patients to placebo.

Dose escalation decisions will use safety, tolerability, and available PK data through the first dose administered to the last patient in each group and a minimum of 14 days from the respective dose group that has been dosed in the SAD study (Protocol number TB006HV1101). Data will be reviewed by a blinded Safety Review Committee (SRC).

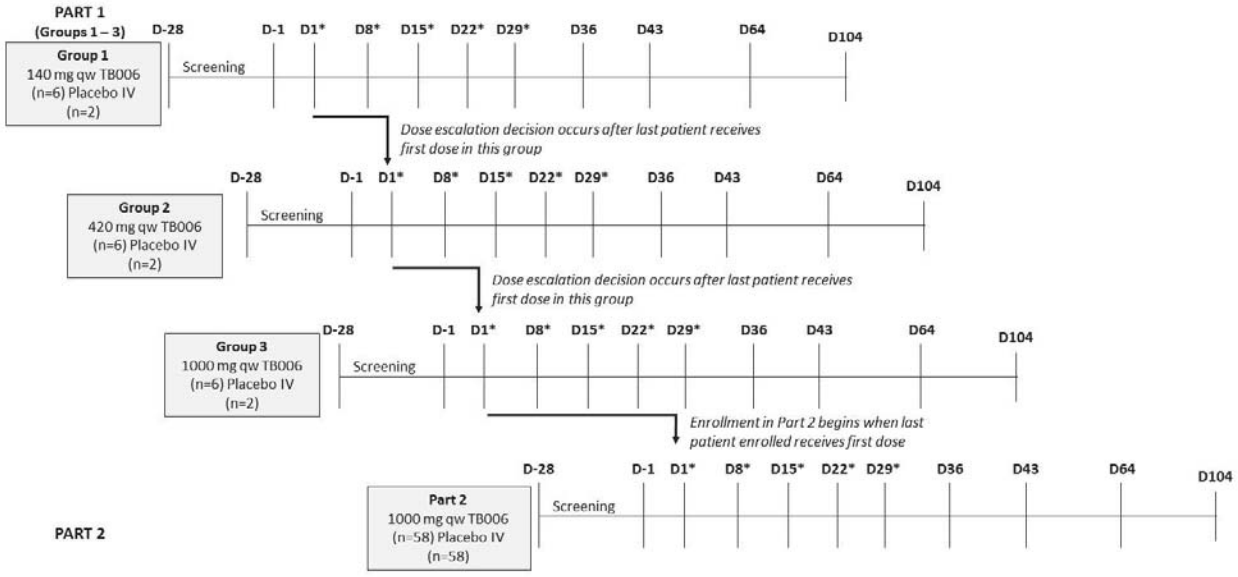
Part 2 will commence after the last patient in Part 1 has received their first dose. The planned dose in Part 2 will be 1,000 mg qw × 5 doses, but may be adjusted depending on the safety and tolerability of the doses in Part 1. Patients will be randomized to active TB006 or placebo (1:1) and will follow the same dosing schedule and procedures (with some exceptions – see Part 2 schedule of assessment) as in Part 1. Randomization in Part 2 will be stratified according to baseline patient severity, with mild AD patients [Mini-Mental State Examination (MMSE) 21-24] and moderate-severe AD patients (MMSE ≤ 20) in each stratum.

This is an outpatient study. Patients will return to the clinic for screening and baseline procedures, on dosing days, and on follow-up visits. Patients will have the option of checking into the clinic and staying overnight on Day -2 or Day -1, as well as on days prior to the other dosing days.

Assessments for safety and tolerability, efficacy, PK, and PD are performed throughout the study. If a patient reports any adverse events (AEs), they may be required to return to the clinical

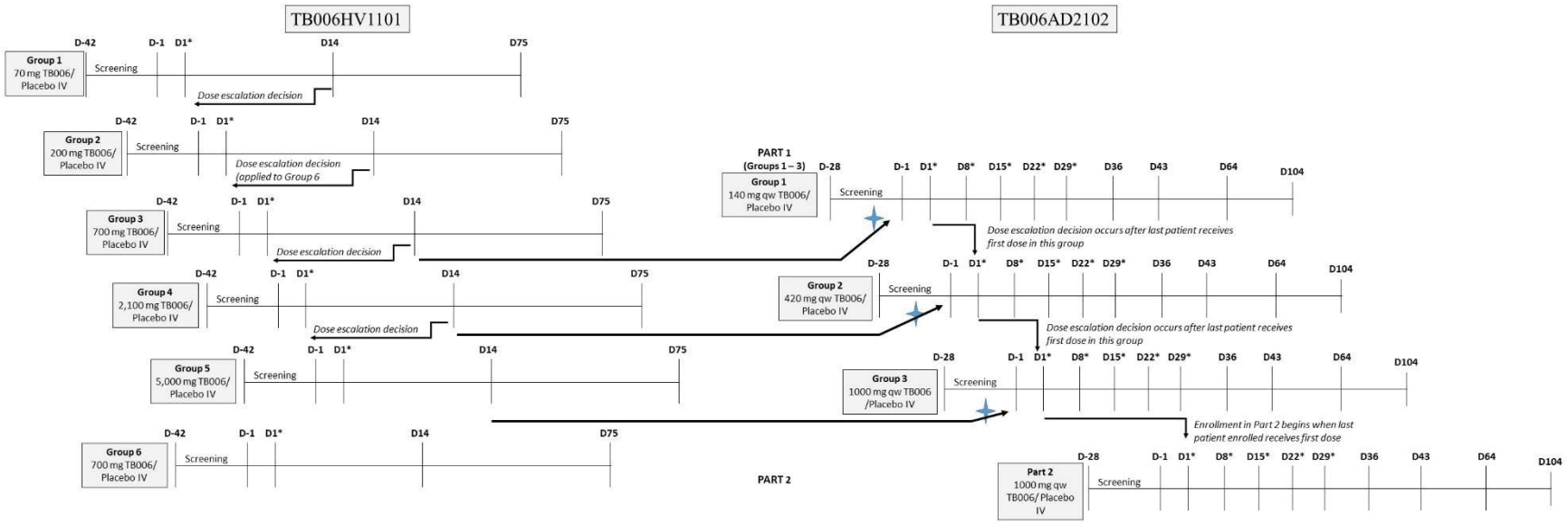
unit at the discretion of the investigator for additional assessments. All AEs must be followed to adequate resolution.

Figure 1 Study Design and Treatment Schema for Part 1 and Part 2



* Study drug administration
Note: Visit days and procedures will occur during a window of ± 2 days from Day 1 to End of Treatment.
D = Day; IV = intravenously, qw = weekly.

Figure 2. Study Design and Treatment Schema – Interleave with Study TB006HV1101



Dosing in Group 1 (140 mg TB006/placebo aww) will commence when the safety and tolerability of the 700 mg single dose in the SAD study has been established. Groups 2 (420 mg TB006/placebo qw) and 3 (1,000 mg TB006/placebo qw) will begin after a review of the available safety, tolerability and PK data from the previous group; and after the 2,100 and 5,000 mg, respectively, have been administered.

* Study drug administration

Note: Visit days and procedures will occur during a window of ± 2 days from Day 1 to End of Treatment

D = Day; IV = intravenously; PK = pharmacokinetic; qw = weekly; SAD = single ascending dose.

6.1.1. Justification of Sample Size

In Part 1, patients will be recruited sequentially in separate increasing dose groups, with each group randomizing 6 patients to a specific dose of TB006 and 2 randomized to placebo. If all 3 planned dose levels are investigated, the study will recruit approximately 24 patients in total (18 receiving TB006 treatment at the different dose levels, and 6 receiving placebo).

In Part 2, patients will be randomized to TB006 or placebo in a 1:1 ratio so that approximately 58 patients will be randomized to each group. Randomization in Part 2 will be stratified according to baseline patient severity, with mild AD patients (MMSE 21-24) and moderate-severe AD patients (MMSE $\leq$ 20) in each stratum. Patients enrolled at the same TB006 dose level in Part 1, as well as all placebo patients, will be included in the efficacy analyses in Part 2. Thus, the number of patients in each group for the primary efficacy analysis will be approximately 64.

Assuming that the standard deviation (SD) of change from baseline (CFB) Clinical Dementia Rating Scale (CDRS) - Sum of Boxes at Day 104 is 0.5, a total of 128 patients will provide 80% power to detect a mean CFB difference of 0.25 at Day 104 using a 2-sided, 2 sample t-test at the 5% level of significance.

