Statistical Analysis Plan

Protocol Title:		A Multi-center Open-label Long Term Extension Study to Assess the Safety of TB006 in Patients who have completed Protocol TB006AD2102 and in De Novo Patients with Alzheimer's Disease	
Protocol Number:		TB006AD2104	
Compound Number:		**TB006**	
Short Title:		An open-label long term extension study to assess the safety of TB006 in patients with Alzheimer's Disease	
Acronym:		NA	
Sponsor	**Sponsor Name:**	TrueBinding, Inc.	
	Legal Registered Address:	[redacted]	
	Sponsor Phone Number:	[redacted]	
Statistical Analysis Plan	**Name:**	[redacted]	
	Function:	Biostatistics	
Regulatory Agency Identifier Number(s)		**Registry**	**Identifier Number**
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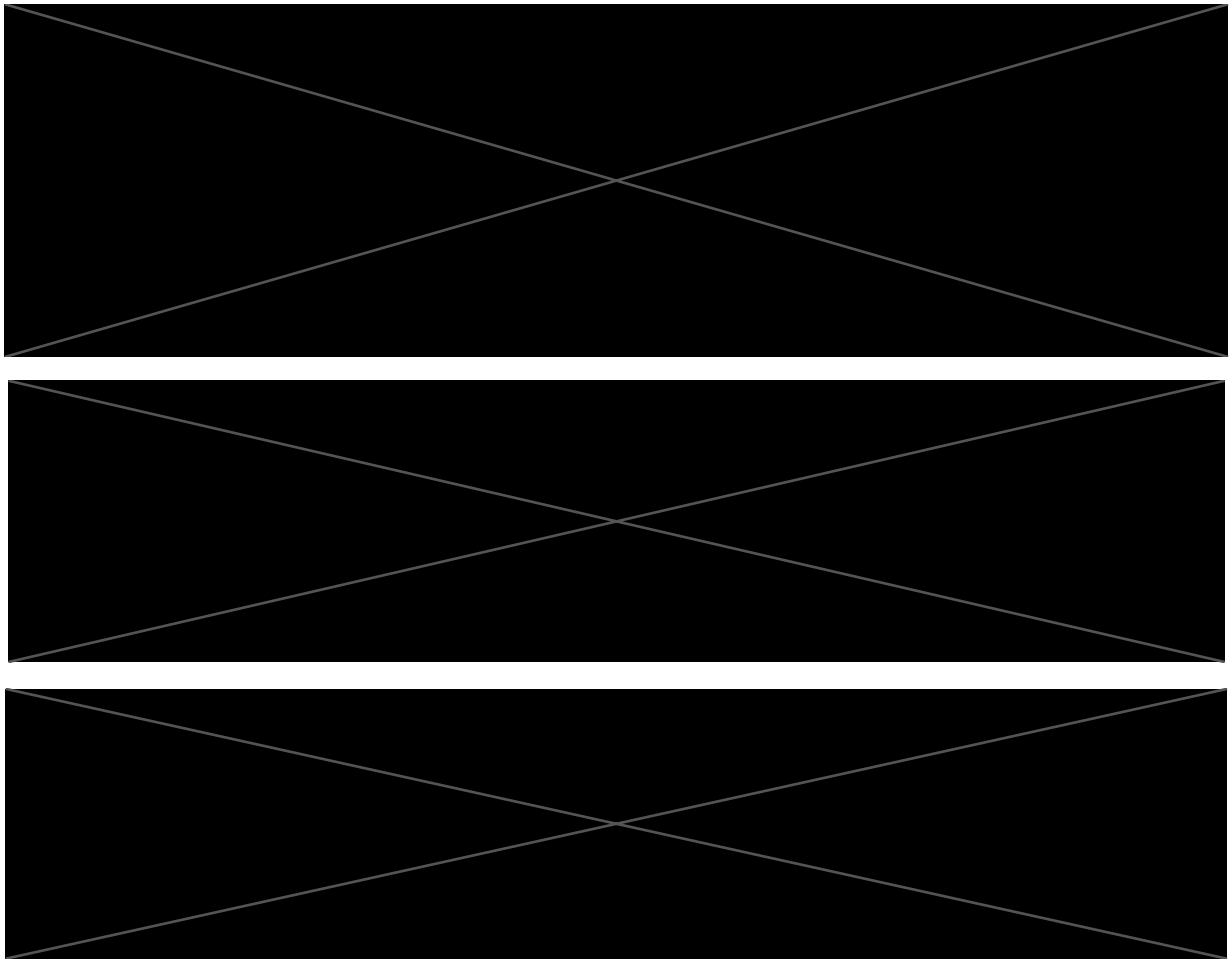
Statistical Analysis Plan Date:	Document Version	Date
	Original (v 1.0)	25 Oct 2023
	v 2.0	05 Jan 2024

CONFIDENTIALITY NOTICE

Study Title: A Multi-center Open-label Long Term Extension Study to Assess the Safety of TB006 in Patients who have completed Protocol TB006AD2102 and in De Novo Patients with Alzheimer's Disease

Study Number: TB006AD2104



Version History

This statistical analysis plan (SAP) for Study: A Multi-center Open-label Long Term Extension Study to Assess the Safety of TB006 in Patients who have completed Protocol TB006AD2102 and in De Novo Patients with Alzheimer's Disease is based on protocol Amendment 2 (V3.0) dated 16 Feb 2023.

SAP Version	Approval Date	Change	Rationale
1	25 Oct 2023	Not applicable	Original version
2	05 Jan 2024	CDR System battery analyses description in Section 4.8.1.2 have been removed and replaced with text referencing the CDR System battery SAP	The CDR System analyses will be analyzed separately as described in the CDR System battery SAP.

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List of Abbreviations

Abbreviation	Definition
ACR	Assessment/Collection/Result
AD	Alzheimer's Disease
ADA	Anti-Drug Antibody
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti-HBc	Hepatitis B Core Antibodies
Anti-HCV	Hepatitis C Virus Antibodies
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
[redacted]	
bpm	Beats per minute
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
CDR	Cognitive Drug Research
CDR-SB	Clinical Dementia Rating Scale-Sum of Boxes
CEC	Clinical Endpoint Criteria
CFB	Change from Baseline
COVID-19	Coronavirus Disease
CS	Clinically Significant
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Arithmetic Coefficients of Variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EoS	End of Study
EQ-5D-5L	EuroQoL 5-Dimension 5-Level
ET	Early Termination
EuroQol	EuroQuality of life
eCRF	electronic Case Report Form
[redacted]	
GCV%	Geometric Coefficients of Variation

Abbreviation	Definition
GSD	Geometric Standard Deviation
HBsAg	Hepatitis B Surface Antigen
HR	Heart Rate
IgM	Immunoglobulin M Antibodies
IP	Investigational Product
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
[redacted]	
msec	Milliseconds
NCI	National Cancer Institute
NCS	Not Clinically Significant
[redacted]	
NPI	Neuropsychiatry Inventory
NPI-D	Neuropsychiatry Inventory Caregiver Distress
OLE	Open-label Extension
PCI	Potentially Clinically Important
PCS	Potentially Clinically Significant
PD	Pharmacodynamics
PDS	Pharmacodynamic Set
[redacted]	
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PT	Preferred Term
q28day	Every 28 Days
QoL	Quality of Life
QTc	QT interval corrected
QTcB	QT Corrected Interval Using Bazett Formula
QTcF	QT Corrected Interval Using Fridericia's Formula
RA	Regulatory Approval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SAS-AE	Safety Analysis Set-Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation

Abbreviation	Definition
SoA	Schedule of Assessment
SOC	System Organ Class
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WHO-DD	World Health Organization-Drug Dictionary

1. Introduction

The purpose of this SAP is to describe the framework and methodology for the reporting, summarization and statistical analyses of the safety and efficacy parameters measured throughout the study. It is based on Protocol TB006AD2104 Amendment 2 (v3.0) dated 16 Feb 2023. All planned analyses specified in this document will be performed. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the clinical study report. Any changes to this plan, in the form of "post-hoc" or "data driven" analyses will be identified as such in the clinical study report.

