CLINICAL PROTOCOL

Protocol 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	
Protocol Number:		TB006AD2102	
Amendment:		2.0	
Compound:		TB006	
Study Phase:		Phase 1b/2a	
Short Title:		A Phase 1b/2a, multi-dose, multi-center study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of TB006 in patients with Alzheimer's Disease.	
Sponsor	**Sponsor Name:**	TrueBinding, Inc.	
	Legal Registered Address:	300 Lincoln Center Drive Suite 200 Foster City, CA 94404	
Protocol Approver	**Name:**	[redacted], PharmD	
	Function:	Clinical Development Lead, TrueBinding, Inc.	
Regulatory Agency Identifier Number		Not applicable	
Protocol Date:		**Document Version**	**Date**
		Original (v 1.0)	25 Mar 2021
		Amendment 1.0 (v 2.0)	02 Aug 2021
		Amendment 2.0 (v 3.0)	15 Oct 2021

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The information contained in this protocol and all other information relevant to TB006 are the confidential and proprietary information of TrueBinding, Inc. and, except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without the prior written permission of TrueBinding, Inc.

NCT Number: NCT05074498
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

SPONSOR SIGNATORY:

TB006AD2102
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

I, the undersigned, have approved of the clinical trial protocol with the date of 15 Oct 2021.

Name and Title	Signature and Date
[redacted] PharmD Clinical Development Lead TrueBinding, Inc 300 Lincoln Center Drive Suite 200 Foster City, CA 94404	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 15-Oct-2021 | 16:22:13 EDT 10E33B247CD84B92A681F9ED03BD2773

INVESTIGATOR AGREEMENT

TB006AD2102:
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

I have read the protocol, including all appendices, and I agree that it contains all the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in compliance with current Good Clinical Practice (GCP) standards as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for GCP, all applicable national, state, and local laws and regulations, and the applicable Institutional Review Board/Independent Ethics Committee (IRB/IEC) and other institutional requirements.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by TrueBinding, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about TB006, understand this study, and are able to comply.

_____ _____

Principal Investigator (printed) Signature

_____

Date

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LIST OF ABBREVIATIONS

[redacted]

AD	Alzheimer's disease
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
anti-HCV	hepatitis C virus antibody
ApoE4	apolipoprotein E4
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0–tau}$	area under the concentration-time curve from zero time to end of dosing period
$AUC_{0-\tau}$	area under the concentration-time profile over the dosing interval τ at steady state
BMI	body mass index
CFR	Code of Federal Regulation
CIOMS	Council for International Organizations of Medical Sciences
CL	Total clearance
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID	coronavirus disease
CPK	creatine phosphokinase
CRF	Case Report Form
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
C_{trough}	concentration at the end of a dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DRE	disease-related event
E/D	early discontinuation
ECG	electrocardiogram

eCRF	electronic Case Report Form
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
[redacted]	
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HED	human equivalent dose
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IgM anti-HBc	immunoglobulin M antibody to hepatitis B core antibody
INR	international normalized ratio
IRB	Institutional Review Board
IV	Intravenous(ly)
IWRS	Interactive Web Response System
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
MMSE	Mini-Mental State Examination
[redacted]	
NCI	National Cancer Institute
[redacted]	
[redacted]	
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
NOAEL	no observed adverse effect level
NPI	neuropsychiatric inventory
NPI-D	neuropsychiatric inventory caregiver distress
[redacted]	

PD	pharmacodynamic(s)
PDS	PD analysis set
PI	principal investigator
PK	pharmacokinetic(s)
PKS	PK analysis set
PT	preferred term
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
qw	weekly
S228P	point mutation in human IgG4 at serine 228 to proline
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SoA	schedule of activities
SOC	system organ class
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination phase half-life
t_{max}	time at which maximum plasma concentration occurs
ULN	upper limit of normal
US	United States
V_d	Volume of distribution
WOCBP	woman of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol 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

Short Title:
A Phase 1b/2a, multi-dose, multi-center study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of TB006 in patients with Alzheimer's Disease.

Rationale:
The TB006 nonclinical pharmacology program establishes its potential as a therapeutic agent for AD by neutralizing Gal-3, which regulates the production and accumulation of Aβ and tau proteins and is overexpressed in AD. The preclinical data have shown evidence of addressing underlying disease pathology and improving cognition.

The preclinical safety profile of TB006 further supports the clinical investigation of TB006.

This is a seamless, two-part Phase 1b/2a combined MAD and proof of concept study in patients with AD. Part 1 of the study will evaluate the safety, tolerability, PK, PD and efficacy of qw doses of TB006, administered as an IV infusion over 1 hour. Part 1 of this study will be conducted in parallel with the Phase 1 SAD study (Protocol number TB006HV1101). Each dose level in this study will start after the safety, tolerability, and PK of the single dose equivalent to the combined total of the 5 qw doses has been established. In Part 2 of this study, enrollment will continue at the highest tolerated dose from Part 1. Part 2 will assess the efficacy of TB006 on cognition using the Clinical Dementia Rating scale – Sum of Boxes as the primary endpoint. Patients enrolled at the same dose level in Part 1, as well as all placebo patients, will be included in the efficacy analyses in Part 2. Randomization in Part 2 will be stratified according to patient severity.

Objectives and Endpoints:

OBJECTIVES - PART 1	ENDPOINTS
Primary	
• To determine the safety and tolerability of multiple doses of TB006	• Safety endpoints, including the incidence of AEs and SAEs, clinical laboratory parameters, vital signs, ECGs, C-SSRS, and physical and neurological examinations, until Day 104 after the first TB006 dosing
• To determine the PK profile of multiple doses of TB006	• PK parameters derived by noncompartmental analysis using the TB006 plasma

	concentration-time data, including, but not limited to and as appropriate: ○ AUC_{tau}: area under the concentration-time curve over a dosing interval ○ C_{max}: maximum observed plasma concentration ○ t_{max}: time at which maximum plasma concentration occurs ○ C_{trough}: concentration at the end of a dosing interval ○ $t_{½}$: terminal elimination phase half-life ○ CL: total clearance ○ V_d: volume of distribution • Extent of CSF distribution as estimated by TB006 CSF concentrations
• To determine the maximum tolerated dose of multiple doses of TB006	• Safety endpoints as above
• To assess the immunogenicity of TB006 (production of anti-TB006 antibody)	• Detection of anti-TB006 antibodies
[redacted]	
• [redacted]	• Change from baseline through end of study on the Clinical Dementia Rating scale – Sum of Boxes total score • Change from baseline through end of study on the Cognitive Drug Research system battery score, composite scores and individual task measures • Change from baseline through end of study on the MMSE score • Change from baseline through end of study on the NPI score • [redacted] •

	[redacted]

OBJECTIVES - PART 2	ENDPOINTS
Primary	
• To determine the clinical efficacy of TB006 in patients with mild to severe AD	• Change from baseline through Day 104 on the Clinical Dementia Rating scale – Sum of Boxes total score
Secondary	
• To determine the clinical efficacy of TB006 in patients with mild to severe AD	• Change from baseline through Day 36 on the Clinical Dementia Rating scale – Sum of Boxes total score • Proportion of responders on the Clinical Dementia Rating scale – Sum of Boxes at Days 36 and 104 • Change from baseline to Days 36 and 104 on the Cognitive Drug Research System Battery, composite scores and individual task measures • Change from baseline to Days 36 and 104 on the MMSE score • Change from baseline to Days 36 and 104 on the NPI score
• To determine the safety and tolerability of multiple doses of TB006	• Safety endpoints, including the incidence of AEs and SAEs, clinical laboratory parameters, vital signs, ECGs, C-SSRS, and physical and neurological examinations, until Day 104 after the first TB006 dosing
• To determine the PK following multiple doses of TB006	• PK parameters including, but not limited to, by C_{trough}, C_{max}, and $t_{½}$.
[redacted]	
• [redacted]	[redacted]

[redacted] AD = Alzheimer's Disease; AEs = adverse events; C-SSRS = Columbia Suicide Severity Rating Scale; CSF = cerebrospinal fluid; D = Day; ECG = electrocardiogram; [redacted] MMSE = Mini Mental State Examination; [redacted] NPI = Neuropsychiatric Inventory; [redacted] PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event.

Overall Design:
This is a seamless, two-part Phase 1b/Phase 2a, multi-center, randomized, double-blind, placebo-controlled study. Part 1 is a-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 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 (minimum of 14 days from last patient dosing). 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 (1,000 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 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 in the SAD study (Protocol number TB006HV1101). Data will be reviewed by a blinded 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 SoA) as in Part 1. 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 ≤ 20) in each strata.

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 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.

Disclosure Statement: This is a randomized, placebo-controlled, sequential and parallel group treatment study that is patient and investigator blinded.