6.2. Efficacy Endpoints

For Part 1, there is no efficacy endpoint planned for primary and secondary analysis, but following endpoints is planned for exploratory analysis:

- CFB through end of study on the CDRS – Sum of Boxes total score
- CFB through end of study on the Cognitive Drug Research (CDR) System Battery Score, composite scores, and individual task measures
- CFB through end of study on the MMSE score
- CFB through end of study on the Neuropsychiatric Inventory (NPI) score

For Part 2, the planned primary efficacy endpoint is:

- CFB through Day 104 on the CDRS – Sum of Boxes total score.

And the associated secondary endpoints are as under:

- CFB through Day 36 on the CDRS – Sum of Boxes total score
- Proportion of responders on the CDRS – Sum of Boxes at Days 36 and 104
- CFB to Days 36 and 104 on the CDR System Battery, composite scores, and individual task measures
- CFB to Days 36 and 104 on the MMSE score
- CFB to Days 36 and 104 on the NPI score

6.3. Safety Endpoints

The safety endpoints for Part 1 and Part 2 of the study will be recorded and reported throughout the safety reporting period. The safety reporting period is from Day 1 (start of TB006 infusion) through Day 104. Safety endpoints for both protocol parts of this study include:

- Incidence of AEs and serious adverse events (SAEs)

- Clinical Safety Laboratory Assessments
- Vital Signs
- Electrocardiograms
- Suicidal Ideation and Behavior Risk Monitoring
- Physical and Neurological Examinations

The safety endpoints listed above will be reported as primary endpoints for Part 1 of the study and as secondary endpoints for Part 2 of the study.

6.4. PHARMACOKINETIC ENDPOINTS

The PK analysis will be performed using PK parameters derived by non-compartmental analysis (NCA) using the TB006 plasma concentration time data. The PK parameters will be estimated using actual sampling time relative to the start of infusion.

For Part 1 of the study, the PK analysis will be performed as primary endpoint and includes, but not limited to:

- Area under the concentration time curve from time zero to the 6-hour post end of infusion timepoint (AUC_{0-6}) (Days 1, 8, and 29)
- Area under the concentration time curve over a dosing interval (AUC_{tau}) (Days 1 and 29)
- Area under the concentration-time curve from zero time to the last measurable time point (AUC_{0-last}) (Day 29)
- Maximum observed plasma concentration (C_{max}) (Days 1, 8, and 29)
- Time at which maximum plasma concentration occurs (t_{max}) (Days 1, 8, and 29)
- Concentration at the end of a dosing interval (C_{trough}) (Days 8, 15, 22, 29, and 36)
- Terminal elimination phase half-life ($t_{½}$) (Day 29 only)
- Total clearance (CL), calculated as dose/AUC_{tau}. (Day 29 only)
- Volume of distribution (V_z), calculated as dose/kel × AUC_{tau}, where kel is the apparent elimination rate-constant, computed by log linear regression of the terminal log linear segment of the plasma concentration versus time curve (Day 29 only).

The extent of CSF distribution as estimated by TB006 CSF concentrations on Day 36 will also be determined.

For Part 2 of the study, the PK analysis will be performed as secondary endpoint and will include:

- Maximum observed plasma concentration (C_{max}) (Days 1, 8, and 29)
- Concentration at the end of a dosing interval (C_{trough}) (Days 29 and 36)
- Area under the concentration-time curve from zero time to the last measurable time point (AUC_{0-last}) (Day 29)
- Terminal elimination phase half-life ($t_{½}$) (Day 29 only)

Note that no CSF will be collected in Part 2 of the study.

6.5. PHARMACODYNAMIC ENDPOINTS

[redacted]

6.6. OTHER DRUG RELATED ENDPOINTS

Apart from above analysis, following other drug related assessment will also be performed for Part 1, secondary analysis, of the study.

- Assessment of maximum tolerable dose
- Detection of anti-TB006 antibodies (from PK plasma sampling)

7. STUDY POPULATIONS

7.1. ANALYSIS POPULATIONS

7.1.1. FULL ANALYSIS SET (FAS)

The Full Analysis Set (FAS) includes all subjects who are randomized to study drug. The FAS will be used for the analysis of disposition and protocol deviations.

7.1.2. SAFETY ANALYSIS SET (SAS)

The Safety Analysis Set (SAS) includes all subjects in the FAS who received at least one dose of study drug. Subjects in this analysis set will be analyzed according to the study drug they actually received. The FAS and the SAS will be the same if all randomized patients are dosed with study drug. The SAS will be used for all analyses, except for disposition, protocol deviations, PK and PD.

7.1.3. PHARMACOKINETIC ANALYSIS SET (PKS)

The Pharmacokinetic Analysis Set (PKS) includes all subjects who received assigned dose of TB006 and have at least one post-dose blood sample with measurable TB006 concentrations. The PKS will be used for all PK analyses.

7.1.4. PHARMACODYNAMIC ANALYSIS SET (PDS)

The Pharmacodynamic Analysis Set (PDS) includes all subjects who received assigned dose of TB006 or placebo and have at least one post-dose evaluable PD assessment. The PDS will be used for all PD and efficacy analyses.

7.1.5. EFFICACY ANALYSIS SET – PART 2 (EAS2)

The Part 2 – Efficacy Analysis Set (EAS2) includes all subjects who received assigned dose of TB006 in Part 2 and the subjects enrolled at the same TB006 dose level in Part 1, as well as all placebo patients will be included and have at least one post-dose evaluable PD assessment across subject. The EAS2 will be used for all efficacy analysis planned for Part 2 of the study.

7.2. SUBGROUPS

The dispositions, efficacy, PK/PD, biomarker, and immunogenicity analysis for Part 2 will be presented for overall and baseline patient severity: mild AD patients (MMSE 21-24) and moderate-severe AD patients (MMSE ≤ 20).

8. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

The following analyses described in this SAP are not mentioned in the study protocol:

- Assessment of dose proportionality (see Section 10.5: Pharmacokinetics).

[redacted]

9. OVERALL STATISTICAL CONSIDERATIONS

9.1. GENERAL CONVENTIONS

Summary statistics will be presented for categorical data as number and percentage [n (%)] where the percentage is displayed to one decimal point (e.g., 98.1).

Descriptive statistics will be presented for continuous data with applicable decimal precision as follows in relation to the source data (indicated as N), with a maximum of three decimals to be displayed:

- Number (n).
- Mean, (N+1).
- SD, (N+2).
- Median, (N+1).
- Minimum, (N+0).
- Maximum, (N+0).

Study day is calculated relative to the first dose of study drug infusion and will thus in most cases coincide with the visit naming (e.g., Day 1 will be on study day = 1, Day 15 will be on study day = 15 etc.)

- If the current assessment/collection/result (ACR) date is on or after first dose of study drug infusion:

$$Study\ Day = (Current\ ACR\ Date - First\ dose\ of\ Study\ Drug\ infusion\ Date) + 1$$

- If the current ACR date is before first dose of study drug infusion:

$$Study\ Day = (Current\ ACR\ Date - First\ dose\ of\ Study\ Drug\ Infusion\ Date)$$

Study day will not be calculated if either the current ACR or the first dose of study drug infusion date is incomplete or missing.

All the tables in Part 1, will be displayed by treatment groups (i.e., TB006 140 mg qw, TB006 420 mg qw, TB006 1000 mg qw, and Pooled placebo).

The dispositions, efficacy, PK/PD, biomarker, and immunogenicity analysis for Part 2 will be classified by treatment groups (i.e., TB006 and Placebo) and baseline AD severity stratifications [i.e. mild AD (MMSE 21-24) and moderate-severe AD (MMSE ≤ 20)]. For efficacy tables of Part 2, the subjects enrolled at the same TB006 dose level in Part 1, as well as all placebo patients will be included.

For all baseline, safety and efficacy assessments, the subjects will be tabulated using the actually received treatment. For example, if there is a subject who is planned to receive TB006 but accidentally gets treated with one of the other regimens, the subject will be tabulated under the other regimen actually received.

The tables and listing for both protocol parts will be presented separately. The detailed layout will be presented in mock shell.

9.2. BASELINE DEFINITION

Baseline is defined as the last available value prior to the subject receiving first dose of study drug infusion (i.e., Day 1). If the potential Baseline ACR is on Day 1 (and time is not recorded), it is assumed that the ACR occurred before the start of first dose of study drug infusion.