1.1. Study Objectives, Endpoints, and Estimands

1.1.1. Objectives and Endpoints

The primary, secondary, and exploratory objectives and associated endpoints are specified in Table 1.

Table 1. Study Objectives and Associated Endpoints

Objectives	Endpoints
Primary	
• To determine the long-term safety and tolerability of monthly doses of TB006	• Safety endpoints, including the incidence of AEs, and, SAEs, as well as assessment of clinical laboratory parameters, vital signs, ECGs, C-SSRS, [redacted] and physical and neurological examinations, un eek 113 after the first TB006 dosing
• To determine the PK profile of monthly doses of TB006	• Plasma concentration of TB006 over time
• To assess the immunogenicity of TB006 (production of anti-TB006 antibodies)	• Detection of anti-TB006 antibodies
Secondary	
• To determine the effects of monthly TB006 doses on disease progression or recovery using standard measures of cognition and quality of life	• Change from Baseline through Week 101 on the CDR-SB score • Change from Baseline through Week 101 on the CDR battery composite scores and individual task measures* • Change from Baseline through Week 101 on the MMSE score • Change from Baseline through Week 101 on the NPI score • Change from Baseline through Week 101 on the EQ-5D-5L QoL total score [redacted]

	[redacted]
Exploratory	
• To determine the PD effects of TB006 on plasma AD biomarkers	[redacted]

[redacted] D = Alzheimer's Disease; AEs = adverse events; CDR = Cognitive Drug Research System; CDR-SB = Clinical Dementia Rating-Sum of Boxes; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D-5L = EuroQoL 5-Dimension 5-Level; [redacted] MMSE = Mini Mental Status Exam; [redacted] NPI = Neuropsyc atr c Inventory; [redacted]; PD = p armaco ynam c PK = pharmacokinetic(s); SAE = serious a verse event. DR ystem attery will be analyzed separately as defined in the CDR System battery SAP.

1.1.2. Estimands

No formal hypothesis testing, nor any inferential statistics or statistical modelling is planned under this protocol. As such, the usual considerations around estimands and their handling is not applicable. The following intercurrent scenario has been considered in the Amendment 2 protocol though: As Alzheimer's Disease (AD) is a progressive disease, the proposed patient completion rate of this 2-year study is estimated to be below 30%, and additional long-term exposure data may be required prior to moving forward to Phase 3. Adding de novo patients to the study design is expected to provide additional long-term safety data, providing a better baseline of data needs for future intervals.

[redacted]

1.2. Study Design

This is an open-label extension (OLE) study for patients with AD who: 1) have completed Protocol TB006AD2102 (lead-in study) or 2) would have been eligible for the lead-in study but were not enrolled (de novo). This OLE study is designed to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of TB006. The total study duration for each patient will be up to 113 weeks.

Enrollment into this study may begin immediately upon completion of the End of Study (EoS) procedures of the lead-in study, with the first dose administered the same day or within 28 days post EoS procedures. For these patients, the EoS procedures conducted in Protocol TB006AD2102 will be used as baseline values for this OLE study. Patients completing the lead-in study more than 28 days prior to the start of the OLE study must undergo screening procedures with the exception of imaging. De novo patients will be identified by the sponsor and referred to one of the participating sites. De novo patients must undergo all screening procedures. Eligibility must be confirmed (de novo patients) or reconfirmed (lead-in study patients).

In this study, all patients will receive TB006 at a dose of 4,000 mg via a 1-hour continuous intravenous (IV) infusion every 28 days (q28day), (± 5 days). Patients will remain in the clinic for at least 2 hours following the end of the infusion for observation and safety assessments.

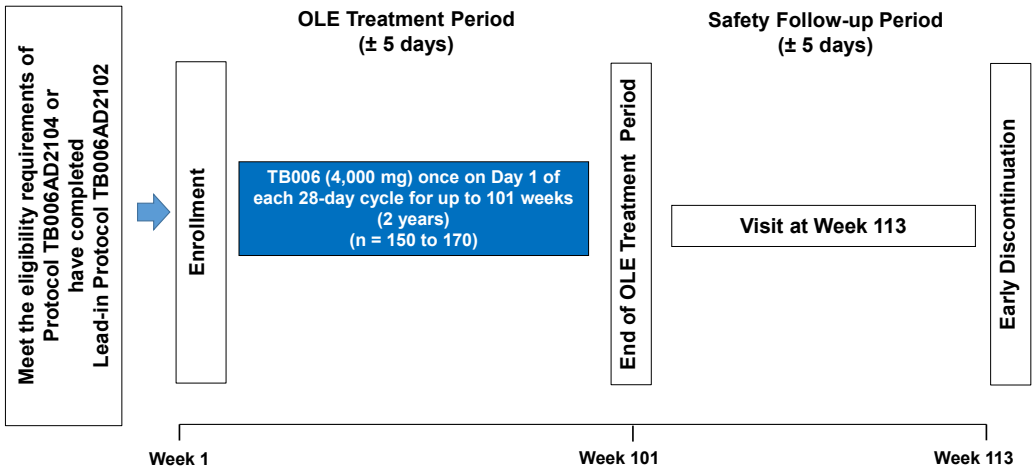
Patients will return to the clinic q28day for dose administration and safety assessments. All visits have a window of 11 days (± 5 days from scheduled visit). The window is based on an original visit schedule planned from the start of the study. If a patient deviates within the window, the original schedule is retained. If a patient misses a visit or is outside the window, the visit is typically skipped but the monitor must be notified for further instructions.

Patients will perform a battery of cognition and quality of life (QoL) tests, and biomarker testing, including the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), the Cognitive Drug Research (CDR), the EuroQuality of life (EuroQol) 5-Dimension 5-Level (EQ-5D-5L) assessment, and the Neuropsychiatry Inventory (NPI). Patients will also undergo [redacted] All procedures and study assessments are presented in the Schedule of ssessments o ection 6.1). Patients will return to the clinic approximately 3 months following the last dose according to the SoA, for the follow-up visit, which includes safety assessments, cognition testing, QoL, [redacted] PK, PD sampling. If a patient reports any Adverse events (AEs), t ey may e requ re to return to the clinical unit at the discretion of the investigator for additional assessments. All AEs must be followed to adequate resolution.

1.3. Schema

The outline for study scheme is described in Figure 1.

Figure 1. Study Schema



OLE = open-label extension

2. Statistical Hypotheses

No formal statistical hypotheses will be tested in this study, since the primary objective is to assess the safety, tolerability, and PK of TB006.

2.1. Multiplicity Adjustment

Not applicable

3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Patient Analysis Set	Description
Screened Population	All patients who have completed the lead-in study TB006AD2102 and eligible de novo patients with AD.
Enrolled Population	All screened patients who agree to participate in this study or met reconfirmed eligibility (if subject discontinued from lead-in study > 28 days before screening for this study) and provided signed informed consent (or assent).
Safety analysis set (SAS)	All patients who take at least 1 dose of study drug under this protocol.
Safety analysis set-Adverse event (SAS-AE)	All patients who take at least 1 dose of study drug under this protocol or lead-in study TB006AD2102.
Pharmacokinetic set (PKS)	All subjects who received their assigned dose of TB006 and have at least 1 post-dose blood sample with measurable TB006 concentrations.
Pharmacodynamic set (PDS)	All subjects who received at least one dose of study drug and have at least 1 post-dose evaluable PD/efficacy assessment.