Number of Participants:
In Part 1, 8 patients will be enrolled into each dose group, thus a total of approximately 24 patients will be randomized in this portion of the study. In Part 2, 116 patients will be enrolled, 58 into active TB006 treatment and 58 to placebo.

Dose Groups and Duration:

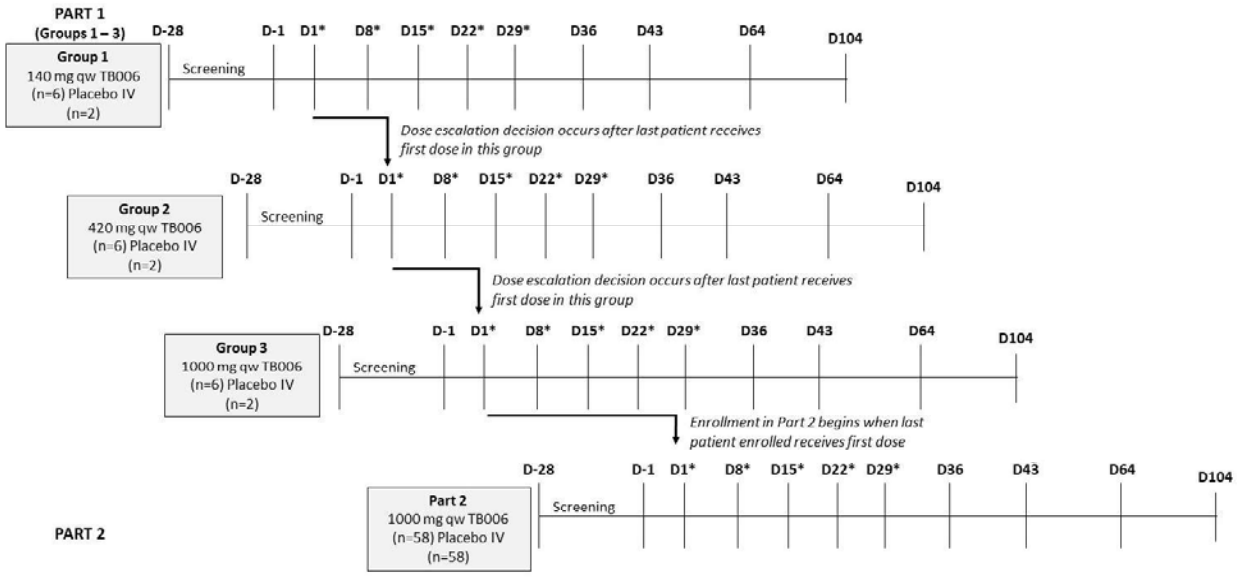
In Part 1, three dose groups are planned, each representing one dose level of TB006 or placebo. In Part 2, two groups (active TB006 and placebo) are planned.

Each patient will be screened for eligibility up to 28 days prior to first dosing, and study assessments will be performed up to 104 days after first dosing. The total study duration for each patient will therefore be up to approximately 19 weeks.

Data Monitoring/Other Committee: In Part 1 only

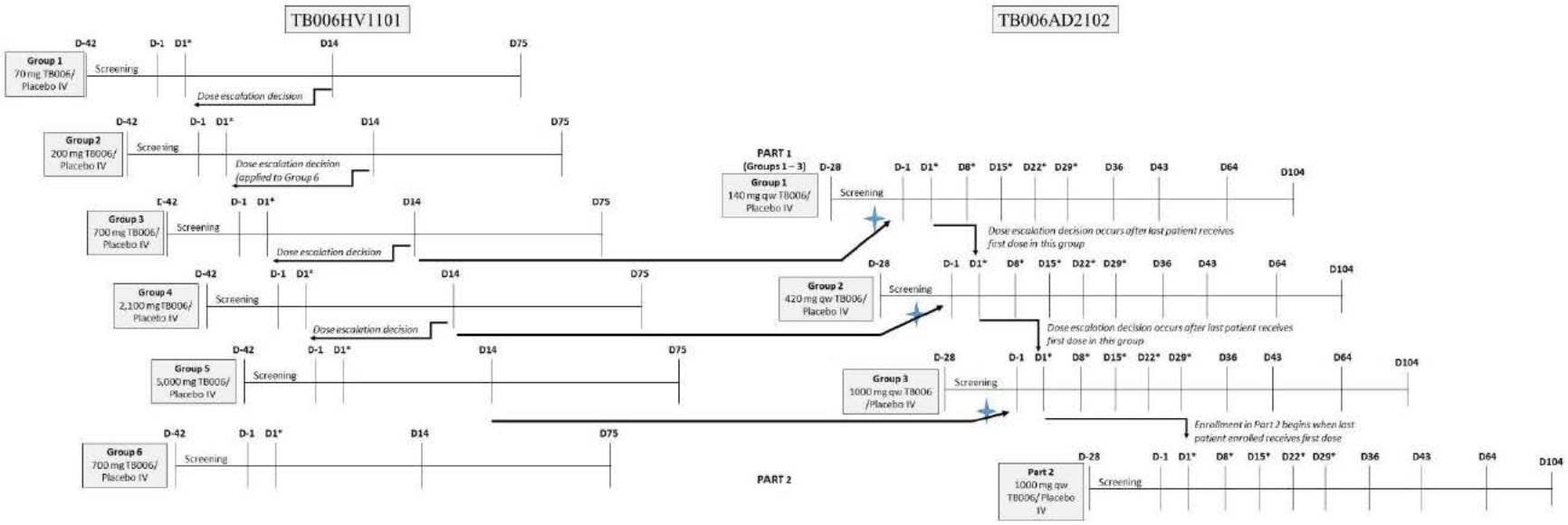
1.2 Schema

Figure 1. Study Design and Treatment Schema for Part 1 and 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 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 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 = severe Alzheimer's Disease.

1.3 Schedule of Activities (SoA)

Table 1. 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
Randomization			X															

Table 1. 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]	
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 for vital signs assessments
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	

Table 1. 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]	
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
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				

Table 1. 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]	
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 1. 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)
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, Appendix 4) and the NINCDS-ADRDA (Note: ADRDA is now the Alzheimer's Association) (Section 10.5, 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.
f [redacted]

Table 2. 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
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 for vital signs assessments

Table 2. 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)

Table 2. 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]	
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
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	

Table 2. 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]	
[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						
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)

[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; [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, Appendix 4) and the NINCDS-ADRDA (Note: ADRDA is now the Alzheimer's Association) (Section 10.4, 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 [redacted]

2 INTRODUCTION

TB006 is a humanized IgG4 (S228P) type monoclonal antibody, being developed by TrueBinding, Inc. for the treatment of AD.

2.1 Study Rationale

The TB006 nonclinical pharmacology program establishes its potential as a therapeutic agent for AD by neutralizing Gal-3, which regulates the production and accumulation of Aβ and tau proteins and is overexpressed in AD. The preclinical data have shown evidence of addressing underlying disease pathology and improving cognition.

The preclinical safety profile of TB006 further supports the clinical investigation of TB006.

This is a two-part Phase 1b/2a combined MAD and proof of concept study in patients with AD. Part 1 of the study will evaluate the safety, tolerability, PK, PD and efficacy of TB006, administered qw as an IV infusion over 1 hour. Part 1 of this study will be conducted in parallel with the Phase 1 SAD study (Protocol number TB006HV1101). Each dose level in this study will start after the safety, tolerability, and PK of the single dose equivalent to the combined total of the 5 qw doses has been established. In Part 2 of this study, enrollment will continue at the highest tolerated dose from Part 1. Part 2 will assess the efficacy of TB006 on cognition using the Clinical Dementia Rating scale – Sum of Boxes as the primary endpoint. Patients enrolled at the same dose level in Part 1, as well as all placebo patients, will be included in the efficacy analyses in Part 2. Randomization in Part 2 will be stratified according to patient severity.

This study will characterize TB006 safety, tolerability, plasma and CSF PK, and efficacy. In addition, the effect of TB006 on CSF and plasma biomarkers [redacted], as well as cognition, using the Clinical Dementia Rating Scale, the MMSE, the Cognitive Drug Research system battery, and the NPI, will be evaluated. [redacted]

2.2 Background

2.2.1 Disease Background

AD is a chronic progressive neurodegenerative disorder and is the leading cause of dementia among older adults. In the US, AD is one of the leading causes of death, ranking sixth among US adults and fifth among adults aged 65 years or older (CDC, 2020).

The most common and thoroughly investigated hypotheses proposed to explain the pathophysiology of AD are the amyloid hypothesis and tau hypothesis. Considerable evidence suggests that toxic changes in Aβ and tau initiate the disease cascade. Abnormal tau accumulates to form neurofibrillary tangles inside nerve bodies, where they destroy cell structure and interfere with neuronal function and communication. Eventually, cell death and brain atrophy result.