CFB is calculated as:

$$CFB = Observed\ value - Baseline\ Value$$

Percentage change from Baseline (CFB%) is calculated as:

$$CFB\% = (CFB \div Baseline\ Value) \times 100$$

9.3. HANDLING OF PK CONCENTRATION VALUES BELOW LOWER LIMIT OF QUANTIFICATION

For PK concentrations, values that are below the lower limit of quantification (BLQ) the following handling measures will be applied:

- For NCA, pre-dose concentrations prior to the first dose of TB006 that are BLQ will be set to zero. Post-dose concentrations that are BLQ and occur before the first quantifiable concentration will also be treated as zero. Post-dose concentrations that are BLQ but occur after the first quantifiable concentration will be treated as missing.
- For summary statistics, BLQ concentrations will be treated as zero.
- In listing presentation these values will be marked/footnoted as being BLQ.

9.4. HANDLING OF MISSING DATA

No formal imputation of missing data is planned for Part 1 of the study. There are however a few handling conventions and assumptions applicable to partial/missing data points which are described in the following subsections.

9.4.1. PARTIAL DATES

Although partial dates will not be 'filled up' in this study, some assumptions will be made in regards partial dates for background calculation/classification purposes as appropriate (for AEs, prior/concomitant medications etc.)

Table 1. Handling of Partial Dates

Parameter	Missing	Additional Conditions	Imputation
Start date	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M and Y	None - date completely missing	Date of first dose of study drug
Stop date	D	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Dec 31
	D, M and Y	None - date completely missing	No imputation, but assume ongoing

D = day, M = month, Y = year
Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.
In all cases, if it cannot be determined if the AE/medication occurred prior to or after the first dose of study drug infusion, the AE should be defined as treatment emergent, and medication will be considered as concomitant medication.

9.4.2. Missing Value Imputation for Efficacy Endpoints – Part 2

Apart from handling conventions and assumptions applicable to partial/missing data points mentioned above, there will be additional imputation for missing efficacy assessments listed under:

- CDRS – Sum of Boxes total score
- MMSE score
- NPI score

For these imputations, the missingness will be considered as missing at random (MAR). There will be no imputation for individual missing values, but missing data will be imputed implicitly using Mixed Model Repeated Measures (MMRM).

The MMRM analysis will be performed for above listed efficacy endpoints as described in Section 9.5.

9.5. MMRM Method

The primary and secondary efficacy endpoints associated with efficacy assessments listed in Section 9.4.2 will be analyzed using a MMRM model. The model will include treatment group, visit, stratification factor (MMSE $\leq$ 20 and 21-24), and treatment by visit as fixed effects and associated baseline assessment as covariate. The model will use visit as repeated component in the model.

An unstructured (UN) covariance structure will be applied for the MMRM. In the event the UN covariance matrix results in non-convergence of the model, then the Heterogeneous Toeplitz (TOEPH) and auto regressive [i.e. AR(1)] covariance structures will be used, respectively, with separate subject random effect. The Kenward-Roger (KR) approximation will be used to estimate denominator degrees of freedom.

The least square (LS) mean for CFB and associated 95% confidence interval (CI), and standard error will be presented for each treatment group.

The MMRM model will utilize all available data values for respective efficacy assessments.

9.6. Seriousness, Relationship and Severity of AEs

Missing seriousness, severity and relationship of AEs that have been queried and remain missing after such, will be treated ‘worst case’ for presentation filtering purposes as follows:

- Missing seriousness: Will be considered as serious and included in the SAE displays.
- Missing relationship: Will be considered as related and included in the related AE displays.
- Missing severity:
    - If subject has died, will be considered as Grade 5 severity across all associated displays.

- If subject has not died but subject had intervention indicated for the AE, will be considered as Grade 4 severity across all associated displays.
- If none of the previous conditions are met, will be considered as Grade 3 severity across all associated displays.

9.7. Visit Windows/Unscheduled Visits

No mapping/renaming of visits (unscheduled or otherwise) will be done for this study. That is, only regular scheduled visit data will be used for summarization in tables. However, all collected data will be listed.

Unscheduled visits will be considered eligible for Baseline values. Unscheduled visit results will also be considered eligible for testing of potentially clinically significant (PCS) values (laboratory, Electrocardiogram (ECG) and vital signs).

10. STATISTICAL ANALYSIS METHODS

10.1. Subject Disposition

The following disposition related items are planned to be listed using the protocol part and analysis set indicated in parentheses:

- Screening failures (Part 1 – All subjects)
- Screening failures (Part 2 – All subjects)
- Randomized subjects (Part 1 – FAS)
- Randomized subjects (Part 2 – FAS)
- Unblinded subjects, if any (Part 1 – FAS)
- Unblinded subjects, if any (Part 2 – FAS)
- Inclusion/Exclusion violations (Part 1 – FAS)
- Inclusion/Exclusion violations (Part 2 – FAS)
- Subject completion/discontinuation information (Part 1 – FAS)
- Subject completion/discontinuation information (Part 2 – FAS)
- Subject analysis set inclusions (Part 1 – FAS)
- Subject analysis set inclusions (Part 2 – FAS)
- Subject deviations (Part 1 – FAS)
- Subject deviations (Part 2 – FAS)

The following disposition related items are planned to be tabulated using summary and descriptive statistics as applicable, by treatment groups and baseline AD severity stratifications (for Part 2 only), using the protocol part and analysis set indicated in parentheses:

- Subject completion/discontinuation information (Part 1 – All subjects). Including breakdown by reason for subject discontinuation.
- Subject completion/discontinuation information (Part 2 – All subjects). Including breakdown by reason for subject discontinuation.
- Subject analysis set inclusions (Part 1 – All subjects). Including reason for exclusion from analysis set, if required.
- Subject analysis set inclusions (Part 2 – All subjects). Including reason for exclusion from analysis set, if required.
- Subject deviations (Part 1 – FAS).
- Subject deviations (Part 2 – FAS).

The data for these presentations are obtained from the following electronic Case Report Forms (eCRFs):

- Informed Consent
- Screen Failure
- Inclusion Exclusion Criteria
- Randomization
- End of Study

10.2. Demographics and Baseline Characteristics

The following demographics and baseline characteristic items will be listed using SAS for both protocol parts:

- Subject demographics:
  - Age
  - Sex
  - Race
  - Ethnicity
- Baseline vital characteristics:
  - Height (cm)
  - Weight (kg)
  - BMI (kg/m^2)
- Substance usage, including checking for:
  - Tobacco/nicotine use
  - Alcohol use
  - Drug use

The above demographic, baseline characteristics and substance use items are planned to be tabulated using summary and descriptive statistics as applicable, by treatment groups for SAS.

The data for these presentations will be obtained from the following eCRFs:

- Demography
- Physical Examination (for baseline height/weight)
- Medical History (for substance usage medical history)
- Drug and Alcohol Screening

The following items will be derived:

- Body mass index (BMI) at Baseline:

$$Baseline\ BMI = Baseline\ weight\ (kg) \div [Baseline\ height\ (m)]^2$$

10.3. Medical History And Viral Serology

The medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1, Sep 2019.

The following medical history and viral serology baseline characteristic items will be listed using SAS for both protocol parts:

- Medical history:
  - Medical conditions or allergies reported
- Viral serology
  - HBsAg
  - IgM anti HBc
  - anti HCV
  - HIV
- COVID-19 status

The above medical history is planned to be tabulated using summary statistics, by treatment groups using SAS.

The data for these presentations will be obtained from the following eCRFs and external data:

- Medical History
- Viral Serology
- Laboratory Data

10.4. Prior and Concomitant Medications and Procedures

A prior medication or procedure is defined as having started and ended prior to first dose of study drug infusion. Conversely, a concomitant medication or procedure is defined as either having started prior to first dose of study drug infusion and ended on/after first dose of study

drug infusion, is ongoing at Baseline or, having started on/after first dose of study drug infusion. Medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Global Sep 2019 B3/C3 format.

Listings of prior and concomitant medications/procedures will be presented for both protocol parts as recorded in the eCRF (SAS).

Summary tables by WHO-DD Anatomical Therapeutic Chemical (ATC) level 3 and preferred name will be presented, by treatment groups on the following items:

- Prior medications/procedures (Part 1 – SAS).
- Prior medications/procedures (Part 2 – SAS).
- Concomitant medications/procedures (Part 1 – SAS)
- Concomitant medications/procedures (Part 2 – SAS)

The data for these presentations will be obtained from the Concomitant Medications Details eCRF.

The Prior/Concomitant status will be derived using the medication start and stop dates as per definition provided at the start of this section. For partial dates see Section 9.4.1.