The Enrolled Population is used to analyze disposition and protocol deviations. The SAS-AE will be used for all AE related displays and SAS will be used for all other safety analyses. The PKS will be used for all PK analyses. Efficacy and PD analysis will be performed using the PDS.

If there is any case of an enrolled subject not treated, then demographic tables will be repeated for the Enrolled Population.

4. Statistical Analyses

4.1. Overall Statistical Considerations

4.1.1. General Considerations

Summary statistics will be presented for categorical data as number and percentage [n (%)] where the percentage is displayed to one decimal point (eg, 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)
- Standard Deviation (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 under this protocol and will thus in most cases coincide with the visit naming (eg, Day 1 will be on study day = 1, Day 29 will be on study day = 29 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 tables will be displayed by treatment group: TB006 4,000 mg q28day.

4.1.2. Baseline and Change from Baseline Definition

Values from the most recent ACR (including ACRs from planned or unscheduled visits) prior to the first dose of study drug (ie, on Day 1) will be considered for the Baseline value. 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.

Change from baseline (CFB) is calculated as difference between post baseline observation and associated baseline observation, ie, CFB is calculated as:

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

Percentage CFB (CFB%) is calculated as:

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

If Baseline value is non-missing and zero (ie, 0) for biomarker records, then the record will not be considered for CFB% calculation.

4.1.3. Handling of PK Concentrations Values Below Limit of Quantification

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

- Observed BLQ concentrations will be set to zero for calculation of summary statistics.
- The BLQ concentration will be excluded from semi-log plots for PK concentrations.
- In listing presentation these values will be marked/footnoted as being BLQ.

4.1.4. Handling of Missing Information

There will be no imputation of missing data. Only the missing dates for adverse events, medications/procedures will be imputed for identification/calculation purposes.

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

Table 2. 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
		Y prior to Y of first dose of study drug and not the same as Y of Screening date	Jan 01
		Y post to Y of first dose of study drug	Jan 01

Parameter	Missing	Additional Conditions	Imputation
	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.

The imputed dates will not be included in any displays and will not be used for study day calculation.

4.1.5. Pooling Strategy for Study Sites

Patient pooling by study site will not be conducted. Patients will be summarized per treatment arm only (TB006 4,000 mg q28day).

4.1.6. 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 identification of Baseline values. Results from unscheduled visits will also be considered eligible for testing of marked abnormalities, potentially clinically important (PCI), and potentially clinically significant (PCS) values (eg, electrocardiogram [ECG], and vital signs).

4.2. Patient Disposition

Criteria for study inclusion, exclusion, screen failure and discontinuation of study drug or patient withdrawal from the study are described in detail in Sections 5.1, 5.2, 5.4 and Sections 7.1 and 7.2 of the Protocol. The following disposition listings are planned, using the analysis set indicated in parentheses:

- Screen failures (Screened)

- Inclusion/exclusion violations (Screened)
- Disposition: includes patient completion/discontinuation information (Enrolled)
- Inclusion/exclusion from analysis sets (Enrolled)

The following disposition related items are planned to be tabulated using summary and descriptive statistics (as applicable), using the analysis set indicated in parentheses:

- Patient disposition (Screened): Includes breakdown by reason for patient discontinuation; the number of patients screened, enrolled, and treated; and the number of patients completed and discontinued; number of patients within each analysis set

The data for these presentations are obtained from the following electronic Case Report Form (eCRF) pages:

- Informed consent
- Screen failure
- Inclusion and exclusion Criteria
- EoS

4.3. Protocol Deviations

All patient data will be reviewed for the occurrence of protocol deviations (as defined in Section 10.1.9 of the Protocol). Protocol deviations will be listed for the Enrolled population.

Summaries will be presented showing the number and percentage of patients within each deviation category for:

- Major protocol deviations (Enrolled)
- All protocol deviations (Enrolled)

Deviation categories are as follows:

- Informed Consent
- Eligibility and Entry Criteria
- Concomitant Medication Criteria
- Laboratory Assessment Criteria
- Study Procedures Criteria
- Serious Adverse Event Criteria
- Visit Schedule Criteria
- Administrative Criteria

- Investigational Product (IP) Compliance
- Source Document Criteria
- Efficacy Criteria
- Regulatory Approval (RA) or Clinical Endpoint Criteria (CEC) Approvals Criteria
- Other Criteria

The data for these presentations are obtained from the following eCRF:

- Protocol deviation

4.3.1. Definition of Major Protocol Deviations

Major Protocol Deviations are defined as procedures that are not followed or implemented per protocol that could affect or have adversely affected the rights, safety or welfare of the patients in a study. This definition also includes any situation that may significantly impact the completeness, accuracy, interpretability, and/or reliability of the study data.

Major Protocol Deviations include but are not limited to:

- Written informed consent not obtained or not appropriately obtained before initiation of study-related procedures
- Patient not meeting protocol defined eligibility criteria
- A drug dispensing or dosing error
- A significant protocol-required assessment or procedure not being performed
- Intentional misconduct, fraud, or falsification of data

4.4. Demographics and Baseline Characteristics

Demographics and baseline characteristic information will be obtained as specified in Section 8.1 of the Protocol. The following demographic and baseline characteristics are planned to be listed, using the SAS:

- Patient demographics:
    - Age
    - Sex
    - Race
    - Ethnicity
- Baseline vital characteristics:
    - Height (cm)

  - Weight (kg)
  - Body mass index (BMI) (kg/m^2)
  - Childbearing potential
- Baseline recreational substance usage (medical history page), including:
  - Tobacco/nicotine use
  - Alcohol use
  - Recreational drug use history
- Drug and alcohol screening (listed in the safety section of the shells 16.2-8.1.5):
  - Breathalyzer test results
  - Recreational drug screen test results

The above demographic, baseline characteristics and substance use (history and screening) items, are planned to be tabulated using summary and descriptive statistics (as applicable) for SAS. If there is any case of an enrolled patient not treated, then demographic tables will be repeated for the Enrolled Population.

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

- Demography
- Physical and neurological examination (for baseline height/weight). BMI will be re-derived and not presented as collected.
- Medical history (for tobacco/nicotine and alcohol use medical history)
- Drug and Alcohol Screening

The BMI at Baseline will be derived using the following formula:

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

4.5. 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 Mar 2022 format or later.

Details for recording prior and concomitant medications and procedures are described in Section 6.8 of the Protocol.

Listings of prior and concomitant medications/procedures will be presented using SAS.

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

- Prior medications/procedures (SAS)
- Concomitant medications/procedures (SAS)

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

- Concomitant Medications
    - Prior and Concomitant Medications
    - Prior and Concomitant Medications Details
- Concomitant Procedures
    - Concomitant Procedures
    - Concomitant Procedures Details

The prior/concomitant status will be derived using the medication/procedure start and stop dates as per definition provided at the start of this section. For partial dates see Section 4.1.4.

4.6. Medical History and Viral Serology

The medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0, Mar 2022 or later. Sample collection for viral serology and Coronavirus Disease (COVID-19) screening will be conducted as specified in Section 10.2 and Section 10.6 of the Protocol, at the timepoints indicated in the SoA (Section 6.1). Viral serology analysis and COVID-19 screening will be done by an external vendor and therefore will not form part of this SAP.

The following medical history, and COVID-19 baseline characteristic items will be listed using SAS:

- Medical history
    - Medical conditions or events reported
- Viral serology
    - Hepatitis B surface antigen (HBsAg)
    - Immunoglobulin M antibodies (IgM) Hepatitis B core antibodies (Anti-HBc)
    - Hepatitis C virus antibodies (Anti-HCV)
- COVID-19 screening

Medical history will be tabulated by system organ class (SOC), preferred term (PT), using SAS.