Other factors that may also contribute to AD include insufficient blood and nutrient delivery of the vascular system to the brain and neuroinflammation which damages neurons in the brain.

Drug development in the dementia arena has been highly active in the past 20 years. There are approximately 5 compounds with market approval, all of which aim to improve the symptoms of dementia. These "symptomatic" treatments may improve cognition in the short term but have no effect on the progression of the disease. More recently, therapies with large molecule antibodies have explored the impact of targeting the underlying pathology such as amyloid or damaged tau. These treatments seek to modify the course of the disease by slowing disease progression. Although some of these compounds have shown efficacy in patient subtypes and have demonstrated an acceptable safety and tolerability profile in clinical studies (Panza et al, 2019; Van Dyck, 2017), none have met their primary endpoint; ergo none have been approved for marketing. Therefore, an urgent unmet medical need remains for the treatment of AD.

Key to the success of drug development in this patient population is the need to identify patients early in the course of their disease for treatment intervention. Patients with advanced symptomatic disease have significant demyelination, neuronal cell loss, and loss of volume. Early identification measures include advanced imaging, most notably MRI, CSF testing for the presence of abnormal Aβ and tau, and sensitive cognition testing (NIA, 2020; Risacher and Saykin, 2013).

2.2.2 Truebinding, Inc. Investigational Product Background: TB006

Galectins are a ubiquitous group of proteins found in a variety of cells and tissues and are involved in numerous metabolic processes and functions. At least 15 galectin isotypes have been identified in epithelial cells of the respiratory system, digestive tract, urinary tract, skin, cardiovascular system, liver, immune cells, and in the CNS. Gal-3 plays an important role in different pathogenic conditions, including in neuroinflammatory and neurodegenerative disorders such as multiple sclerosis, AD, Parkinson's disease, and Huntington's disease. In addition, Gal-3 also plays a protective role due to its anti apoptotic effect in target cells. In vivo data from several investigators suggest that Gal-3 may be an important therapeutic target in pathological conditions including the disorders of the CNS.

TB006 is a humanized IgG4 (S228P) type monoclonal antibody that is highly specific and has high affinity to human Gal-3. It has demonstrated the potential to treat neurodegenerative disorders such as AD and traumatic brain injury, with an apparent wide safety margin, in preclinical models.

Detailed information can be found in the TB006 IB (see latest available version of IB).

2.3 Benefit/Risk Assessment

Based on preclinical pharmacology data and nonclinical toxicity studies with TB006, the overall benefit/risk profile favors clinical development of TB006 for treatment of AD.

More detailed information about the known and expected benefits and risks of TB006 based on data from the preclinical program may be found in the IB.

2.3.1 Risk Assessment

A standard battery of toxicology studies was conducted with TB006. The pivotal safety assessment was a 1 month GLP toxicology study in cynomolgus monkeys. Doses ranged from 10 to 200 mg/kg, and evaluation included clinical and laboratory observations, a 5 week recovery period, and full histopathology. No treatment related adverse findings were observed. Mild lymphoid hyperplasia occurred in males at the 10, 100, and 200 mg/kg dose levels, but based on mild severity, lack of dose dependency and historical test facility data from similar studies in cynomolgus monkeys, this finding was considered a species specific mild, reactive immune response and not an adverse toxicological finding. It is likely an immunogenicity reaction. No other findings were observed in this or any of the other toxicology studies.

TB006 is a first in class monoclonal antibody, therefore there are no known class adverse effects or risks to report from clinical studies. In general, risks associated with other monoclonal antibodies include allergic reactions such as hives or itching, flu like symptoms such as chills, fatigue, fever, and muscle aches and pains, nausea and vomiting, skin rashes and decreases in blood pressure. These effects have not been observed in preclinical studies to date. Other marketed IgG4 humanized monoclonal antibodies, such as natalizumab, eculizumab, and pembrolizumab, are used clinically. These antibodies largely target the immune system. There appears to be a spectrum of target-related negative effects when the total antibody dose gets too high. This pattern is not evident with TB006 in the preclinical toxicology profile, but will be closely observed in Phase 1 studies.

When performed correctly and according to industry standards, venipuncture complications are rare. However, even when properly performed, complications can include fainting, dizziness, hematoma, nerve injury, and arterial puncture or laceration. Blood draws and administration of the IV infusion in this study will be performed adequately trained medical staff to minimize any risk to patients.

Risks associated with a lumbar puncture can include headache, pain or numbness, bleeding, infection, puncture pain, and herniation. The lumbar puncture procedure will be performed by medical staff experienced with the technique and using aseptic techniques to minimize any risk to patients.

MR images are performed without the use of ionizing radiation, so patients are not exposed to the harmful effects of ionizing radiation. AEs for MRI scans are very rare. Millions of MRI scans are performed in the US every year, and the FDA receives around 300 AE reports for MRI scanners and coils each year from manufacturers, distributors, user facilities, and patients. The majority of these reports describe heating and/or burns (thermal injuries). To produce good

quality images, patients must generally remain very still throughout the entire MRI procedure. The MRI procedure will be performed by medical staff experienced with the equipment and the technique to minimize any risk to patients.

The safety assessments to be performed in this study, including clinical chemistry, hematology and urinalysis analyses, vital signs, ECGs, physical and neurological examinations, and assessments of AEs, SAEs, and C-SSRS are standard evaluations to ensure patient safety in this clinical study.

2.3.2 Benefit Assessment

TB006 is a humanized IgG4 (S228P) type monoclonal antibody that is highly specific and has high affinity to human Gal-3. It has demonstrated efficacy in preclinical models of neurodegenerative disorders such as AD and traumatic brain injury, and results are consistent with or superior to other compounds that have advanced into late-stage clinical studies. Thus, there is potential for TB006 to be effective in these disorders. The preclinical safety profile of TB006 supports the further investigation of TB006 in clinical studies.

Understanding that this therapy may have no clinical benefits to patients themselves, patients in this study will contribute to the process of developing new therapies in an area of unmet need.

Patients will undergo clinical evaluations/assessments associated with study procedures (eg, safety laboratory tests, vital sign and ECG measurements, and physical and neurological examinations), which would be a potential benefit for their own health awareness.

During confinement in the clinic, meals and access to forms of entertainment will be provided to patients. Patient expenses for time, travel, and other costs will be offset by a monetary compensation, consistent with standards for such study participations and after approval from the IRB to ensure that no coercion or undue influence are imposed on patients.

2.3.3 Overall Benefit Risk Conclusion

The above benefit risk assessment supports the conduct of this clinical study.

The preclinical data on TB006 to date suggests a wide margin of safety and minimal risk of adverse effects. The risks associated with study procedures, including lumbar puncture and blood draws, are also very low. Any potential adverse effects associated with the study drug and procedures are further minimized by intense safety monitoring and medical oversight by the investigator and study staff. Therefore, the potential risks identified in association with TB006 are justified by the anticipated benefits that may be afforded to patients with AD, if TB006 is successfully developed.

This study will be the second clinical study conducted with TB006. This study will be conducted in parallel and combined with the Phase 1 SAD study (Protocol number TB006HV1101). Each group in this study will commence after the safety, tolerability, and available PK of the single dose equivalent to the combined total of 5 qw doses planned in this study has been established.

3 OBJECTIVES AND ENDPOINTS

Table 3. Objectives and Endpoints

OBJECTIVES - PART 1	ENDPOINTS
Primary	
• To determine the safety and tolerability of multiple doses of TB006	• Safety endpoints, including the incidence of AEs and SAEs, clinical laboratory parameters, vital signs, ECGs, C-SSRS, and physical and neurological examinations, until Day 104 after the first TB006 dosing
• To determine the PK profile of multiple doses of TB006	• PK parameters derived by noncompartmental analysis using the TB006 plasma concentration-time data, including, but not limited to and as appropriate: ○ AUC_{tau}: area under the concentration-time curve over a dosing interval ○ C_{max}: maximum observed plasma concentration ○ t_{max}: time at which maximum plasma concentration occurs ○ C_{trough}: concentration at the end of a dosing interval ○ $t_{½}$: terminal elimination phase half-life ○ CL: total clearance ○ V_d: volume of distribution • Extent of CSF distribution as estimated by TB006 CSF concentrations
• To determine the maximum tolerated dose of multiple doses of TB006	• Safety endpoints as above
• To assess the immunogenicity of TB006 (production of anti-TB006 antibody)	• Detection of anti-TB006 antibodies
[redacted]	
• [redacted]	• Change from baseline through end of study on the Clinical Dementia Rating scale – Sum of Boxes total score