10.5. PHARMACOKINETICS

The following PK listings are planned for presentation (PKS) for both protocol parts:

- TB006 plasma concentration levels
- TB006 CSF concentration level (Part 1 only)
- Pharmacokinetic parameters of plasma TB006
- Dose-normalized plasma exposure PK parameters (AUCs and C_{max}) – (Part 1 only).

The following descriptive summary tables are planned to be presented for subjects who received TB006 (PKS), by treatment groups and baseline AD severity stratifications (for Part 2 only):

- Plasma concentration of TB006 at each time points
- CSF concentration of TB006 at each time points (Part 1 only)
- Plasma PK parameters
- Dose-normalized exposure PK parameters (AUCs and C_{max}) (Part 1 only, Days 1, 8, and 29, as applicable)
- Power model slope estimate for dose proportionality assessment (including 95% CI) (Part 1 only)

Figures of the following PK items are planned for presentation (PKS) for both protocol parts:

- Overlaid individual plasma concentration versus time plots (linear and semi-logarithmic scale) by treatment groups

- Overlaid mean plasma concentration versus time plots, presented by treatment groups (linear scale with and without SD)
- Overlaid mean plasma concentration versus time plots, presented by treatment groups (semi-logarithmic scale with and without SD)
- Boxplots of dose-normalized PK parameters (AUCs and C_{max}), grouped by treatment groups grouped within each figure (Part 1 only, Days 1, 8, and 29, as applicable)
- Scatterplots of PK parameters (AUCs and C_{max}), versus dose (as part of power model results), by treatment groups (Part 1 only, Days 1, 8 and 29, as applicable)

Assessment of dose proportionality will be performed by PK Day (Day 1, 8, and 29, as applicable) and will not be based strictly on statistical rule criteria but rather, several factors will be taken into account when assessing dose proportionality, such as:

- Power model results (e.g., the slope estimate and the width of the 95% CIs)
- Graphical evaluation (box plots of dose normalized AUCs and C_{max})
- Descriptive statistics by treatment groups of dose-normalized PK parameters

Evaluations of the dose proportionality of these parameters will include using the Power Model if there will be at least 3 dose levels available. A statistical linear relationship between the ln-transformed PK parameters and the ln-transformed dose will be fitted by using a mixed model with ln-transformed dose as a covariate and random effect for intercept and subject. Here, (ln-) stands for natural logarithm. Additional predictors may be included in the model. The general form of the Power Model is described as:

$$Ln(Y) = \beta_0 + \beta\, Ln(Dose) + \varepsilon$$

Where, Y represents the PK parameter (AUCs and C_{max}), and β_0 is constant. This approach is usually referred to as a power model because after exponentiation:

$$Y = \alpha\, (Dose)^{\beta}$$

Note that $\beta = 1$ would correspond to perfect dose proportionality.

The following example SAS® code can be utilized and modified as needed:

```
Proc Mixed Data = <Dataset>;
    Class <subjectnum>
    Model <lnY> = <lnDose> / ddfm=kr;
    Random <intercept> /  subject = <subjectnum>  type=UN;
    Estimate 'Logdose  - 1 unit' <lndose> 1/cl  alpha=0.05;
    ods output estimates = <estimate>;
Run;
```

Where <*Dataset*> is the input dataset, <*subjectnum*> is the subject number, <*LnY*> is Ln(Y) (Y being the PK parameter in question, <*LnDose*> is Ln(Dose), <*intercept*> is the intercept and <*estimate*> is the output dataset containing the estimate.

The data for these presentations will be obtained from the external PK laboratory data and eCRF.

[redacted]

Descriptive summary tables of biomarker levels from both plasma and CSF (for Part 1 only) collection will be presented, by treatment groups and baseline AD severity stratifications (for Part 2 only), using PDS for both protocol parts, including CFB and CFB% through end of study.

The relationship between dose, Day 29 plasma TB006 PK exposure parameters (AUC_{tau} and C_{max}), Day 36 CSF TB006 concentration and PD biomarkers listed in Section 10.6 will be assessed graphically. Scatter plots of CFB and CFB% will be presented next to another in grid format for PD endpoint values versus TB006 AUC_{tau} and C_{max}. The PD endpoints will be for timepoints Day 36 and end of study. The main measure of interest for consideration will be the CFB of PD biomarkers.

The data for these presentations will be obtained from the external laboratory data and eCRF.

10.7. Treatment Compliance and Exposure

A listing of subject exposure to all the doses of TB006 will be presented including the date/time of dose and dose level exposed to (SAS) for both protocol parts separately. Also, the treatment compliance information will be listed.

A table containing summary statistics of dose level exposure, by treatment groups will also be presented using SAS.

Treatment compliance is defined as the number of IV doses (including partial doses, active and placebo) actually received divided by the number of doses expected (× 100) over the time period defined by the first infusion date and the last dose date.

Descriptive statistics for treatment compliance and the number and percentage of subjects with at least 80% compliant will be presented using SAS.

The data for these presentations will be obtained from the Study drug infusion eCRF.

11. EFFICACY PARAMETERS

All the efficacy analysis planned for Part 1 will be performed using PDS and efficacy analysis planned for Part 2 will be performed using EAS2. The EAS2 include all PDS subjects of Part 2, placebo subjects of Part 1 and subjects with same dose level in Part 1 pooled together.

11.1. PRIMARY ANALYSIS

There is no primary efficacy analysis planned for Part 1.

For Part 2, the CFB through Day 104 on the CDRS – Sum of Boxes total score is primary efficacy endpoint, and it will be analyzed using MMRM with treatment group, randomization strata (MMSE ≤ 20 and 21-24), visit, and treatment group (treated vs. placebo) by visit interaction as fixed effects and a baseline CDRS - Sum of Boxes score as a covariate. The LS mean difference, the 95% CI of the difference, and the p-value will be presented as well as the descriptive statistics.

11.2. SECONDARY ANALYSIS

There is no secondary efficacy analysis planned for Part 1.

For Part 2, the following secondary analysis are planned.

11.2.1. CHANGE FROM BASELINE AT DAY 36 ON THE CLINICAL DEMENTIA RATING SCALE – SUM OF BOXES TOTAL SCORE

The secondary efficacy endpoint, CFB at Day 36 on the CDRS – Sum of Boxes, and will be analyzed and reported as described for the primary analysis in Section 11.1.

Also, the summary statistics will be tabulated for CDRS individual scores, sum of box total score and Global CDRS score by treatment groups and baseline AD severity stratifications.

11.2.2. RESPONDER ON THE CLINICAL DEMENTIA RATING SCALE AT DAYS 36 AND 104

A responder is defined as at least 1-point improvement from baseline on the Sum of Boxes score. The patients with missing data will be included in the denominator and treated as a non-responder.

The proportion of the responders between treatment groups will be tested using the Cochran Mantel-Haenszel (CMH) test, adjusting for randomization strata (MMSE ≤ 20 and 21-24) and the common risk difference and the 95% CI will be presented.

Also, the number and percentages of responders over time will be tabulated by treatment groups and baseline AD severity stratifications.

The CDRS individual scores, sum of box total score, Global CDRS score and responder status will be listed as well.

11.2.3. CHANGE FROM BASELINE COGNITIVE DRUG RESEARCH SYSTEM BATTERY AT DAYS 36 AND 104

This endpoint is analyzed separately, and detail of analysis is described in CDR system battery SAP [5].

11.2.4. CHANGE FROM BASELINE MMSE TOTAL SCORE AT DAYS 36 AND 104

The secondary efficacy endpoint, CFB at Day 36 and Day 104 on the MMSE total score will be analyzed using MMRM with treatment group, visit, and treatment group by visit interaction as fixed effects and a corresponding MMSE total baseline score as a covariate. The LS mean difference, the 95% CI of the difference, and the p-value will be presented as well as the descriptive statistics.

Also, the summary statistics will be tabulated for MMSE score by treatment groups and baseline AD severity stratifications.

The MMSE scores will be listed as well.

11.2.5. CHANGE FROM BASELINE NPI TOTAL SCORE AT DAYS 36 AND 104

The secondary efficacy endpoint, CFB at Day 36 and Day 104 on the NPI total score will be analyzed using MMRM with treatment group, randomization strata (MMSE ≤ 20 and 21-24), visit, and treatment group by visit interaction as fixed effects and a corresponding NPI total baseline score as a covariate. The LS mean difference, the 95% CI of the difference, and the p-value will be presented as well as the descriptive statistics.