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

- Medical History
- Medical History Details
- COVID-19 Screening

4.7. Exposure and Drug Accountability

A listing of patient exposure to all the study drug infusions of TB006 will be presented using SAS, including date/time of start and EoS drug infusion, treatment compliance information, and dose interruption information.

A table containing summary statistics of the number of study drug infusions will be presented using SAS.

Treatment compliance is defined as the number of IV infusions (including partial doses) received, divided by the number of doses expected (× 100), over the time defined by the first infusion date and the last infusion date for the following:

- End of participation: considering the number of doses expected until the last scheduled assessment of the patient before discontinuation or completed study protocol.

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

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

- Study Drug IV Infusion

4.8. Efficacy

All the efficacy analysis will be performed using the PDS. Summary statistics will be presented for the overall PDS.

Table 3. Summary of Efficacy Analysis:

Parameter	Population	Statistical Method	Interpretation	Table Number
CDR-SB	PDS	Descriptive statistics	Secondary analysis	14.2-1.1
CDR-SB Proportion of Responders	PDS	Descriptive statistics	Secondary analysis	14.2-1.2
CDR System Battery*	PDS	Descriptive statistics	Secondary analysis	14.2-1.3
MMSE Score	PDS	Descriptive statistics	Secondary analysis	14.2-1.4
NPI Score	PDS	Descriptive statistics	Secondary analysis	14.2-1.5
EQ-5D-5L Health score	PDS	Descriptive statistics	Secondary analysis	14.2-1.6
EQ-5D-5L Individual Items	PDS	Descriptive statistics	Secondary analysis	14.2-1.7

*CDR System battery will be analyzed separately as defined in the CDR System battery SAP

4.8.1. Secondary Analysis: Cognition Tests and Quality of Life Assessments

4.8.1.1. Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB)

The Clinical Dementia Rating Scale is a global assessment instrument that yields a global score and a sum of boxes score. The Clinical Dementia Rating Scale is derived from a semi-structured interview with the patient and an appropriate informant, and it rates impairment in 6 categories (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) on a 5-point scale for which 0 = no impairment, 0.5 = questionable impairment, and 1, 2, and 3 indicates mild, moderate, and severe impairment, respectively.

From the 6 individual category CFB ratings, or box scores, the Clinical Dementia Rating Scale – Global Score is established by clinical scoring rules, for which the Clinical Dementia Rating of 0 = no dementia and Clinical Dementia Rating of 0.5, 1, 2, or 3 indicates questionable, mild, moderate, or severe dementia, respectively (Morris, 1993).

The CDR-SB will be performed at the time points listed in the SoA (Section 6.1).

The observed values and CFB scores for the following individual and composite CDR-SB scores through Week 101, and Week 113/Early Termination (ET) (if applicable), will be summarized descriptively and listed per time points listed in the SoA (Section 6.1):

- Memory
- Orientation

- Judgment and problem solving
- Community affairs
- Home and hobbies
- Personal care
- Global Clinical Dementia Rating Scale score
- Sum of Boxes (Memory + Orientation + Judgment and problem solving + Community affairs + Home and hobbies + Personal care)

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

- CDR Sum of Boxes

4.8.1.1.1. Responders on CDR-SB

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 number and percentage of responders over time will be tabulated overall and by baseline AD severity subgroup (Subgroup 1: Mild AD patients [MMSE 21-24] and Subgroup 2: moderate-severe AD patients [MMSE ≤ 20]). Responder status will be listed alongside the Sum of Boxes score.

4.8.1.2. Cognitive Drug Research (CDR) System

The CDR is an automated battery amenable to measurement of cognitive deficits in patients with AD. It consists of performance tasks measuring attention, working memory, episodic memory, and executive function. It contains 11 tests and is performed on a tablet-like device. The average duration of the battery is approximately 25 minutes.

The observed values and CFB scores for the CDR System battery individual and composite scores through Week 101, and Week 113/ET (if applicable), will be analyzed separately as described in the CDR System battery SAP.

4.8.1.3. Mini-Mental State Examination Scale (MMSE)

The MMSE is a brief 30-point questionnaire used to assess cognitive impairment with lower scores indicating greater impairment. The MMSE assesses 11 categories of cognition including orientation to time, memory, attention, concentration, naming, repetition, comprehension, and the ability to create a sentence and to copy 2 intersecting polygons. The total scores on the scale ranges from 0 to 30 with lower scores indicating greater impairment.

The MMSE will be performed at the time points listed in the SoA (Section 6.1).

The observed and CFB MMSE total score through Week 101, and Week 113/ET (if applicable), will be summarized descriptively, per time points indicated in the SoA (Section 6.1).

The following individual and composite MMSE scores will be listed per time points indicated in the SoA (Section 6.1):

- Orientation to time
- Orientation to place
- Registration
- Attention and calculation
- Recall
- Naming
- Repetition
- Comprehension
- Reading
- Writing
- Drawing
- MMSE Total score (sum of all individual items)

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

- MMSE

4.8.1.4. Neuropsychiatry Inventory (NPI)

The NPI is a rater-administered, fully structured interview in which all questions are provided and read verbatim. The sole source of information is the interview with a caregiver who knows the patient well. This study uses the NPI version with 10 behavioral domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, and aberrant motor behavior. The NPI total score is calculated by adding the scores of the domains (each domain scores range from 0 to 12). The NPI total score ranges from 0 to 120 with higher scores indicating greater behavioral impairment.

The Neuropsychiatry Inventory Caregiver Distress (NPI-D) scores in each of the domains are not included in the NPI total score. The NPI-D total score is calculated by adding the scores of caregiver distress in each of the domains (score ranges from 0 to 5 in each domain). The NPI-D total score ranges from 0 to 50 with higher scores indicating greater distress.

The observed and CFB total NPI and total NPI-D scores through Week 101, and Week 113/ET (if applicable), will be summarized descriptively per timepoints indicated in the SoA (Section 6.1).

The following individual and composite NPI scores will be listed per time points indicated in the SoA (Section 6.1):

- Delusions
- Hallucinations
- Agitation/aggression
- Depression/dysphoria
- Anxiety
- Elation/euphoria
- Apathy/indifference
- Disinhibition
- Irritability/lability
- Aberrant motor behavior
- Total NPI Score
- Total NPI-D Score

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

- NPI

4.8.1.5. EuroQol 5-Dimension 5 -Level Health Related Quality of Life Scale (EQ-5D-5L)

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 5-point categorical scales ranging from “no problem” to “severe problem”. Two different administrations of the EQ-5D-5L will be performed at baseline and timepoints indicated in the SoA (Section 6.1). First, the patient’s caregiver will provide a proxy-rating of the patient’s health status. Second, the caregiver will provide a self-report of his or her own health status. In both situations, the EQ-5D-5L questionnaire will be completed by the patient’s caregiver. The health score is a scale numbered from 0-100, where 100 means the best health and 0 the worst health.

The observed and CFB health score, of the patient’s health status and the caregiver’s self-report, through Week 101, and Week 113/ET (if applicable), will be summarized descriptively per timepoints indicated in the SoA (Section 6.1).