	• Change from baseline through end of study on the Cognitive Drug Research system battery score, composite scores and individual task measures • Change from baseline through end of study on the MMSE score • Change from baseline through end of study on the NPI score [redacted]

OBJECTIVES - PART 2	ENDPOINTS
Primary	
• To determine the clinical efficacy of TB006 in patients with mild to severe AD	• Change from baseline through Day 104 on the Clinical Dementia Rating scale – Sum of Boxes total score
Secondary	
• To determine the clinical efficacy of TB006 in patients with mild to severe AD	• Change from baseline through Day 36 on the Clinical Dementia Rating scale – Sum of Boxes total score • Proportion of responders on the Clinical Dementia Rating scale – Sum of Boxes at Days 36 and 104 • Change from baseline to Days 36 and 104 on the Cognitive Drug Research System Battery, composite scores and individual task measures • Change from baseline to Days 36 and 104 on the MMSE score • Change from baseline to Days 36 and 104 on the NPI score

• To determine the safety and tolerability of multiple doses of TB006	• Safety endpoints, including the incidence of AEs and SAEs, clinical laboratory parameters, vital signs, ECGs, C-SSRS, and physical and neurological examinations, until Day 104 after the first TB006 dosing
• To determine the PK following multiple doses of TB006	• PK parameters including, but not limited to, by C_{trough}, C_{max}, and $t_{½}$.
[redacted]	
• [redacted]	[redacted]

[redacted]; AD = Alzheimer's Disease; AEs = adverse events; C-SSRS = Columbia Suicide Severity Rating Scale; CSF = cerebrospinal fluid; D = Day; ECG = electrocardiogram; [redacted] MMSE = Mini Mental State Examination; [redacted] NPI = Neuropsychiatric Inventory; [redacted] PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event.

4 STUDY DESIGN

4.1 Overall Design

This is a seamless, two-part, Phase 1b/2a, multi-center, randomized, double-blind, placebo-controlled, MAD escalation study to evaluate the safety, tolerability, PK, PD and efficacy of TB006 in patients with AD. 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 dosing group schedule is presented in Table 4). 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 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 (minimum of 14 days from last patient dosing). 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 (700 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 (see Section 6.4.1 for details of randomization within each dose group).

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 SRC. Dose escalation and stopping rules are described in Section 6.2.1 and details on the SRC are described in Section 9.6.

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 SoA) as in Part 1. 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 strata.

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.

Study assessments will be conducted, and patients will be dosed according to the SoA (Table 1 and Table 2). Assessments for safety and tolerability, efficacy, PK, and PD are performed throughout the study (see Section 8). If a patient reports any 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.

4.1.1 Study Duration for Participation

Each patient will be screened for eligibility up to 28 days prior to dosing, and study assessments will be performed up to 104 days after the first dose. The total study duration for each patient will therefore be up to approximately 19 weeks.

4.1.2 Number of Participants

In Part 1, 8 patients will be enrolled into each dose group, thus a total of approximately 24 patients will be randomized in this portion of the study (see Section 6.4.2 for details on randomization). In Part 2, 116 patients will be enrolled; 58 into active TB006 treatment and 58 to placebo.

The sample size determination is presented in Section 9.2.

4.1.3 Replacement of Patients

Patients who discontinue early from Part 1 of the study may be replaced, depending on when the discontinuation occurs. Replacement patients will receive the same treatment to which the discontinued patient was assigned. Patients who discontinue from Part 2 of the study will not be replaced.

4.1.4 Number of Sites

There are approximately 12 to 15 sites in this multi-center study, all in the US.

4.2 Scientific Rationale for Study Design

This is a seamless, two-part, Phase 1b/2a combined MAD and proof of concept study to assess the safety, tolerability, efficacy, PK, and PD of TB006 in AD patients.

An AD patient population is included in the study to determine the safety and tolerability of TB006 in the patient population that is being pursued for development. A mild to severe patient population is the tentative population of interest because they have the greatest medical need of the AD population and afford a large opportunity for improvement. TB006 may do more than simply halt disease progression. If it can improve cognition, the mild to severe population is where it is most likely to be detected. Patients with significant comorbidities are excluded to avoid confounding the interpretation of safety data.

Randomization will be used in this study to avoid bias in the assignment of patients to treatment, to prevent introducing bias into evaluations, to increase the likelihood that known and unknown patient attributes (eg, demographics and baseline characteristics) are balanced across dose groups, and to ensure the validity of statistical comparisons across treatment groups.

In Part 1, 8 patients per dose group (6 patients randomized to TB006 and 2 patients to placebo) are considered adequate to evaluate initial safety and PK in AD patients, and to support dose escalation decisions. In Part 2, patients will be randomized to TB006 or placebo in a 1:1 ratio (stratified by MMSE score at baseline [≤ 20 and 21-24]) so that approximately 58 patients are assigned to each group. Part 2 will assess the efficacy of TB006 on cognition using the Clinical Dementia Rating Scale – Sum of Boxes as the primary endpoint. Patients enrolled at the same dose level in Part 1, as well as all placebo patients, will be included in the efficacy analyses in Part 2.

Dose escalation decisions in Part 1, as well as dose selection for Part 2, will use safety, tolerability, and available PK data through the first dose administered to the last patient in each group and single dose safety and tolerability data from the SAD study (Protocol number TB006HV1101).

All clinical and laboratory assessments are standard measurements commonly used in Phase 1 studies to ensure patient safety.

Serial sampling to evaluate the repeat-dose PK profile of TB006 will be applied in Part 1 of this study, sparse sampling will be used in Part 2.

The interleave design with the SAD study is to ensure an efficient completion of the Phase 1 studies, while ensuring that safety and tolerability at the exposures in this study are adequately established in the SAD study.

Biomarkers specific to AD, such as [redacted] as well as nonspecific biomarkers such as [redacted], are being collected and measured to assess target binding and target engagement. Patients will perform a battery of cognition tests, including the MMSE, the Cognitive Dementia Rating Scale, the Cognitive Drug Research system battery, and the NPI throughout the study to assess cognition. [redacted]

The rationale for the selection of doses in this study is described in Section 4.3.

4.3 Justification for Dose

The selection of doses in the SAD study was made after a careful assessment of the preclinical pharmacology and toxicology data while allowing for cautious escalation to the highest safe exposures or the maximum tolerated dose (FDA, 2005). The doses planned for this study are tentative and may be adjusted based on safety, tolerability, and available PK data from the SAD study and the previous group(s) in this study. The intent is to maintain the safety margins as described here.

The preclinical safety of TB006 was explored in a definitive 1 month GLP toxicology study in cynomolgus monkeys. Doses used in this study were 10, 30, 100, and 200 mg/kg, administered qw for 5 doses. Mild lymphoid hyperplasia occurred in males at the 10, 100, and 200 mg/kg dose levels, but based on mild severity, lack of dose dependency and historical test facility data from

similar studies in cynomolgus monkeys, this finding was considered a species specific mild, reactive immune response and not an adverse toxicologic finding. No other adverse effects occurred, and so the NOAEL in cynomolgus monkeys dosed once qw for 4 weeks was 200 mg/kg. The mean Day 29 exposures associated with this dose were C_{max} and $AUC_{0-\tau}$ of ~13,000 μg/mL and ~135,000 h*μg/mL, respectively.

Using a body surface area calculation and a 10 × safety factor, the maximum recommended safe starting dose would be 6.4 mg/kg, ~440 mg in a 70 kg person in the SAD study. Consideration, however, was given to preclinical efficacy data, where activity was demonstrated at a dose level of 10 mg/kg in mice. The HED conversion of this dose was approximately 70 mg in a 70 kg person. Subsequent planned doses in the SAD study were 200, 700, 2,100 and 5,000 mg. At the highest dose, a predicted safety margin from the NOAEL was estimated to be 8-fold on C_{max} and a 6-fold margin on $AUC_{0-\tau}$ based on early PK projections. Planned doses are to be modified based on safety and tolerability and PK (to retain these margins).

If TB006 behaves like other IgG4 antibodies, the half-life will likely be longer than the approximate 10 to12 days observed in monkeys. Qw dosing will result in accumulation. Despite this, the safety and tolerability of a single dose is a conservative approach to estimating the safety and tolerability of the same dose divided into qw administration for 1 month. In addition, a similar conservative approach can be applied to establishing initial safety margin estimates by using one compartment simulations derived from monkey toxicokinetic data. The highest proposed dose of 1,000 mg qw (total regimen = 5,000 mg) affords a safety margin of > 8-fold on the C_{max} and 6-fold on the AUC from the NOAEL in the 1 month toxicology study. The lowest dose of 140 mg qw (total regimen = 700 mg) results in a safety margin of nearly 60- and 30-fold on the C_{max} and AUC, respectively. Using the HED conversion from the 200 mg/kg dose level in monkeys, the margins from the NOAEL range from ~30-fold at the lowest dose to ~5-fold at the highest dose for a 70 kg person.