Also, the summary statistics will be tabulated for NPI by treatment groups and baseline AD severity stratifications.

The individual and composite NPI scores will be listed as well.

11.3. SENSITIVITY ANALYSIS

Not applicable for either part of this study.

[redacted]

11.4.1. CHANGE FROM BASELINE THROUGH END OF STUDY – COGNITION PARAMETERS

The observed and change/shift from baseline in results from the cognition parameters - CDRS individual scores, sum of box total score, Global CDRS score, Responders for CDRS-sum of boxes total score, MMSE score, and NPI total score will be summarized by treatment groups using continuous and categorical descriptive statistics.

The assessment associated with cognition parameters - CDR system battery, will be analyzed separately, and detail of analysis is described in CDR system battery SAP [5].

[redacted]

11.5. INTERIM ANALYSIS

No formal interim analysis planned for this study.

A SRC will meet for each dose cohort before continuing to the next dose cohort.

11.6. SUBGROUP ANALYSES

The subgroup analysis for Part 2 will be performed as described in Section 7.2.

12. SAFETY AND TOLERABILITY

12.1. ADVERSE EVENTS

The following AE definitions are applicable to both protocol parts of this study:

- AE reporting period: Defined from start of first dose of study drug infusion on Day 1 up to and including End of Study.
- AE: Any untoward medical occurrence in a subject.
- Treatment-emergent AE (TEAE): Defined as any AE that started on or after first dose of study drug infusion within the studies' AE reporting period.
- SAE: Defined as any AE that is indicated as serious on the AEs Details eCRF, as per investigator's assessment.
- Related AE: Defined as any AE that is indicated as related to study drug on the AEs Details eCRF, as per investigator's assessment.
- AE leading to discontinuation: Defined as any AE that has an "other action taken" indicated as "withdrawn from study" on the AEs Details eCRF.

All AEs will be coded using the MedDRA version 22.1, Sep 2019. The following AE items will be listed separately for each protocol parts using the SAS:

- All AEs
- AEs leading to study discontinuation
- Serious AEs
- AEs leading to death (if applicable)

The following items are planned to be presented in summary tables showing event incidence and corresponding subject count, experiencing said AE/AE type using the SAS, by treatment groups using SAS:

- AE overview, including row items for frequency of subjects [n(%)] experiencing:
    - At least one AE
    - AEs by toxicity grade
        - Grade 1
        - Grade 2
        - Grade 3
        - Grade 4
        - Grade 5
    - Serious AEs

- Related AEs
- Non-related AEs
- AEs leading to study discontinuation
- AEs leading to death

- AEs by system organ class (SOC) and preferred term (PT)
- AEs by descending incidence of PT
- AEs by toxicity grade (Common Terminology Criteria for Adverse Events [CTCAE] grading)
- Related AEs by SOC and PT
- Related AEs by descending incidence of PT.
- Serious AEs
- AEs resulting in death
- AEs leading to study discontinuation

Only TEAEs will be used for summarization of all tables, but for listing all AEs will be counted. The TEAE status will be derived using the AE start and stop dates as per definition provided at the start of this section. For partial dates see Section 9.4.1.

The data for these presentations will be obtained from the Adverse Events Details eCRF.

AE assignment to CTCAE toxicity grades is explained in Table 2 below.

Table 2. CTCAE Grades

Grade	Grade Description	Grade Details
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Minimal, local, or non-invasive intervention indicated, limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL*
Grade 4	Life-threatening	Life-threatening consequences: urgent intervention indicated
Grade 5	Fatal	Death related to AE

ADL: activities of daily living.
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.2. LABORATORY RESULTS

In the context of this study the difference between potentially clinically important (PCI) and PCS results are defined as follows:

- A PCS result is defined as an abnormal laboratory assay result marked as clinically significant in the Investigator's opinion.
- A PCI result is defined as a laboratory assay result that meets criteria tested against as used by the local laboratory for identifying as PCI.

The following subject safety laboratory result items are planned to be listed using the SAS for both protocol parts:

- Chemistry
- Hematology
- Urinalysis
- Drug and Alcohol Screening
- Abnormal results
- PCS results
- PCI results

The following local laboratory result items are planned for table presentation, by treatment groups for each applicable visit using the SAS:

- Chemistry:
  - CFB with descriptive statistics
  - Shift from Baseline with summary statistics
- Hematology:
  - CFB with descriptive statistics
  - Shift from Baseline with summary statistics
- Urinalysis:
  - CFB with descriptive statistics for numeric results
  - Qualitative summary of Urinalysis
- PCI laboratory results as tested against local laboratory criteria set (see Appendix IV: Potentially Clinically Important Values for list of criteria)
- Marked abnormalities, including the following criteria:
  - Alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN)
  - Bilirubin > 1.5 x ULN (where if fractioned, direct bilirubin >= 35%)
  - ALT or aspartate aminotransferase (AST) > 3 x ULN and total bilirubin (TBL) > 2 x ULN and alkaline phosphatase (ALP) > 1.5 x ULN (Hy's law)

A list of local laboratory assays planned to be performed can be found in Appendix III:Appendix III:Summary of Laboratory Assays Performed. The planned timings of laboratory sample collection are given in Appendix I: Schedule of Assessments and Procedures.

The following ECG listings will be presented for both protocol parts using the SAS:

- Quantitative results containing all the measurements listed in Table 3.
- Potentially clinically significant results.

The following ECG summary tables are planned, by treatment groups using the SAS:

- CFB with descriptive statistics on all the measurements listed in Table 3.
- Categorical Outliers and marked abnormalities, including the following criteria:

  For marked abnormalities:

  - QTcB > 450 (msec) for male subjects.
  - QTcB > 470 (msec) for female subjects.
  - Increase in QTcB from baseline ≥ 60 (msec).
  - Increase in heart rate CFB% ≥ 30% AND observed heart rate > 90 (bpm).

  For categorical outliers:

  - QTcB > 500 (msec).
  - Increase in QTcB from baseline ≥ 30 (msec) and < 60 (msec).
  - Increase in QTcB from baseline ≥ 60 (msec).
- Time-matched, placebo-adjusted QTcB CFB for all post-dose timepoints ≤ 24 hours.

The following figures are planned for presentation ECG parameter QTcB for both parts of study by treatment groups using the SAS:

- Mean observed values after study drug infusion on dosing days (by dose group)
- Mean observed values over time (excluding post-dose assessments on dosing days)
- Mean CFB after study drug infusion on dosing days (by dose group)

- Mean CFB over time (excluding post-dose assessments on dosing days)
- Placebo-corrected mean CFB in QTcB with 90% CI whiskers across post-dose timepoints up to 24 hours (by dose group)

A time-matched analysis of change in QTcB will be graphically explored. The mean CFB in QTcB versus placebo will be plotted at the different timepoints ≤ 24 hours post-dose, along with 90% 2-sided CI. The upper limit of the 90% CI should be below the 10 (msec) bound as provided by the International Conference on Harmonization (ICH) E14 guideline to be deemed as having no QTc prolongation effect. Due to the small number of subjects planned per cohort, subjects from the different cohorts will be pooled into active treatment and placebo. If any upper limits are observed above the 10 (msec) mark from the pooled plot, further exploration by cohort may be explored. The estimates and 90% CI will be obtained through an analysis of covariance (ANCOVA), using baseline QTcB as covariate and treatment (pooled active and placebo) as effect.

The following example SAS® code can be utilized and modified as needed:

```
Proc GLM Data = <Dataset>;
   By <Tmpt>;
   Class <TRT>;
   Model <CFB> = <TRT> <BaseVal> / solution;
   LSmeans <TRT> / diff cl Alpha = 0.1 pdiff;
   ods output LSMeanDiffCL = <estmt>;
   Run;
Quit;
```

Where <Dataset> is the input dataset, <Tmpt> is the timepoint, <TRT> if is the treatment group, <BaseVal> is the baseline value and <estmt> is the output set containing the estimate and corresponding 90% CI.

The data for these presentations will obtained from the following eCRFs:

- 12-Lead Electrocardiogram Details.
- Vital Signs (for heart rate).

Table 3 below gives the ECG measurements to be assessed.

Table 3. ECG Measurements

Measurement
QT interval (msec)
QT, corrected with Bazett's formula (QTcB) interval (msec)
QRS interval (msec)
PR interval (msec)
Heart Rate (HR) (bpm)

The planned timings of these ECG are given in Appendix I: Schedule of Assessments and Procedures.