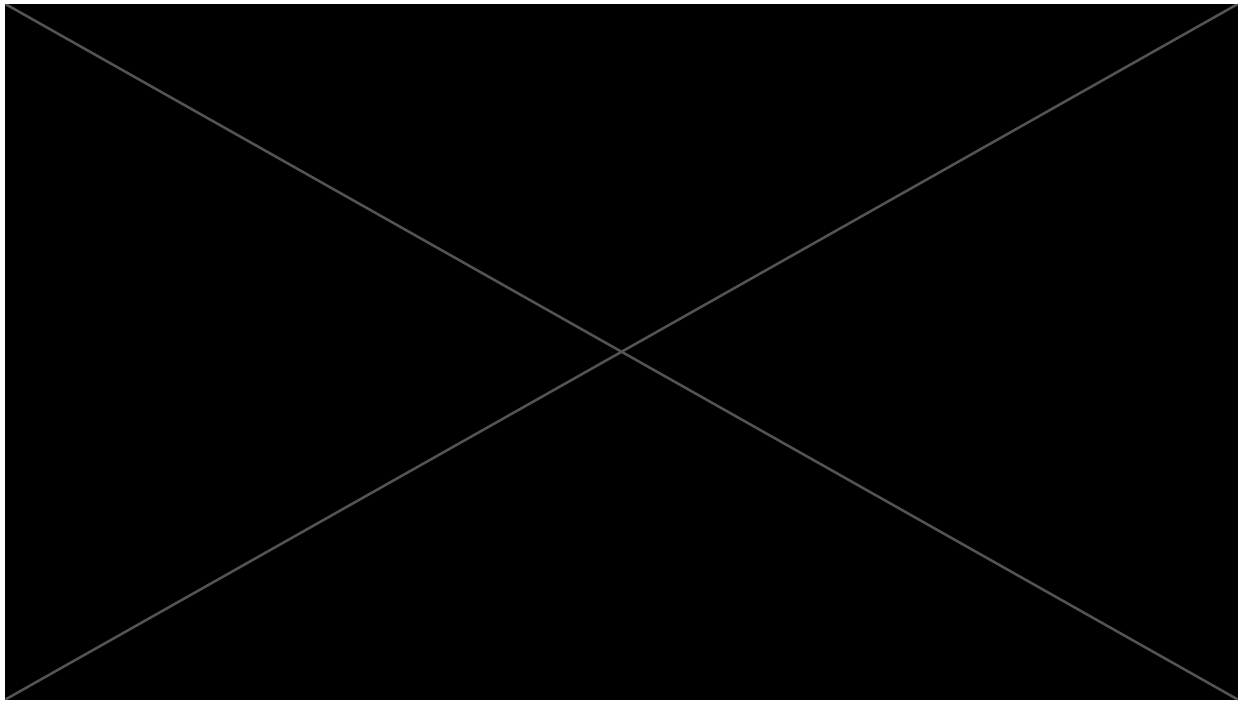
The individual health scores (from 0 to 100) for the patient and caregiver, will also be listed per time points indicated in the SoA (Section 6.1).

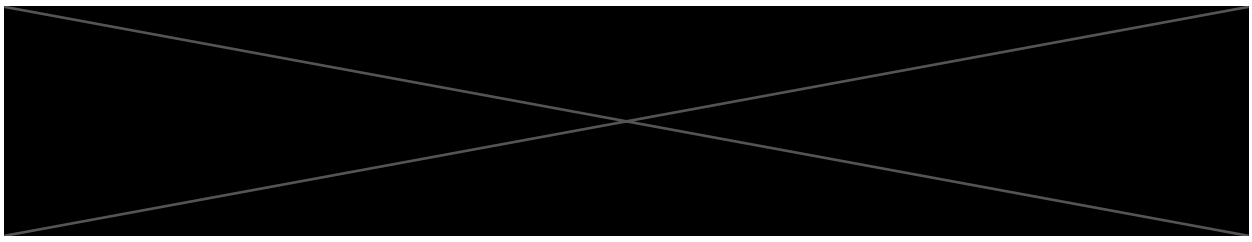
The following individual items will be listed and summarized by number of patients and percentage per visit:

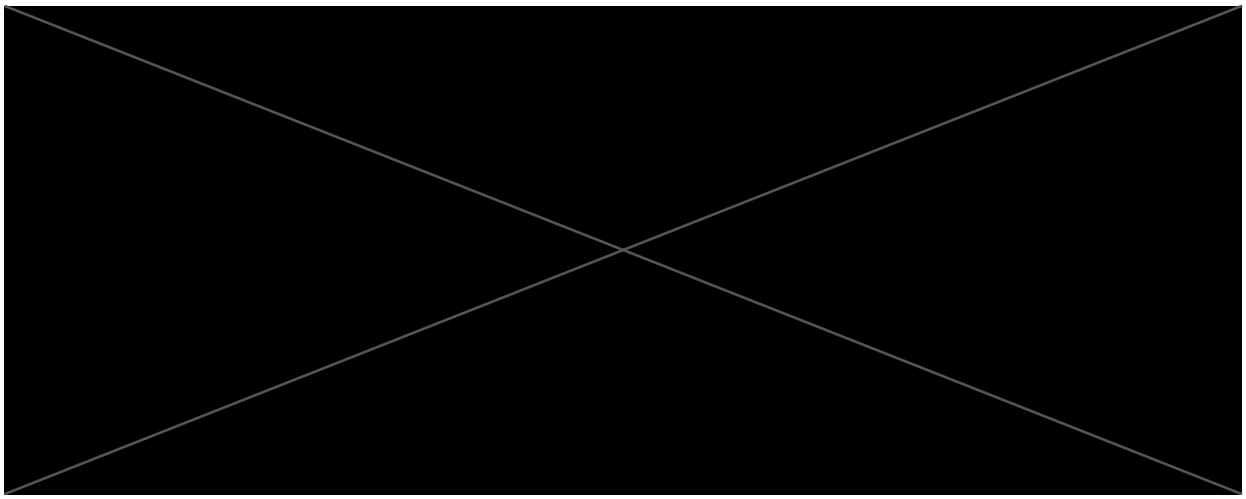
- Mobility problems
- Self-care problems
- Usual activity problems
- Pain/Discomfort
- Anxiety/Depression

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

- EuroQol 5D
- EuroQol 5DP







4.9. Pharmacokinetics

PK is considered a primary endpoint and will be assessed through a summary of plasma concentrations of TB006 over time throughout the study, using the PKS. Sample collection for PK will be conducted as specified in Section 8.5 of the Protocol, at the timepoints indicated in the SoA (Section 6.1). All PK samples will be pre-dose.

For PK analysis, descriptive summary statistics along with geometric mean, geometric standard deviation (GSD), arithmetic coefficients of variation (CV%), and geometric coefficients of variation (GCV%) for plasma concentration of TB006 over time (per timepoints indicated in the SoA [Section 6.1]), will be presented. Only pre-dose samples will be considered for summary statistics and figures. Samples inadvertently taken after start of infusion will be removed before analysis.

Individual TB006 plasma concentration levels over time (per timepoints indicated in the SoA), will be listed for the PKS.