The mid dose of 420 mg qw enables a cautious escalation between doses. Evidence of intolerance or other safety signals, or PK differences that result in reductions in safety margins from the SAD study or previous doses in this study, may necessitate a change in planned doses. While TB006 is a first in class anti-Gal-3 antibody, a wider array of approved IgG4 human monoclonal antibodies have been used clinically. Most of these target the immune system, and there appears to be a spectrum of negative effects, largely immune-mediated, when the total antibody dose gets too high. These and all other toxicities will be closely monitored. Dose escalation will either be modified or will cease when evidence of toxicity appears.

The proposed dose range covers a potentially efficacious dose to a projected supratherapeutic dose. Successful safety, tolerability and PK characterization of a wide dose range will enable efficient drug development. Traditionally, MAD studies employ the planned clinical dosing interval, and patients are dosed to steady state to determine steady state PK and safety. The projected half-life of TB006 is expected to enable monthly dosing in later clinical studies. The qw dosing schedule used in this study will enable a determination of multiple dose PK and provide an estimate of repeat dose safety and tolerability.

4.4 End of Study

End of Study (Individual Patient): A patient is considered to have completed the study if he/she has completed all study visits through the Day 104 assessments as shown in the SoA (Table 1 and Table 2).

End of Study (End of Trial): The end of the study is defined as the date of the last visit of the last patient in the study or last scheduled procedure shown in the SoA (Table 1 and Table 2) for the last patient in the study.

5 STUDY POPULATION

Before any study specific activities/procedures, the appropriate written informed consent must be obtained (see Section 10.1.3) [Appendix 1]). Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Male and/or female > 50 years of age at the time of signing the informed consent.
2. Body weight of ≥ 50 kg and BMI between 18 and 35 kg/m^2, inclusive.
3. MMSE score of 24 or less.
4. Must be ambulatory.
5. Clinical diagnosis of AD consistent with the following:
    a. Probable AD, according to NINCDS-ADRDA (Section 10.5 [Appendix 5])
    b. Meets the DSM 5 – Criteria for Major Neurocognitive Disorder (previously dementia) (Section 10.4 [Appendix 4])
6. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
    a. Male patients:

    Male patients are eligible to participate if they agree to the following from the first day of dosing through 6 months following the last dose of study drug:

    - Refrain from donating sperm

      PLUS, either:

    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent unless partner is not a WOCBP

      OR

    - Must agree to use contraception/barrier as detailed below:
        - Agree to use a male condom and female partner use of an additional highly effective contraceptive method with a failure rate of < 1% per year when having sexual intercourse with a WOCBP who is not currently pregnant.

    b. Females must be of non-childbearing potential defined as:

    - At least 12 months post-menopausal
    - Surgically sterile, resulting from but not limited to tubal ligation, hysterectomy, and oophorectomy.
    - Documented infertility from other causes, such as endometriosis or uterine fibroids.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

7. Patients or caregiver has the ability to understand the purpose and risks of the study and provide signed and dated informed consent as described in Section 10.1.3 (Appendix 1) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. Patients whose caregiver signs the informed consent must provide their assent.
8. May or may not be receiving 1 or more of the currently marketed cognition enhancing AD medications, including, but not limited to donepezil, memantine, rivastigmine, and galantamine. If receiving, it must be the same medication and dose the past 2 months prior to screening.
9. Either currently or previously (in pre AD condition) literate and capable of reading, writing, and communicating effectively with others.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Any medical or neurological condition other than AD that in the opinion of the investigator could be a contributing cause of the patient's dementia (eg, medication use, vitamin B12 deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, diffuse Lewy body disease, head trauma).
2. History within the past 6 months or evidence of clinically significant psychiatric illness (eg, major depression, schizophrenia, or bipolar affective disorder).
3. Diagnosis of a dementia-related CNS disease other than AD (eg, Parkinson's Disease, Huntington's Disease, frontotemporal dementia, multi-infarct dementia, dementia with Lewy bodies, normal pressure hydrocephalus).
4. Identification of other known cause of dementia or any other clinically significant contributing co-morbid pathologies at screening MRI, in the opinion of the investigator.
5. Participation in any other drug, biologic, device, or clinical study or treatment with any investigational drug or approved therapy for investigational use within 30 days (or 5 half lives, whichever is longer) prior to screening, and/or participation in any other clinical study involving experimental medications for AD within the 60 days (or 5 half lives, whichever is longer) prior to screening.
6. Any contraindications to having a brain MRI eg, pacemaker; non-MRI-compatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia).
7. Any untreated or unstable clinically significant medical condition (ie, hypertension, diabetes, chronic obstructive pulmonary disorder, asthma, depression, etc) as judged by the investigator.
8. Any clinically significant findings in medical examination, including physical examination, 12-lead ECG, clinical laboratory tests (specifically, ALT > 1.5 × ULN, bilirubin > 1.5 × ULN [bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%], QTcB > 450 msec for male patients or > 470 msec for female patients).
9. Undergone major surgery ≤ 2 months before study drug administration.
10. Abnormalities in lumbar spine previously known or determined by a screening lumbar X-ray (if conducted).
11. History of clinically significant back pain, back pathology, and/or back injury (eg, degenerative disease, spinal deformity, or spinal surgery) that may predispose patient to complications or technical difficulty with lumbar puncture.
12. Evidence or history of significant active bleeding or coagulation disorder or use of non-steroidal anti-inflammatory drugs or other drugs that affect coagulation or platelet function within 14 days prior to lumbar catheter insertion.
13. Allergy to lidocaine (Xylocaine®) or its derivatives.
14. Medical or surgical conditions for which lumbar puncture is contraindicated.

15. Loss of more than 100 mL blood (eg, a blood donation) within 2 months before first study drug administration, or has received any blood, plasma, or platelet transfusions within 3 months before Day 1, or plans to donate blood during the study or within 3 months after the study.
16. Recent (1-month) history of a positive COVID-19 test result or disease symptoms of COVID-19 disease such as shortness of breath, cough, rhinorrhea, and sore throat, etc.
17. Known history of, or a positive test result for, HBsAg, IgM anti HBc, anti HCV, or HIV types 1 or 2 at screening. Patients with a documented history of treatment for Hepatitis C are otherwise eligible to participate.
18. Regular alcohol consumption within 6 months prior to the study defined as: an average weekly intake of > 20 units for males or > 16 units for females. One unit is equivalent to 8 g of alcohol: a half pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
19. Meets DSM-5 criteria for moderate or severe substance use disorder within the past 12 months, or has a positive test for substances of abuse, or has used substances, including but not limited to opiates, methadone, buprenorphine, methamphetamine, cocaine, amphetamines recreationally within the past 12 months.
20. Unable to complete this study for other reasons or the investigator believes that he or she should be excluded.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

No fasting or other dietary restrictions, including caffeine, are applicable. Dietary restrictions may apply to patients undergoing PET scans, depending on the requirements of the facility. These restrictions could include reduced carbohydrate intake for up to 24 hours and fasting for 6 hours prior to the procedure.

5.3.2 Alcohol

Moderate alcohol consumption (up to 2 units/day [males] and 1 unit/day [females]) is allowed throughout the study. One unit is equivalent to 8 g of alcohol: a half pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.

5.3.3 Activity

Patients will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Patients may participate in light recreational activities during the study (eg, moderate exercise such as walking or bicycling).

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes

demography, screen failure details, eligibility criteria, medical history, prior therapies, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if they have the potential to be included. Rescreened patients should be assigned the same patient number as for the initial screening. Informed consent is required before patients can be rescreened. See Section 10.1.3 (Appendix 1) for Informed Consent Process details.

6 STUDY DRUG

Study drug is defined as TB006 or placebo, intended to be administered to a study patient according to the study protocol.

Refer to the IB and Pharmacy Manual for more detailed information regarding the storage, preparation, destruction, and administration of study drug.

6.1 Study Drug Administered

The study drug for this study is TB006 and the control drug is placebo.

Study drug will be administered as a 1 hour IV infusion, at planned dose levels as outlined in Table 4.