12.4. VITAL SIGNS

Listings will be presented on the following vital sign items separately for both protocol parts using the SAS:

- Quantitative results on all the tests listed in Table 4.
- Potentially clinically significant results (Refer marked abnormalities listed under).

The following vital sign tables are planned to be presented, by treatment groups using the SAS:

- CFB with descriptive statistics on all the tests listed in Table 4.
- Marked abnormalities including the following criteria:
    - Decrease in systolic blood pressure (SBP) of ≥ 25 (mmHg) versus baseline (orthostatic hypotension).
    - Decrease in diastolic blood pressure (DBP) of ≥ 15 (mmHg) versus baseline (orthostatic hypotension).
    - Increase/decrease in SBP of ≥ 20 (mmHg) versus baseline.
    - Increase/decrease in DBP of ≥ 10 (mmHg) versus baseline.
    - Increase/Decrease in Weight of ≥ 7% versus baseline.
    - Increase/Decrease in Heart Rate by 15 bpm.

The data for these presentations will be obtained from the following eCRFs:

- Vital Signs.
- Physical Examination (for weight).

Table 4 below gives the vital sign tests to be performed.

Table 4. Vital Sign Tests Performed

Test
Pulse (bpm)
Pulse oximetry, SPO_2 (%)
Respiratory rate (brpm)
Supine DBP (mmHg)
Supine SBP (mmHg)
Temperature (℃)
Weight (kg)

The planned timings for the vital signs measurements are given in Appendix I: Schedule of Assessments and Procedures.

12.5. COLUMBIA SUICIDE SEVERITY RATING SCALE

The Columbia Suicide Severity Rating Scale (C-SSRS) will be listed for both protocol parts separately using the SAS.

The information for these presentations will be obtained from the following eCRFs:

- C-SSRS Screening
- C-SSRS Since Last Visit

The C-SSRS responses over time will be tabulated using count and percent by treatment groups throughout the study, using SAS.

13. OTHER RELEVANT DATA ANALYSES/SUMMARIES

13.1. HOSPITALIZATIONS AND CLINICAL UNIT CONFINEMENT

A combined listing on the following items will be presented using the SAS separately for both protocol parts:

- Hospitalizations
- Clinical unit confinement

The information for these presentations will be obtained from the following eCRFs:

- Adverse Events Details eCRF
- Clinical Unit Confinement

Duration per hospital stay is calculated in days as:

Hospitalization Duration (days) = (Discharge Date – Admission Date) + 1

Duration of clinical unit confinement is calculated in days as:

Clinical Unit Confinement Duration (days) = (Discharge Date – Admission Date) + 1

It should be noted that the above duration definitions consider part of a day to count as a whole day.

13.2. PHYSICAL AND NEUROLOGICAL EXAMINATIONS

A listing of physical and neurological examination findings for both protocol parts will be presented separately using the SAS.

The information for the listing will be obtained from the following eCRFs:

- Physical and Neurological Examination
- Physical and Neurological Exam Abnormalities

It should be noted that weight will be presented and summarized alongside the vital signs (see Section 12.4 for details), and height will be presented alongside demographics and baseline characteristics (see Section 10.2 for details).

Body systems to assess include:

- Cardiovascular
- Respiratory
- Gastrointestinal
- Neurological (Mental status, Motor and Sensory Skills, Hearing and Speech, Vision, Coordination, Balance)

13.3. IMMUNOGENICITY ANALYSIS

To assess the immunogenicity of TB006, the presence of anti TB006 antibodies, and associated titer values will be listed by patient and time point for both protocol parts using SAS.

The anti-drug antibody titer values will be summarized descriptively for all subjects, by treatment groups and baseline AD severity stratifications (for Part 2 only), using SAS. Also, the status of anti-drug antibody will be tabulated by treatment groups and baseline AD severity stratifications (for Part 2 only), using SAS.

14. REFERENCES

1. ICH E3: Structure and Content of Clinical Study Reports, CDER, FDA (1996).
2. ICH E9: Statistical Principles for Clinical Trials, CDER, FDA (1998).
3. TB006AD2102_MAD_Protocol_V3_Am2_Docusign_15Oct2021.
4. TB006AD2102_eCRF_Specification_v2.0_09NOV2021_Final
5. TRU212572_CDR_System_Statistical_Analysis_Plan_V2.0_13_Jan_2022.

15.APPENDICES

Appendix I: SCHEDULE OF ASSESSMENTS AND PROCEDURES

Table 5. Part 1 - Schedule of Activities

	Screening D -28 to D -2[a]	D -2[a]	D -1[a]	Study Drug Administration Period														Notes
				D1[a]	D2-6[a]	D8	D9-13[a]	D15[a]	D16-20[a]	D22[a]	D23-27[a]	D29[a]	D30-34[a]	D36[a]	D64[a]	D104[a]	E/D[b]	
General and Safety Assessments																		
Informed consent	X																	
Eligibility criteria	X		X															Recheck eligibility before randomization and/or first dose of study drug
Medical history[c] (includes substance usage)	X	X	X															Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section
Demography	X																	
Physical and neurological examination	X		X											X		X	X	Physical examination will include height (screening only) and weight measurements; see also Section 8.2.1 of Protocol
Randomization			X															
Vital signs	X		X	X		X		X		X		X		X	X	X	X	Pre-dose, then 2 and 6 hours after the end of the study drug infusion on D1, D8, D15, D22, D29; otherwise once on the days indicated; see Section 8.2.2 of Protocol for vital signs assessments

Table 5. Part 1 - Schedule of Activities

	Screening D -28 to D -2[a]	D -2[a]	D -1[a]	Study Drug Administration Period														Notes
				D1[a]	D2-6[a]	D8	D9-13[a]	D15[a]	D16-20[a]	D22[a]	D23-27[a]	D29[a]	D30-34[a]	D36[a]	D64[a]	D104[a]	E/D[b]	
12-lead ECG	X		X	X		X		X		X		X		X	X	X	X	D1, D8, D15, D22, D29: pre-dose, then 2 and 6 hours after end of study drug infusion D -1, D36, D64, D104, E/D: time-matched with D1, D8, D15, D22, D29 pre-dose to the extent possible
AE monitoring				X	X	X	X	X	X	X	X	X	X	X	X	X	X	All AEs and SAEs will be collected from the time of the first study drug administration until D104.
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X			X		X		X		X		X		X	X	X	X	
Clinical unit confinement		X	X	X		X		X		X		X						At least 6 hours following study drug administration on dosing days; discharge from the clinical unit will be at the discretion of the investigator provided there are no safety concerns identified from review of the clinical data. Optional overnight confinement from either D -2 or D -1 and on days prior to other dosing days (D7, D14, D21, D28)
Outpatient visit			X											X	X	X	X	If the patient is not overnight confined on D -1 (see above), the D -1 visit will be an outpatient visit

Table 5. Part 1 - Schedule of Activities

	Screening D -28 to D -2[a]	D -2[a]	D -1[a]	Study Drug Administration Period													Notes
				D1[a]	D2-6[a]	D8	D9-13[a]	D15[a]	D16-20[a]	D22[a]	D23-27[a]	D29[a]	D30-34[a]	D36[a]	D64[a]	D104[a]	E/D[b]	
Site to contact patient					X		X		X		X		X					Investigator or designee to telephone the patient between D2-6, D9-13, D16-20, D23-27, and D30-34
Central Laboratory Assessments																		
Viral serology (HBsAg, IGM anti-HBc, anti-HCV, HIV) and COVID-19	X																	
Urine alcohol	X		X									X		X				Locally performed at site
Drug screening	X		X									X		X				
Clinical laboratory tests (clinical chemistry, hematology, urinalysis)	X		X			X				X				X		X	X	
Pharmacodynamic Assessments: Cognition Testing, MRI, Blood Samples																		
MMSE	X		X					X						X	X	X	X	
Clinical Dementia Rating scale			X					X						X	X	X	X	
Cognitive Drug Research Dementia Rating battery[d]	X		X			X		X		X		X		X	X	X	X	
NPI			X											X	X	X	X	
[redacted]																		
Blood sample for PD assessment			X											X		X	X	Fluid biomarkers will be determined in plasma
Study Treatment																		
Study drug IV infusion				X		X		X		X		X						