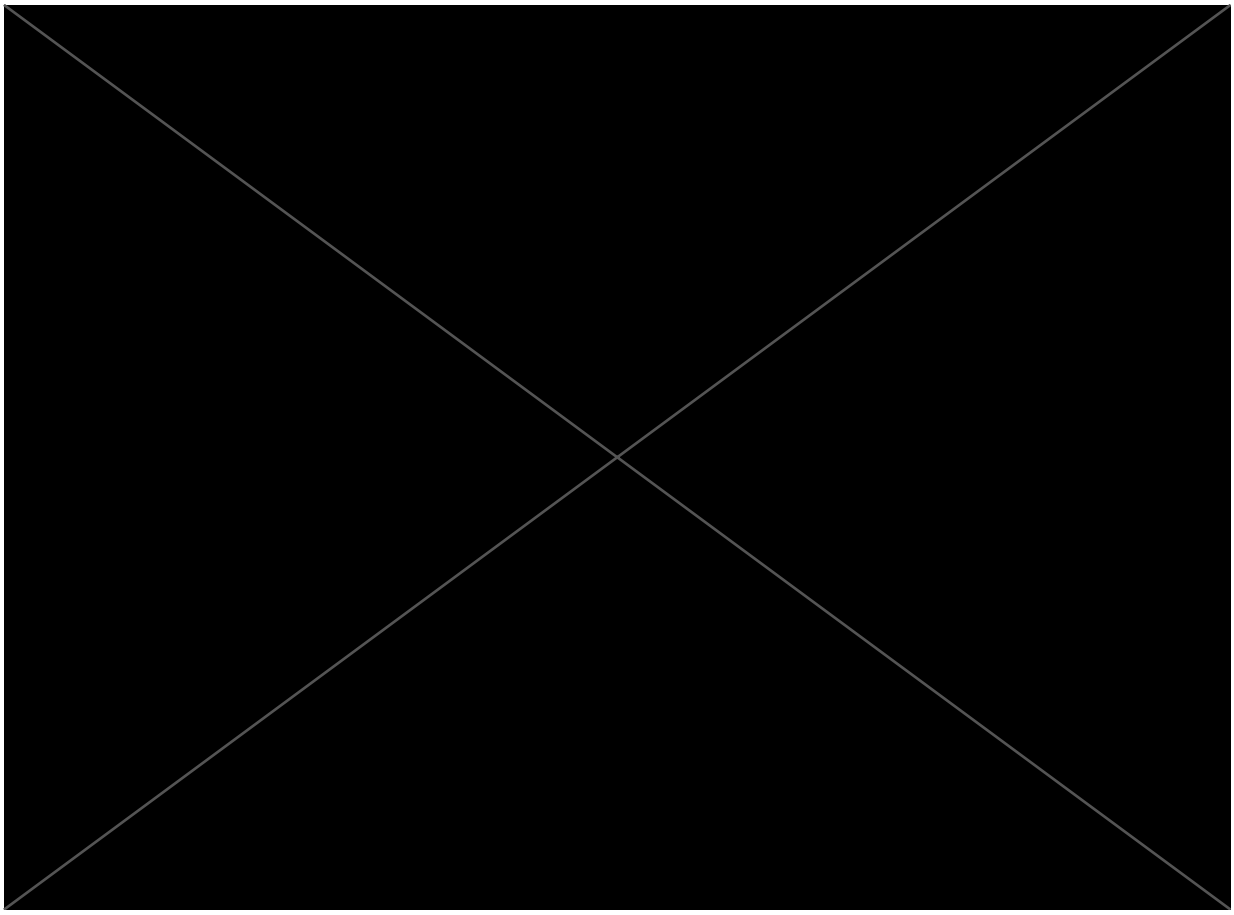
Figures of the following PK items are planned for presentation:

- Overlaid individual plasma concentration versus time plot (linear and semi-logarithmic scale)
- Mean plasma concentration versus time plot (linear scale with and without SD)
- Mean plasma concentration versus time plot (semi-logarithmic scale with and without SD)

The data for these presentations will be obtained from external PK laboratory data and eCRF page:

- Blood sample for PK assessment

4.10. Pharmacodynamics



4.11. Safety and Tolerability

All AE related assessments will be listed and tabulated using the SAS-AE. All other safety assessments will be listed and tabulated using the SAS.

The safety assessments (clinical laboratory values, vital signs, ECG, and physical assessments) are collected according to the SoA (Section 6.1).

4.11.1. Adverse Events

The following AE definitions are applicable to this study:

- AE: Any untoward medical occurrence in a clinical study/patient, temporally associated with the use of study intervention, whether considered related to the study intervention or not.

- AE reporting period: Defined from the time of the first study drug administration until Week 113. Any AE that begins in the lead-in study and is ongoing at the time of the first dose of study drug in the OLE will be included as an AE in the OLE. This includes events occurring during the initial visit in the study, regardless of whether the study drug has been administered.
- 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.
- Serious AE (SAE): Defined as any AE that is indicated as serious on the AEs Details eCRF, as per investigator's assessment.
- Drug Related AE: Defined as any AE that is indicated as "Definite", "Possibly" or "Probably" 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 25.0, Mar 2022. The following AE items will be listed using the SAS:

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

The following items are planned to be presented in summary tables showing event incidence and corresponding patient counts:

- AE overview, including row items for frequency of subjects [n (%)] experiencing:
    - At least one AE
    - At least one TEAE
    - Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade
        - Grade 1
        - Grade 2
        - Grade 3
        - Grade 4
        - Grade 5
    - Serious TEAEs
    - Study drug related TEAEs

  - Study drug unrelated TEAEs
  - AEs leading to study discontinuation
  - TEAEs leading to study drug discontinuation
  - AEs leading to death
  - TEAEs leading to death
- TEAEs by SOC and PT
- TEAEs by descending incidence of PT
- TEAEs by SOC, PT, and toxicity grade (CTCAE)
- TEAEs related to study drug by SOC and PT
- TEAEs related to study drug by descending frequency of PT
- TEAEs related to study drug by SOC, PT, and toxicity grade (CTCAE)
- Serious TEAEs by SOC and PT
- TEAEs resulting in death by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT

TEAEs will be used for summarization of all tables. 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 4.1.4.

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

AE assignment to the National Cancer Institute (NCI) CTCAE Version 5.0. toxicity grades are explained in Table 4:

Table 4. National Cancer Institute CTCAE Grades Version 5.0

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.

4.11.2. Laboratory Assessments

In the context of this study PCI results are defined as follows:

- A PCI result is defined as a laboratory assay result that falls outside of the reference range used by the central laboratory.

Clinical laboratory assessments to be performed are detailed in Appendix 2 (Section 6.2) and Section 10.2 of the Protocol and will be conducted at timepoints indicated in the SoA (Section 6.1). The following patient safety laboratory results are planned to be listed:

- Chemistry
- Hematology
- Urinalysis (Quantitative and Qualitative results)
- Drug and alcohol screening
- Abnormal laboratory results
- Marked liver abnormal laboratory results
- PCI abnormal laboratory results

The following local laboratory result items are planned for table presentation, for each applicable visit:

- Chemistry:
  - Summary statistics for chemistry laboratory values by time point
  - Shift from baseline to post-baseline in chemistry values (summary statistics)
- Hematology:
  - Summary statistics for hematology laboratory values by time point
  - Shift from baseline to post-baseline in hematology values (summary statistics)
- Urinalysis:
  - Summary statistics for urinalysis quantitative results by time point
- PCI laboratory abnormalities at any time point post-baseline, as tested against local laboratory criteria set (see Appendix 3 for list of criteria)
- Marked liver abnormalities at any time point post-baseline, with stopping criteria including the following:

- Alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN)
- Bilirubin > 1.5 x ULN (where if fractioned, direct bilirubin > 35%)
- ALT > 3 x ULN and bilirubin < 2 x ULN
- ALT > 3 x ULN and bilirubin ≥ 2 x ULN
- 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)

The data for these presentations will be obtained from the following eCRF pages (and associated laboratory analysis results):

- Safety Laboratory
- Drug and Alcohol Screening
- Viral Collection

4.11.3. Vital Signs

Vital sign assessments, listed in

Table 5 below, will be performed as detailed in Section 8.3.2 of the Protocol, and will be conducted at every drug administration visit as indicated in the SoA (Section 6.1).

Table 5. Vital Sign Tests Performed

Test
Body temperature (°C)
HR (bpm)
Respiratory rate (breaths/min)
DBP (mmHg)
SBP (mmHg)
*Orthostatic DBP (mmHg)
*Orthostatic SBP (mmHg)
Weight (kg) (from physical examination eCRF)

DBP = Diastolic Blood Pressure; HR = Heart Rate; SBP = Systolic Blood Pressure.