Table 4. Study Intervention(s) Administered

Drug Name	TB006	Placebo
Type	Drug	
Dose Formulation	Sterile, white, off-white or light-yellow solution for injection	Placebo will be normal saline
Unit Dose Strength(s)	20 mg/mL in 8 mL vials (160 mg total)	-
Dose Levels	Group 1 = 140 mg TB006/placebo, Group 2 = 420 mg TB006/placebo, Group 3 = 1,000 mg TB006/placebo Prior to administration, the drug product, at the correct dose, is diluted in 250 mL of sterile normal saline; drug preparation and administration instructions will be provided in a separate Pharmacy Manual.	
Frequency	Each patient will receive a total of 5 doses, given qw for 5 weeks	
Route of Administration	IV infusion over 1 hour	
Sourcing	Provided centrally by the sponsor	
Packaging and Labeling	TB006 will be provided as single-use injectable glass vials sealed with rubber stopper and aluminum plain flip top for sterile vial. Each vial will be labeled as required per country requirement. TB006 should always be stored at 2°C-8°C (36°F-46°F).	An unblinded pharmacist will prepare the study drug. The placebo is plain saline bag and will be identical in appearance to the active drug.

IV = intravenous(ly); qw = weekly

6.2 Dose Modification

All planned dose levels may be adjusted upon review of the available PK and safety data from the SAD and Part 1 of this study as referenced previously. Every effort will be made to achieve the safety margins described in Section 4.3 through the highest dose. In addition, safety, tolerability and available PK data from this study will be taken into consideration for the second and third dose levels of Part 1, and the selected dose in Part 2. Lastly, dose groups in Part 1 may be added or removed from the planned design based on emerging data.

6.2.1 Dose Escalation and Stopping Considerations

While concrete dose escalation stopping criteria will not be included, the following variables (at a minimum) will be taken into account by the SRC at the protocol-specified time points for these decisions, and when events arise during the course of study treatment:

- Number and frequency of treatment-related AEs characterized as moderate or severe in severity
- Number and frequency of treatment-related SAEs
- Discontinuation due to AEs
- Emergent cardiovascular events, such as QTc increases or vital sign changes
- Liver function enzyme increases

6.3 Preparation, Handling, Storage, and Accountability

- The investigator or designee must document that appropriate temperature conditions have been maintained during transit and storage for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- Only patients enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Randomization

All patients will be centrally assigned to randomized study drug using an IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

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 (with 3 dose groups planned, for a total of 18 patients receiving TB006 treatment at different dose levels, and a total of 6 patients receiving placebo). In Part 2, 116 patients will be randomized to active TB006 or placebo (1:1) and will follow the same dosing schedule and procedures (with some exceptions – see SoA) as in Part 1. 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 strata.

On Day 1, patients will be assigned a unique number (randomization number) in ascending numerical order as patients are enrolled. Once a randomization number has been assigned, it must not be re assigned. The randomization number encodes the patient's assignment to either active TB006 treatment or placebo, according to the randomization schedule generated prior to the study. Each patient will receive blinded study drug, labeled with his/her unique randomization number.

6.4.2 Blinding

In Part 1, in each dose group, 6 patients will be randomized to active TB006 treatment, and 2 patients to placebo. In Part 2, 58 patients will be randomized to active TB006 treatment, and 58 patients to placebo. Investigators will remain blinded to each patient's assigned study drug throughout the course of the study. In order to maintain this blind, an unblinded pharmacist will be responsible for the reconstitution and dispensation of all study drug. Active study drug and placebo are made to be identical in appearance. Refer to the Dose Preparation Manual for further details on dose preparation and blinding.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study drug records at the site(s) to verify that randomization/dispensing has been performed accurately.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

6.5 Study Intervention Compliance

When the individual dose for a patient is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

The investigator is responsible for study drug administration. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study drug and study patient identification will be confirmed at the time of dosing by a second member of the study site staff.

6.6 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of screening or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical/Scientific Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The use of 1 or more of the currently marketed cognition enhancing AD medications, including, but not limited to donepezil, memantine, rivastigmine, and galantamine, are allowed in this study. Patients should not be considered for inclusion if dose changes or changes in medication are anticipated during the course of the study.

Other medications to treat stable, chronic medical conditions are acceptable as long as they had been started more than 30 days before screening and their chronic use is anticipated. In general, patients receiving other monoclonal antibodies on a chronic basis are not acceptable, as are medications used on an acute (ie, < 2 weeks) basis. Examples include:

- Anti-infectives/antibiotics
- Corticosteroids
- Opioid analgesics
- Anxiolytics (for acute anxiety)
- Muscle relaxants

Paracetamol/Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study.

Any questions or uncertainties about concomitant medication may be discussed with the Medical/Scientific Monitor.

6.7 Study Drug After the End of the Study

There will be no post-study access to the study drug for any of the patients.

7 DISCONTINUATION OF STUDY DRUG AND PATIENT DISSCONTINUATION/WITHDRAWAL

A patient may stop study drug or withdraw from the study at any time for any reason or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

Reasons for removal from study drug and/or from the study include any of the following:

- Liver injury (see Section 7.1 below)]
- Cardiac changes (see Section 7.2 below)
- Adverse events
- Pregnancy
- Protocol deviation
- If the patient meets an exclusion criterion (either newly developed or not previously recognized) that poses a greater risk to the patient with continued participation
- If, in the investigator's opinion, continuation of the study would be harmful to the patient's well being
- Sponsor decision
- Patient request to discontinue study drug or withdraw consent for study participation
- Death
- Lost to follow-up

At the time of discontinuing from the study, if possible, an E/D visit should be conducted, as shown in the SoA (Table 1 and Table 2). See Table 1 and Table 2 for data to be collected at the time of study discontinuation.

Every effort should be made by the site to follow the patient and maintain scheduled safety visits through the Day 104 visit if at all possible, even for patients who voluntarily withdraw their consent.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.1 Liver Injury

Discontinuation of study drug for abnormal liver function should be considered by the investigator when a patient meets one of the conditions outlined in Section 10.3 (Appendix 3) or if the investigator believes that it is in best interest of the patient.

7.2 Cardiac Changes

A patient who meets the below criteria based on the average of triplicate ECG readings will be withdrawn from the study:

- Change from baseline: sustained QTc > 60 msec

If a clinically significant finding is identified (including, but not limited to changes from baseline in QTcB or QTcF after study drug infusion), the investigator or qualified designee will determine if the patient can continue in the study and if any change in patient management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.3 Lost to Follow up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient or caregiver (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled in Section 10.1.8.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1 and Table 2). Protocol waivers or exemptions are not allowed. Specifications related to protocol deviations are presented in Section 10.1.7.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoA (Table 1 and Table 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1 and Table 2).
- The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 250 mL (see Table 6 and Table 7). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 General Study Periods

8.1.1 Screening, Enrollment and/or Randomization

Screening will occur between Day -28 and Day -2. The purpose of the screening period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each patient and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 10.1.3 (Appendix 1).

Screening assessments are performed as outlined in the SoA (Table 1 and Table 2).

8.1.2 Study Drug Administration and Follow-up Period

Following randomization, patients will receive study drug as an IV infusion at qw intervals, for 5 doses. Study assessments will be performed up to Day 104 as outlined in the SoA (Table 1 and Table 2).

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1 and Table 2).

8.2.1 Physical and Neurological Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems.
- The neurological examination will assess mental status, motor and sensory skills, hearing and speech, vision, coordination, and balance.
- Height and weight will also be measured and recorded. Height will only be measured at screening.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed as indicated in the SoA (Table 1 and Table 2).
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest with the patient in a quiet setting without distractions (eg, television, cell phones). Blood pressure measurements will be taken with the patient in the sitting position.
- Vital signs will be taken before blood collection for laboratory tests, if that is scheduled for the same time point.

8.2.3 Electrocardiograms

- 12-lead ECG measurements will be obtained as outlined in the SoA (Table 1 and Table 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals (triplicate measurements will be obtained at all-time points, except at the screening visit where a single measurement will be obtained). Refer to Section 7.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained at 2-minute intervals.
- On non-dosing days, effort should be made to perform 12-lead ECGs time-matched with the pre-dose time point on dosing days.
- The PI or designated site physician will review and assess all ECGs as Normal, Abnormal, or Not Evaluable. Once signed, the original ECG tracing will be retained with the patient's source documents. At the request of the sponsor, a copy of the original ECG will be made available to the sponsor.
- On Part 1 only, ECGs will be transferred electronically to an ECG central reader for analysis according to the study-specific recommendations included in the ECG manual. The central ECG reader will review machine reads and provide corrected values as specified in the manual. The following parameters will be recorded: PR interval, RR interval, QRS complex/duration, QT interval, QTc, heart rate, and clinical interpretation.

- The results from the central reader will be captured in the study database, together with the investigator assessment of the ECG.
- In Part 2, only the machine readings and investigator interpretations will be recorded in the study database.