Table 5. Part 1 - Schedule of Activities

	Screening D -28 to D -2[a]	D -2[a]	D -1[a]	Study Drug Administration Period														Notes
				D1[a]	D2-6[a]	D8	D9-13[a]	D15[a]	D16-20[a]	D22[a]	D23-27[a]	D29[a]	D30-34[a]	D36[a]	D64[a]	D104[a]	E/D[b]	
Pharmacokinetics																		
Blood sample for PK assessment				X		X						X		X	X	X	X	Pre-dose, end of infusion, then 1, 2, 4, and 6 hours after the end of infusion on D1, D8, and D29; single time point on other days
Blood sample for ApoE4 genotyping	X																	Optional ApoE4 sampling is collected at screening but can be taken at any visit until the last study visit (Section 8.7 of Protocol)
Pharmacokinetics and Pharmacodynamics																		
Blood sample for ADA assessment				X		X								X		X		ADA assessment is performed on blood sample collected for PK assessments; D1 and D8 assessment is performed on the pre-dose sample
Lumbar puncture for CSF collection[e]			X											X				Lumbar puncture indicated for D-1 can be performed any time between D-8 and D-1 CSF biomarkers, and TB006 levels will be determined in CSF

[redacted] AD = Alzheimer's Disease; ADA = anti-drug antibody; AE = adverse event; anti-HCV = hepatitis C virus antibody; ApoE4 = apolipoprotein E4; COVID = coronavirus disease; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; CSF = cerebrospinal fluid; D = Day; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG = electrocardiogram; E/D = Early Discontinuation; HBsAg = hepatitis B surface antigen; IgM anti-HBc = immunoglobulin M antibody to hepatitis B core antibody; IV = intravenous(ly); MMSE = Mini-Mental State Examination; [redacted] NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association; NPI = Neuropsychiatric Inventory; PD = pharmacodynamic(s); [redacted] PK = pharmacokinetic(s); SAE = serious adverse event.

a Visit days and procedures are allowed a window of ± 2 days from Day 1 to End of Treatment.

b Applicable only for patients who discontinue early from the study.

c The medical history assessed at the screening visit should include prior AD treatment assessment(s). Establishing the clinical diagnosis of AD should include use of criteria from the DSM-5 – Criteria for Major Neurocognitive Disorder (previously dementia) (Section 10.4 of Protocol, Appendix 4) and the NINCDS-ADRDA (Note: ADRDA is now the Alzheimer's Association) (Section 10.5 or Protocol, Appendix 5).

d The Cognitive Drug Research battery is to be performed twice during the screening visit in both Part 1 and Part 2.

e The lumbar puncture procedure is optional.

[redacted]

Table 6. Part 2 - Schedule of Activities

	Screening D -28 to D -2[a]	D -2[a]	D -1[a]	Study Drug Administration Period														Notes
				D1[a]	D2-6[a]	D8	D9-13[a]	D15[a]	D16-20[a]	D22[a]	D23-27[a]	D29[a]	D30-34[a]	D36[a]	D64[a]	D104[a]	E/D[b]	
General and Safety Assessments																		
Informed consent	X																	
Eligibility criteria	X		X															Recheck eligibility before randomization and/or first dose of study drug
Medical history[c] (includes substance usage)	X	X	X															Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section
Demography	X																	
Physical and neurological examination	X		X											X		X	X	Physical examination will include height (screening only) and weight measurements; see also Section 8.2.1 of Protocol.
Randomization			X															
Vital signs	X		X	X		X		X		X		X		X	X	X	X	Pre-dose, then 2 and 6 hours after the end of the study drug infusion on D1, D8, D15, D22, D29; otherwise once on the days indicated; see Section 8.2.2 of Protocol for vital signs assessments

Table 6. Part 2 - Schedule of Activities

	Screening D -28 to D -2[a]	D -2[a]	D -1[a]	Study Drug Administration Period													Notes
				D1[a]	D2-6[a]	D8	D9-13[a]	D15[a]	D16-20[a]	D22[a]	D23-27[a]	D29[a]	D30-34[a]	D36[a]	D64[a]	D104[a]	E/D[b]	
12-lead ECG	X		X	X		X		X		X		X		X		X	X	D1, D8, D15, D22, D29: pre-dose, then after end of study drug infusion D -1, D36, D104, E/D: time-matched with D1, D8, D15, D22, D29 pre-dose to the extent possible
AE monitoring				X	X	X	X	X	X	X	X	X	X	X	X	X	X	All AEs and SAEs will be collected from the time of the first study drug administration until D104.
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X			X		X		X		X		X		X	X	X	X	
Clinical unit confinement		X	X	X		X		X		X		X						At least 6 hours following study drug administration on dosing days; discharge from the clinical unit will be at the discretion of the investigator provided there are no safety concerns identified from review of the clinical data. Optional overnight confinement from either D -2 or D -1 and on days prior to other dosing days (D7, D14, D21, D28)
Outpatient visit			X											X	X	X	X	If the patient is not overnight confined on D -1 (see above), the D -1 visit will be an outpatient visit

Table 6. Part 2 - Schedule of Activities

	Screening D -28 to D -2[a]	D -2[a]	D -1[a]	Study Drug Administration Period													Notes
				D1[a]	D2-6[a]	D8	D9-13[a]	D15[a]	D16-20[a]	D22[a]	D23-27[a]	D29[a]	D30-34[a]	D36[a]	D64[a]	D104[a]	E/D[b]	
Site to contact patient					X		X		X		X		X					Investigator or designee to telephone the patient between D2-6, D9-13, D16-20, D23-27, and D30-34
Central Laboratory Assessments																		
Viral serology (HBsAg, IGM anti-HBc, anti-HCV, HIV) and COVID-19	X																	
Urine alcohol	X		X									X		X				Locally performed at site
Drug screening	X		X									X		X				
Clinical laboratory tests (clinical chemistry, hematology, urinalysis)	X		X			X				X				X		X	X	
Pharmacodynamic Assessments: Cognition Testing, MRI, Blood Samples																		
MMSE	X		X					X						X	X	X	X	
Clinical Dementia Rating scale			X					X						X	X	X	X	
Cognitive Drug Research System battery[d]	X		X			X		X		X		X		X	X	X	X	
NPI			X											X	X	X	X	
[redacted]																		
Blood sample for PD assessment			X											X		X	X	Fluid biomarkers will be determined in plasma
Study Treatment																		
Study drug IV infusion				X		X		X		X		X						

Table 6. Part 2 - Schedule of Activities

	Screening D -28 to D -2[a]	D -2[a]	D -1[a]	Study Drug Administration Period														Notes
				D1[a]	D2-6[a]	D8	D9-13[a]	D15[a]	D16-20[a]	D22[a]	D23-27[a]	D29[a]	D30-34[a]	D36[a]	D64[a]	D104[a]	E/D[b]	
Pharmacokinetics																		
Blood sample for PK assessment				X								X		X	X	X	X	Pre-dose and the end of infusion on D1 and D29; single sample on other days
Blood sample for ADA assessment				X										X		X		ADA assessment is performed on blood sample collected for PK assessments; D1 assessment is performed on the pre-dose sample
Blood sample for ApoE4 genotyping	X																	Optional ApoE4 sampling is collected at screening but can be taken at any visit until the last study visit (Section 8.7 of Protocol)

[redacted] AD = Alzheimer's Disease; ADA = anti-drug antibody; AE = adverse event; anti-HCV = hepatitis C virus antibody; ApoE4 = apolipoprotein E4; COVID = coronavirus disease; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG = electrocardiogram; E/D = Early Discontinuation; HBsAg = hepatitis B surface antigen; IgM anti-HBc = immunoglobulin M antibody to hepatitis B core antibody; IV = intravenous(ly); MMSE = Mini-Mental State Examination; [redacted] NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association; NPI = Neuropsychiatric Inventory; [redacted] PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event.

a Visit days and procedures are allowed a window of ± 2 days from Day 1 to End of Treatment.

b Applicable only for patients who discontinue early from the study.

c The medical history assessed at the screening visit should include prior AD treatment assessment(s). Establishing the clinical diagnosis of AD should include use of criteria from the DSM-5 – Criteria for Major Neurocognitive Disorder (previously dementia) (Section 10.3 of Protocol, Appendix 4) and the NINCDS-ADRDA (Note: ADRDA is now the Alzheimer's Association) (Section 10.4 of Protocol, Appendix 5).

d The Cognitive Drug Research battery is to be performed twice during the screening visit in both Part 1 and Part 2.