*Orthostatic blood pressure will be derived as follows:

Orthostatic Systolic Blood Pressure (SBP) = SBP in supine position – SBP in standing position.

Orthostatic Diastolic Blood Pressure (DBP) = DBP in supine position – DBP in standing position.

The following listings will be presented for vital sign measurements:

- Quantitative results
- PCS abnormal vital sign results (refer to marked abnormalities listed below)

The following vital sign tables are planned to be presented:

- Summary statistics for vital sign results by time point
- Marked abnormalities at any time post-baseline, which will include the following criteria:
    - Decrease in SBP of ≥ 25 mmHg versus baseline
    - Decrease in DBP of ≥ 15 mmHg versus baseline
    - Increase/decrease in SBP of ≥ 20 mmHg versus baseline.
    - Increase/decrease in DBP of ≥ 10 mmHg versus baseline.
    - Orthostatic hypotension:
        - Orthostatic SBP of ≥ 20 mmHg (decline from supine to standing)
        - Orthostatic DBP of ≥ 10 mmHg (decline from supine to standing)
    - Increase/Decrease in weight of ≥ 7% versus baseline
    - Increase/Decrease in heart rate (HR) by 15 bpm from baseline

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

- Vital Signs
- Vital Signs-Study Drug Infusion
- Physical Examination (for weight)

4.11.4. Electrocardiograms

ECGs (12-lead) will be obtained as outlined in the SoA (Section 6.1) using an ECG machine that measures HR, QRS, and QT intervals; and calculates the QT interval corrected (QTc) interval. Single measurements are acceptable at all-time points.

For this study, for primary analysis of the QT interval, QT corrected interval using Bazett formula (QTcB) will be used. However, if there are a disproportionate number of patients with high resting HR(s) or if drug treatment results in an increased HR, consideration will be given for using QT corrected interval using Fridericia's formula (QTcF). All applicable measurements are listed in Table 6, below.

Table 6. ECG Measurements

Measurement
Heart Rate (bpm)
PR interval (msec)
QRS duration (msec)
QT (msec)

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

msec = milliseconds.

The following ECG listings will be presented:

- Quantitative measurements
- PCS (as determined by the investigator on site) abnormal ECG measurements

The following ECG summary tables are planned:

- Summary statistics for ECG measurements by time point
- ECG assessments interpretation by visit
- ECG marked abnormalities and categorical outliers, according to the following criteria:

For marked abnormalities:

  - QTcB > 450 milliseconds (msec) for male patients
  - QTcB > 470 (msec) for female patients
  - Increase in QTcB from baseline ≥ 60 (msec)
  - Increase in HR CFB% ≥ 30%

For categorical outliers:

  - QTcB > 500 (msec)
  - Increase in QTcB from baseline ≥ 30 (msec) and ≤ 60 (msec)
  - Increase in QTcB from baseline > 60 (msec)

The following figures are planned for presenting ECG parameters QTcB and HR:

- Mean observed QTcB over time
- Mean CFB QTcB over time (including visits with a predose, following the first infusion, and 2-hour post infusion value)
- Mean observed HR over time
- Mean CFB HR over time

The data for these presentations will be obtained from the following eCRF pages (and associated results from ECG machine and PI):

- 12-Lead ECG
- 12-Lead ECG Details

4.11.5. Physical and Neurological Examination

Physical examination as part of EoS procedures in Protocol TB006AD2102 will be used as baseline assessment for this study if they are done within 28 days, and will be conducted at timepoints indicated in the SoA (Section 6.1).

A listing of physical and neurological examination abnormal findings will be presented.

The physical and neurological examination results will be tabulated using summary statistics for the parameters listed below:

- Qualitative statistics of abnormalities – Physical Examination:
    - Cardiovascular
    - Respiratory
    - Gastrointestinal
    - Dermatological
    - Hepatic
    - Lymphatic
    - Other
- Qualitative statistics of abnormalities – Neurological Examination:
    - Mental Status
    - Motor and sensory skills
    - Hearing and speech
    - Vision
    - Coordination
    - Balance

The shift from baseline to post-baseline in abnormal physical and neurological examination (for systems listed above), will also be tabulated by normal, clinically significant (CS) and not clinically significant (NCS) subgroups, using summary statistics.

In the presence of multiple investigator-interpretation results for a patient per visit, a worse case approach will be adapted, ie, a CS result will be considered for analysis above a NCS abnormal result.

The information for the listing will be obtained from the following eCRF pages:

- Physical and Neurological Examination
- Physical and Neurological Abnormalities

4.11.6. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a prospective semi structured interview comprised of the following areas of assessment: Ideation, Intensity of Ideation, Behavior, and Lethality. It is used to determine eligibility to enroll at screening and at every follow-up visit to prospectively monitor suicidality during the study.

The C-SSRS will be performed as outlined in the SoA (Section 6.1).

The C-SSRS response over time will be listed.

The C-SSRS responses over time will also be tabulated using number of patients and percentage for each response.

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

- C-SSRS Screening
- C-SSRS (Since Last Clinic Visit)

4.12. Primary Endpoint(s) Analysis

4.12.1. Safety and Tolerability

Primary safety and tolerability endpoints include:

- Incidence of AEs and SAEs throughout the study
- Summary of ECGs throughout the study
- Summary of clinical laboratory assessments throughout the study
- Summary of vital signs assessments throughout the study
- Summary of C-SSRS, MRI, and physical and neurological examinations throughout the study

Refer to Section 4.11 for definitions and analytical approach.

4.12.2. Pharmacokinetics

Primary PK endpoint include:

- Summary of plasma concentration of TB006 over time throughout the study

Refer to Section 4.9 for definitions and analytical approach.

4.12.3. Immunogenicity

Primary Immunogenicity endpoint include:

- Incidence (%) of TB006 anti-drug antibody (ADA) status over time.

Antibodies to TB006 will be evaluated in plasma samples collected from all patients according to the SoA (Section 6.1). Blood sample collection and screening for ADA assessment will be conducted as specified in Section 8.8 of the Protocol, at the timepoints indicated in the SoA. ADA analysis will be done by an external vendor and therefore will not form part of this SAP.

To assess the immunogenicity of TB006, the incidence of ADA status will be listed by patient and time point, using the SAS.

The ADA status will be summarized by frequency count and percentage, using the SAS.

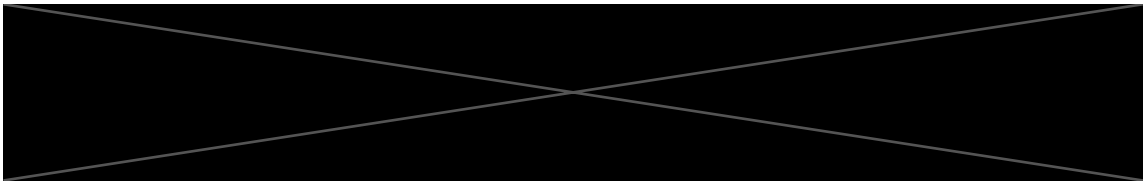
The data for these presentations will be obtained from the external immunogenicity laboratory data and eCRF page:

- Blood sample for ADA assessment.

4.13. Secondary Endpoint(s) Analysis

The PD(s)/cognitive measures are the secondary endpoints for the study and includes following measures:

- Change from Baseline through Week 101 on the CDR-SB score
- Change from Baseline through Week 101 on the CDR battery composite scores and individual task measures
- Change from Baseline through Week 101 on the MMSE score
- Change from Baseline through Week 101 on the NPI score
- Change from Baseline through Week 101 on the EQ-5D-5L QoL total score



Refer to Section 4.7 for definitions and analytical approach.