8.2.4 Clinical Safety Laboratory Assessments

- The tests detailed in Table 5 will be performed by the central laboratory; see the SoA (Table 1 and Table 2) for the timing and frequency.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- The investigator must review the laboratory report and document this review. The investigator should consider documenting any clinically relevant changes as AEs in the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated at appropriate intervals until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Medical/Scientific Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in this section, must be conducted in accordance with the laboratory manual and the SoA (Table 1 and Table 2).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in patient management or are considered clinically significant by the investigator (eg, SAE, or AE, or dose modification), then the results must be recorded in the CRF.

Table 5. Protocol-required Clinical Safety Laboratory Assessments

Hematology	Clinical Chemistry	Urinalysis
Platelet count RBC count Hemoglobin Hematocrit RBC Indices: MCV MCH %Reticulocytes WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	BUN Creatinine CPK Glucose (nonfasting) Potassium Sodium Calcium AST/SGOT ALT/SGPT Alkaline phosphatase Total and direct bilirubin Total protein Albumin Total cholesterol HDL LDL Triglycerides TSH HbA1c	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)
Other Screening Tests Urine alcohol and drug screen (including but not limited to opiates, methadone, buprenorphine, methamphetamine, cocaine, and amphetamines) Viral serology (HBsAg, IgM anti-HBc, anti-HCV, HIV) and COVID-19 The results of each test must be entered into the CRF.		

ALT = alanine aminotransferase; anti-HCV = hepatitis C virus antibody; AST = aspartate aminotransferase; BUN = blood urea nitrogen; COVID = coronavirus disease; CPK = creatine phosphokinase; CRF = case report form; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HDL = high-density lipoprotein; IgM anti-HBc = immunoglobulin M antibody to hepatitis B core antibody; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; SGOT = Serum Glutamic-Oxaloacetic Transaminase; SGPT = Serum Glutamic-Pyruvic Transaminase; TSH = thyroid-stimulating hormone; WBC = white blood cell.

8.2.5 Suicidal Ideation and Behavior Risk Monitoring

The C-SSRS is a prospective semi-structured interview comprised of the following areas of assessment: Ideation, Intensity of Ideation, Behavior, and Lethality. It has been used extensively in global clinical studies (academic and industry sponsored) and in a range of therapeutic areas, disorders and indications, including psychiatry, neurology, obesity, urology and endocrinology and is FDA-approved. It has been used to determine eligibility to enroll at screening and at every follow-up visit to prospectively monitor suicidality during the study. The C-SSRS was developed for use in clinical studies and can be administered by non-mental health professionals with training. All C-SSRS raters for this study will have a certificate that verifies training completion and allows them to rate in this study.

There are 2 versions of the C-SSRS. The “Past 6 months” version of the C-SSRS will be completed at screening and the “Since Last Visit” version will be completed at all remaining visits according to the SoA (Table 1 and Table 2). The “Since Last Visit” version will also be completed at any unscheduled clinic visits.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.2 (Appendix 2).

AE(s) will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the patient to discontinue the study (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

All AEs and SAEs will be collected from the time of the first study drug administration until Day 104. 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.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.2 (Appendix 2). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

The investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2 (Appendix 2).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.2 (Appendix 2).

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

- Notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study drug under clinical investigation are met.
- The sponsor has a legal responsibility to notify the FDA about new safety information of a study drug under clinical investigation. The sponsor will comply with regulatory requirements relating to safety reporting to the FDA, IRB/IEC, and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Disease-related Events and/or Disease-related Outcomes not Qualifying as Adverse Events or Serious Adverse Events

The following DREs are common in patients with AD and can be serious/life threatening:

- Anxiety and psychosis
- Dysphagia and other eating disorders
- Exacerbation of AD
- Injuries from falls

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded in the patient's CRF when reported. These DREs will be monitored by the SRC on a routine basis.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater severity, frequency, or duration than expected for the individual patient.

OR

- The investigator considers that there is a reasonable possibility that the event was related to study drug.

8.4 Treatment of Overdose

For this study, any dose of study drug greater than the planned doses of study drug indicated in this protocol, will be considered an overdose. There is no recommendation for a specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the Medical/Scientific Monitor immediately.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities until TB006 can no longer be detected systemically until the next scheduled dose.
- Obtain a plasma sample for PK analysis according to the protocol schedule unless otherwise advised by the Medical/Scientific Monitor.
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical/Scientific Monitor based on the clinical evaluation of the patient.

8.5 Pharmacokinetics

- Whole blood samples of approximately 5 mL will be collected for measurement of plasma concentrations of TB006 as specified in the SoA (Table 1 and Table 2). Additional samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of TB006. Each plasma sample will be divided into 2 aliquots (1 each for PK and a back-up). Samples collected for analyses of plasma TB006 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Other than ApoE4 genetic testing from a sample at the Screening visit, genetic analyses will not be performed on these plasma samples. Patient confidentiality will be maintained. At visits during which whole blood samples for the determination of multiple aspects of TB006 will be taken, 1 sample of sufficient volume can be used.

- Lumbar puncture procedure will be performed at the time points as specified in the SoA (Part 1 only) (Table 1) to obtain CSF samples for measurement of concentrations of TB006. The lumbar procedure is optional for participating patients.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.6 Pharmacodynamics

8.6.1 Blood Samples for Biomarker Assessments

Venous blood samples of approximately 5 mL will be collected for measurement of plasma [redacted], and other relevant biomarkers at the time points specified in the SoA (Table 1 and Table 2).

8.6.2 Lumbar Puncture (Part 1 only)

Lumbar puncture procedure (optional for participating patients) will be performed at the time points as specified in the SoA (Table 1) to obtain CSF samples for measurement of [redacted], and other relevant biomarkers.

8.6.3 Cognition Testing

Patients will perform a battery of cognition tests, including the MMSE, the Clinical Dementia Rating Scale, the Cognitive Drug Research system battery, and the NPI throughout the study to assess cognition. Tests, with the exception of the Cognitive Drug Research system battery will be performed by paper only. The Cognitive Drug Research system battery will be performed using an electronic device.

8.6.3.1 Clinical Dementia Rating Scale

Clinical Dementia Rating Scale is a global assessment instrument that yields global score and a sum of boxes score. The Clinical Dementia Rating Scale is derived from a semi-structured interview with the participant 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 = mild, moderate, and severe impairment, respectively. From the 6 individual category 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 = questionable, mild, moderate, or severe dementia, respectively (Morris, 1993). The Clinical Dementia Rating Scale – Sum of boxes score is a detailed quantitative general index that provides more information than the Clinical Dementia Rating Scale – Global Score in participants with early (prodromal to mild)

dementia (Coley et al, 2011; Cedarbaum et al, 2013). In particular, the Clinical Dementia Rating Scale – Sum of Boxes has been proposed for use in longitudinal assessment of dementia and is widely used in AD studies as a global measure of disease progression (Williams et al, 2013).

8.6.3.2 Mini-mental State Examination

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 administered at the time points indicated in the SoA (Table 1 and Table 2). The MMSE will be administered by a trained member of the investigational team. At each site, the same individual, whenever possible, will perform the MMSE evaluation on a specific patient throughout the study. The screening MMSE will be used for purposes of determining patient eligibility and does not need to be reconciled with the baseline MMSE score.

8.6.3.3 Cognitive Drug Research System

The Cognitive Drug Research system 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 Cognitive Drug Research system is performed at the time points listed in the SoA (Table 1 and Table 2). Two training sessions will be conducted at least 30 minutes apart during the screening period to allow patients to become familiar with the procedure, reduce test anxiety, reduce learning effects, and produce a stable baseline assessment.

8.6.3.4 Neuropsychiatric Inventory

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 ranges from 0 to 12). The NPI total score ranges from 0 to 120 with higher scores indicating greater behavioral impairment.

The 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 NPI will be administered at the time points indicated in the SoA (Table 1 and Table 2). The NPI will be administered by an independent, trained, and certified member of the investigational team. At each site, the same individual, whenever possible, will perform the NPI evaluation on a specific patient throughout the study.

8.7 Pharmacogenetics

A 2 ml sample of blood will be taken for ApoE4 genotyping at screening from patients who give separate written informed consent for this optional research. If this sample is not taken at screening, it may be taken at any visit until the last study visit.

A general analysis of deoxyribonucleic acid will not be employed. However, other targeted analyses of genetic polymorphisms in AD may be conducted.

Instructions for collection, processing, labelling, storing and shipping samples are detailed in the Laboratory Manual.

8.8 Immunogenicity Assessments

Antibodies to TB006 will be evaluated in plasma samples collected from all patients at the time points according to the SoA (Table 1 and Table 2). These samples will be tested by the sponsor or sponsor's designee.

Anti-TB006 antibodies will be determined on plasma samples collected for plasma PK determinations, and no additional blood samples need to be obtained.

Plasma samples will be screened for antibodies binding to TB006 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to TB006 and/or further characterize the immunogenicity of TB006.