[redacted]

Appendix II: SUMMARY OF EFFICACY ANALYSES

Parameter	*Population*	*Statistical Method*	*Protocol Part*	*Interpretation*
[redacted]				
CDRS – Sum of Boxes total score	*EAS2*	*MMRM*	*Part 2*	*Primary analysis*
CDRS – Proportion of respondent	*EAS2*	*CMH*	*Part 2*	*Secondary analysis*
MMSE score	*EAS2*	*MMRM*	*Part 2*	*Secondary analysis*
NPI score	*EAS2*	*MMRM*	*Part 2*	*Secondary analysis*
CDRS	*EAS2*	*Descriptive statistics*	*Part 2*	*Secondary analysis*
CDRS – Proportion of respondent	*EAS2*	*Descriptive statistics*	*Part 2*	*Secondary analysis*
MMSE score	*EAS2*	*Descriptive statistics*	*Part 2*	*Secondary analysis*
NPI score	*EAS2*	*Descriptive statistics*	*Part 2*	*Secondary analysis*
[redacted]				

Appendix III: Summary of Laboratory Assays Performed

Laboratory Category	*Assay Grouping*	*Assay*
Chemistry	*Electrolytes*	Glucose
		Potassium
		Sodium
		Calcium
	Renal Function	Blood Urea Nitrogen (BUN)
		Creatinine
	Liver Function	Alanine Aminotransferase (ALT)
		Aspartate Aminotransferase (AST)
		Albumin
		Creatine Phosphokinase (CPK)
		Alkaline phosphatase
		Total Bilirubin
		Direct Bilirubin
		Total Protein
	Lipid Profile	Total Cholesterol
		High-density Lipoprotein (HDL) Cholesterol
		Low-density Lipoprotein (LDL) Cholesterol
		Triglycerides
		Thyroid-stimulating Hormone (TSH)
		Hemoglobin A1c (HbA1c)
Hematology	*RBC indices*	Platelet count
		Red Blood Cell (RBC) count / Erythrocytes
		Hemoglobin
		Hematocrit
		Ery. Mean Corpuscular volume (MCV)
		Ery. Mean Corpuscular Hemoglobin (MCH)
		Leukocytes
	White Blood Cell (WBC) Count with differential	Neutrophils Absolute
		Neutrophils Percent
		Lymphocytes Absolute
		Lymphocytes Percent
		Monocytes Absolute
		Monocytes Percent
		Eosinophils Absolute
		Eosinophils Percent
		Reticulocytes Absolute
		Reticulocytes Percent
		Basophils Absolute
		Basophils Percent
Urinalysis (dipstick)		Specific Gravity
		pH
		Glucose
		Protein

Laboratory Category	*Assay Grouping*	*Assay*
		Occult Blood
		Ketones
		Bilirubin
		Urobilinogen
		Nitrite
		Leukocyte esterase
		Microscopic examination if blood or protein is abnormal
Other Screening Tests	*Viral serology*	Hepatitis B surface antigen (HBsAg)
		IgM Hepatitis B core antibody (anti-HBc)
		Hepatitis C antibody (Anti-HCV)
		Human immunodeficiency virus (HIV)
		COVID19
	Non-childbearing potential only	Follicle-stimulating Hormone (FSH)
		Estradiol
	Plasma Alcohol and Urine Blood Screen	Alcohol
		Optiates
		Methadone
		Buprenorphine
		Methamphetamine
		Cocaine
		Amphetamines
	WOCBP	Highly sensitive human chorionic-gonatropin (hCG) pregnancy test

Appendix IV: Potentially Clinically Important Values

The following table contains a list of ranges used by the laboratory to flag critical laboratory values which will also be used in this study to identify any potentially clinically important values within the table and listings presentations. If a planned laboratory assay does not have applicable PCI criteria limits, that assay is not included in the below table.

Laboratory Category	*Assay*	*Unit*	*PCI Criteria Value Limits*	
			Lower	*Upper*
Chemistry	*Albumin*	*g/dL*	*2.0*	*6.0*
	Alkaline Phosphatase	*IU/L*	*NA*	*200*
	Alanine Aminotransferase	*IU/L*	*NA*	*150*
	Aspartate Aminotransferase	*IU/L*	*NA*	*150*
	Bilirubin	*mg/dL*	*NA*	*2.50*
	Blood Urea Nitrogen	*mg/dL*	*NA*	*30.0*
	Calcium	*mg/dL*	*7.0*	*13.5*
	Glucose	*mg/dL*	*40*	*250*
	Potassium	*mmol/L*	*3.2*	*6.0*
	Sodium	*mmol/L*	*130*	*150*
Hematology	*Hematocrit (Female)*	*%*	*24.0*	*54.0*
	Hematocrit (Male)	*%*	*24.0*	*60.0*
	Hemoglobin (Female)	*g/dL*	*8.0*	*18.0*
	Hemoglobin (Male)	*g/dL*	*8.0*	*20.0*
	Lymphocytes	*0^3/uL*	*0.50*	*NA*
	Neutrophils	*0^3/uL*	*1.00*	*NA*
	Platelets	*0^3/uL*	*75*	*750*
	Leukocytes	*0^3/uL*	*2.5*	*25.0*
Other Screening Tests	*Human immunodeficiency virus (HIV)*		*Positive*	
	COVID19		*Positive*	
	Optiates		*Positive*	
	Methadone		*Positive*	
	Buprenorphine		*Positive*	
	Methamphetamine		*Positive*	
	Cocaine		*Positive*	
	Amphetamines		*Positive*	

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Subject: Please DocuSign: TB006AD2102_SAP_Ver 2.0_11Apr2022.docx
Source Envelope:
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[redacted] [redacted] MMS Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signed by link sent to [redacted] Signature ID: CAD557FF-FDB2-4E87-ADA8-0676AEB4ABC2 Using [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 4/12/2022 3:32:45 AM Viewed: 4/12/2022 3:47:29 AM Signed: 4/12/2022 3:50:04 AM
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Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	4/12/2022 3:32:46 AM
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Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
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ADDENDUM TO STATISTICAL ANALYSIS PLAN: TB006AD2102
FINAL VERSION 2.0 DATED 11 APRIL 2022

Study Title:	A Seamless Phase 1b/2a Double-blind, Randomized, Multiple dose, Multi-center, Sequential Dose-escalation Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of TB006 in Patients with Mild to Severe Alzheimer's Disease
Study Number:	TB006AD2102
Study Phase:	Phase 1b/2a
Sponsor:	TrueBinding, Inc. 300 Lincoln Center Drive Suite 200 Foster City, CA, 94404
Addendum Version:	Final ver 1.0
NCT Number:	NCT05074498
Date:	14Nov2022

Confidentiality Statement

Table of Contents

1. SIGNATURE PAGE

Study Title: A Seamless Phase 1b/2a Double-blind, Randomized, Multiple dose, Multi-center, Sequential Dose-escalation Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of TB006 in Patients with Mild to Severe

Study Number: TB006AD2102

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Prepared by: _____ Date:_____
[redacted], PhD
Principal Biostatistician, Biometrics
MMS Holdings, Inc

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Senior Biostatistician II, Biometrics
MMS Holdings, Inc

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Date: Nov 14, 2022 07:20 EST

Approved by: _____ Date:_____
[redacted] PharmD
Clinical Development Lead
TrueBinding, Inc.

2. PURPOSE

The Statistical Analysis Plan (SAP) version 2.0 dated 11 April 2022 need to clarify the definition of Efficacy Analysis Set-Part 2 (EAS2). The EAS2 is defined in SAP as:

> The Part 2 – Efficacy Analysis Set (EAS2) includes all subjects who received assigned dose of TB006 in Part 2 and the subjects enrolled at the same TB006 dose level in Part 1, as well as all placebo patients will be included and have at least one post-dose evaluable PD assessment across subject.

Here "PD assessment" can be mistaken to refer to plasma or imaging biomarkers and hence the definition for EAS2 is clarified in addendum SAP to replace text "PD" with text "efficacy". The updated definition is as under:

> The Part 2 – Efficacy Analysis Set (EAS2) includes all subjects who received assigned dose of TB006 in Part 2 and the subjects enrolled at the same TB006 dose level in Part 1, as well as all placebo patients will be included and have at least one post-dose evaluable **efficacy** assessment across subject.

3. DESCRIPTIONS OF CHANGES IN STUDY CONDUCT AND ANALYSIS PLANNED IN PROTOCOL AND STATISTICAL ANALYSIS PLAN

This change will only impact the analysis population definition in SAP version 2.0 dated 11 April 2022, Section 7.1.5.

4. REFERENCES

1. TrueBinding TB006AD2102 Statistical Analysis Plan Version 2.0 Final signed, dated 11 April 2022.