4.14. Exploratory/Other Endpoint(s) Analysis

Exploratory endpoint includes:

- CFB through EoS in [redacted] and other relevant biomarkers.

Refer to Section 4.9 for definitions and analytical approach.

4.15. Other Safety Analyses

No other safety analyses, other than what is already specified in Section 4.10, is planned for this study.

4.16. Other Analyses

4.16.1. Hospitalizations

Information regarding hospitalization will be listed, using the SAS:

The information for this presentation will be obtained from the following eCRF:

- Adverse Events Details eCRF

Duration per hospital stay is calculated in hours as:

*Hospitalization Duration (hours) = [(Discharge Date – Admission Date) + 1] * 24*

4.16.2. Subgroup Analyses

The disposition, efficacy, and biomarker analysis will be presented for baseline patient severity: mild AD patients (MMSE 21-24) and moderate-severe AD patients (MMSE ≤ 20). Patients with an MMSE score greater than 24 will be included in the MMSE 21-24 category.

4.17. Interim Analysis

No interim analysis is planned for this study.

4.18. Changes to Protocol-Planned Analyses

Not applicable

5. Sample Size Determination

Up to 50 de novo patients identified by the sponsor and meeting the eligibility criteria, and all patients who have completed lead-in Protocol TB006AD2102 (either Part 1 or Part 2) are eligible to participate in this study, where completion of Protocol TB006AD2102 is defined as:

- Following through to the Day 104 visit or
- Early withdrawal for reasons other than adverse events after receiving all 5 doses of TB006 and completing the ET visit.

All eligible patients from lead-in Protocol TB006AD2102 will be contacted to be enrolled in this study, including those eligible for the lead-in study but were not enrolled (de novo). From these eligible patients, all who provided signed informed consent (or assent) to participate and who have passed the screening criteria, will be considered enrolled patients.

No formal sample size calculations were performed for this study. The estimated number of patients is from the proportion of patients who may complete the lead-in study and the proportion of those who historically enroll in OLE studies. The proposed number of enrolled patients from the lead-in study will be 100 to 120. Additionally, up to 50 de novo patients, identified by the sponsor, may be included. Therefore, a total of approximately 150 to 170 patients will be enrolled.

6. Supporting Documentation

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6.1. Appendix 1: Schedule of Activities

Study Period	**SCR (Days -28 or -42 to -1)[a]**	**Study Drug Administration Period (all visits ± 5 days)**																										
Study Week		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**	**89**	**93**	**97**	**101**	**113 or ET**
General and Safety Assessments																												
Informed consent	X																											
Eligibility criteria	X																											
Demography	X																											
Physical (including height and weight) & neurological examination[b]	X							X							X								X					X
Medical history (includes substance use)	X																											
12-lead ECG[c]	X	X		X		X		X			X			X			X			X							X		X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring		X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Laboratory Assessments																											
Viral serology (HbsAg, IgM anti-HBc, anti-HCV) and COVID-19 testing	X																										
Urine drug and alcohol breathalyzer screening	X	X						X							X							X					X	
Clinical laboratory tests (clinical chemistry, hematology, and urinalysis)	X				X			X							X							X						X
Efficacy and Pharmacodynamic Assessments: Cognition Testing, [redacted] and Blood Samples																											
[redacted]																											
Cognition/QoL testing[h]	X				X			X							X				X				X				X	X
[redacted]																											
Study Treatment																											
Study drug IV infusion[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics and Immunogenicity Assessments																											
Blood sample for PK assessment[k]	X	X	X	X	X	X	X	X					X							X						X	X
ADA assessment		X						X					X							X							X

ADA = anti-drug antibody; AE = adverse event; anti-HBc = hepatitis B core antibodies; anti-HCV = hepatitis C virus antibodies; CDR = Cognitive Drug Research; CDR-SB = Clinical Dementia Rating-Sum of Boxes; COVID-19 = coronavirus disease of 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EoS = End of Study; EQ-5D-5L and/or QoL = EuroQuality of life 5-Dimension 5-Level and/or quality of life assessment; HbsAg = hepatitis B surface antigen; IgM = immunoglobulin M antibodies; IV = intravenous(ly); MMSE = Mini Mental Status Exam; [redacted] NPI = Neuropsychiatric Inventory; OLE = Open Label Extension; PD = pharmacodynamic; [redacted] PK = pharmacokinetic; q28day = every 28 days; SCR = screening.

a For patients dosed within 28 days of their EoS procedures from lead-in Protocol TB006AD2102, the EoS procedures will be used as baseline for this study. For de novo patients and patients dosed > 28 days from EoS procedures in lead-in Protocol TB006AD2102, eligibility must be confirmed or reconfirmed, and screening procedures must be completed per this current OLE protocol, with the exception of imaging (lead-in patients only). Additionally, a 42-day screening period is required for de novo patients.

b Physical examinations at the clinic visits other than the Screening Period and EoS procedures may be brief, focused on abnormalities identified on the Screening examination and as related to adverse events. Physical examination as part of EoS procedures in Protocol TB006AD2102 will be used as baseline assessment for this study if they are done within 28 days.

c Singlets; predose and 2 hours (± 30 minutes) post infusion.

d Predose, then at any time between end of infusion and 2 hours (± 30 minutes) post infusion on dose administration days. Includes oral temperature, heart rate, respiratory rate, blood pressure, and orthostatic blood pressure.

e Collected within ± 2 weeks of the scheduled week.

[redacted]

h Order of testing: CDR-SB, CDR battery, MMSE, NPI, and (EQ-5D-5L = EuroQol 5-Dimension 5-Level scale).

[redacted]

j Doses administered q28day on the first day of the week (eg, Days 1, 29, 57, 85, etc.) ± 5 days of the scheduled dosing day.

k All PK samples are predose.

6.2. Appendix 2: Protocol Required Clinical Laboratory Tests

Hematology	**Clinical Chemistry**	**Urinalysis**
hematocrit hemoglobin platelet count RBC count RBC indices: MCH MCV % reticulocytes WBC count with differential: neutrophils lymphocytes monocytes eosinophils basophils	albumin alkaline phosphatase ALT/SGPT AST/SGOT BUN calcium creatinine creatine phosphokinase glucose (non-fasted) HbA1c HDL LDL potassium sodium triglycerides TSH total and direct bilirubin total protein Total cholesterol	specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick microscopic examination (if blood or protein is abnormal)
Study-specific	**Other Screening Tests**	
ADA PK	• Urine alcohol and drug screen including but not limited to opiates, methadone, buprenorphine, methamphetamine, cocaine, and amphetamines) • Serology, COVID-19 nasal swab test	

ADA = antidrug antibody; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; COVID-19 = corona virus disease 2019; HbA1c =glycosylated Hb; HDL = high density lipoprotein; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PK = pharmacokinetics; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid-stimulating hormone; WBC = white blood cell.

6.3. Appendix 3: 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 PCI 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
	Creatinine	mg/dL	NA	1.50
	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	10^3/uL	0.50	NA
	Neutrophils	10^3/uL	1.00	NA
	Platelets	10^3/uL	75	750
	Leukocytes	10^3/uL	2.5	25.0
Other Screening Tests	Serology		Positive	
	COVID-19		Positive	
	Opiates		Positive	
	Methadone		Positive	
	Buprenorphine		Positive	
	Methamphetamine		Positive	
	Cocaine		Positive	
	Amphetamines		Positive	

7. 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. Morris J. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43:2412-2414.

4. Protocol TB006AD2104 OLE Amendment 2, V3.0, dated 16 Feb 2023.

5. TB006AD2104 eCRF Completion Guidelines, V3.0, dated 30 Jan 2023.

TU0006_TB006AD2104 SmartStart SAP Final V2

Final Audit Report 2024-01-05

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