The detection and characterization of antibodies to TB006 will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to study drug will also be evaluated for TB006 plasma concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study drug(s).

8.9 Total Volume of Blood Sampling

Table 6 and Table 7 presents the number of blood samples and the total volume of blood that will be collected throughout the study (Parts 1 and 2).

Table 6. Summary of Blood Sample Volumes for Part 1

	Approximate Sample Volume per Collection (mL)	Number of Collection Time Points	Approximate Total Volume Collected (mL)
Clinical laboratory tests[a]	12.5	6	12.5×6 = 75
Viral serology	3.5	1	3.5×1 = 3.5
PK and/or ADA blood sampling	5	22	5×22 = 110
Pharmacogenetic sampling (optional)	2	1	2
PD blood sampling	6	3	6×3 = 18
Total Blood Volume Estimate			208.50

ADA = anti-drug antibody; PD = pharmacodynamic(s); PK = pharmacokinetic(s).
a 12.5 mL sample for hematology, clinical chemistry, and includes serum pregnancy test where this is performed at the same time point.

Table 7. Summary of Blood Sample Volumes for Part 2

	Approximate Sample Volume per Collection (mL)	Number of Collection Time Points	Approximate Total Volume Collected (mL)
Clinical laboratory tests[a]	12.5	6	12.5×6 = 75
Viral serology	3.5	1	3.5×1 = 3.5
PK and/or ADA blood sampling	5	8	5×8 = 40
Pharmacogenetic sampling (optional)	2	1	2
PD blood sampling	6	3	6×3 = 18
Total Blood Volume Estimate			138.50

ADA = anti-drug antibody; PD = pharmacodynamic(s); PK = pharmacokinetic(s).

a 12.5 mL sample for hematology, clinical chemistry, and includes serum pregnancy test where this is performed at the same time point.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary endpoint in Part 2 is the change from baseline Clinical Dementia Rating Scale – Sum of Boxes score at through Day 104. The primary null hypothesis to be tested is as follow:

- H_0: There is no difference between TB006 group and placebo group in change from baseline Clinical Dementia Rating Scale – Sum of Boxes score at through Day 104.

9.2 Sample Size Determination

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 strata. 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 of change from baseline Clinical Dementia Rating Scale – Sum of Boxes at Day 104 is 0.5, a total of 128 patients will provide 80% power to detect a mean change from baseline difference of 0.25 at Day 104 using a 2-sided, 2 sample t-test at the 5% level of significance.

9.3 Populations for Analyses

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

Full analysis set (FAS)	All patients who are randomly assigned to study drug
Safety analysis set (SAS)	All patients randomly assigned to study drug and who take at least 1 dose of study drug. Patients will be analyzed according to the study drug they actually received
PK analysis set (PKS)	All patients who received at least 1 dose of TB006 and have at least 1 post-dose blood sample with measurable TB006 concentrations
PD analysis set (PDS)	All patients who received blinded study drug and have at least 1 post-dose evaluable PD assessment

The FAS will be used for the analysis of disposition and protocol deviations. The SAS will be used for all other analyses, except specifically for PK and PD. The FAS and the SAS will be the

same if all randomized patients are dosed with study drug. The PKS will be used for all PK analyses and the PDS will be used for all PD and efficacy analyses.

9.4 Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary, secondary, and exploratory endpoints.

9.4.1 General Considerations

Descriptive statistics will be used to summarize the results of the study. Continuous variables will be summarized by reporting the number of observations, mean, standard deviation, median, minimum, and maximum. For the PK parameters and plasma concentrations, geometric mean and coefficient of variation will also be presented. Categorical/discrete variables will be summarized using frequency tables showing the number and percentage of patients within a particular category. All summaries will be presented by dose group and treatment group.

Baseline values will be taken as the most recent assessment prior to dosing, reported during screening and up to and including Day 1.

9.4.2 Part 1 Primary Endpoints

9.4.2.1 Safety and Tolerability

All AEs will be coded using the most recent version of MedDRA. The incidence of AEs will be summarized by SOC and PT. Similar summaries will be produced for AEs by severity, SAEs, treatment related AEs, and AEs leading to discontinuation. AEs are collected from the first dose of study drug, thus all AEs are considered treatment emergent AEs.

The ECG results will be presented by visit, summarizing the continuous measurements based on the average of triplicate values, including the QT, QTc, QRS, RR, PR intervals, as well as change from baseline values, and clinically significant changes in heart rate and rhythm.

Reported values and change from baseline values of hematology, clinical chemistry and urinalysis (and the determinations relevant to the normal ranges and appropriate clinically significant or CTCAE toxicity gradings) will be summarized by laboratory test for each assessment day, using appropriate descriptive statistics.

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature) will be summarized by assessment day showing absolute values, change from baseline values, and clinically significant changes (including orthostasis) using appropriate descriptive statistics.

Physical and neurological examinations will be summarized by assessment day showing shift from baseline.

The C-SSRS assessments will be presented in a by-subject listing.

9.4.2.2 Pharmacokinetics

Plasma and available CSF TB006 concentrations over time will be presented, showing both individual and mean concentrations. Plasma PK parameters will also be calculated and presented descriptively. Plasma PK parameters of interest may include C_{max}, t_{max}, C_{trough}, AUC_{tau}, CL, and Vd.

Additional PK analysis using a population PK approach may be used but will be reported separately from the clinical study report.

9.4.2.3 Immunogenicity

The presence of anti TB006 antibodies will be listed by patient and time point. Analyses will be performed using appropriate descriptive statistics to summarize the results.

9.4.4 Part 1 Other Analyses

The patient disposition showing numbers randomized, treated, completed, treatment discontinuation, and discontinued from the study will be summarized. For those patients who discontinued the study or the study treatment prematurely, the reason for discontinuation will be summarized.

All patient data will be reviewed for the occurrence of protocol deviations. Summaries will be presented showing the numbers of patients with each class and type of deviation.

Demographic variables to be summarized will include age, gender, race, ethnicity, height, weight, and BMI.

Baseline characteristics to be summarized will include medical history and viral serology. Prior and concomitant medications will be summarized showing the number and percentage of patients taking each medication. Medications will be coded using the World Health Organization Drug Dictionary preferred name.

9.4.5 Part 2 Primary and Secondary Endpoints

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.

The primary efficacy endpoint in Part 2, Clinical Dementia Rating Scale – Sum of Boxes change from baseline through Day 104 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 baseline Clinical Dementia Rating Scale - Sum of Boxes score as a covariate. The least square mean difference, the 95% confidence interval of the difference, and the p-value will be presented as well as the descriptive statistics.

The key secondary efficacy endpoint is the change from baseline through Day 36 on the Clinical Dementia Rating Scale – Sum of Boxes, and will be analyzed using the MMRM as previously described. Other secondary efficacy endpoints include change from baseline Cognitive Drug Research System battery at Days 36 and 104, change from baseline MMSE total score at Days 36 and 104, change from baseline NPI total score at Days 36 and 104, and a responder analysis on the Clinical Dementia Rating Scale at Days 36 and 104. A responder is defined as a 1-point improvement on the Sum of Boxes score. The patients with missing data will be included in the denominator and treated as a non-responder. The secondary endpoints except for the responder analysis will be analyzed similarly using the MMRM with treatment group, randomization strata (MMSE ≤ 20 and 21-24), visit, and treatment group by visit interaction as fixed effects and a corresponding baseline score as a covariate. The proportion of the responders between treatment groups will be tested using the Cochran Mantel-Haenszel test, adjusting for randomization strata (MMSE ≤ 20 and 21-24) and the common risk difference and the 95% confidence interval will be presented.

Safety endpoints including AEs, clinical laboratory tests, vital signs, ECGs, C-SSRS, and physical and neurological examination results will be presented as described in Section 9.4.5.

The available noncompartmental PK parameters (eg, C_{max} and C_{trough}) will be summarized descriptively.

[redacted]

9.5 Interim Analysis

No interim analysis is planned for this study.

9.6 Safety Review Committee

An SRC will be involved in the conduct of this study. The SRC will be comprised of the PI and sponsor representatives including the Medical/Scientific Monitor, pharmacokineticist, statistician and others as deemed necessary. The SRC will review safety and available PK data on each accruing dose group after the last patient in each group has received their first dose. Safety, tolerability, and available PK data when the last patient in each group receives the first dose of study drug, will be used for dose escalation decisions. Also, each group in this study will commence after the safety, tolerability, and PK of the single dose equivalent to the combined total of 5 qw doses planned in the SAD study (Study TB006HV1101) has been established (minimum of 14 days from last patient dosing). Data will be reviewed by a blinded SRC. A decision will be made by the committee to either continue dosing for the next group at the planned dose level, continue at a modified dosing schedule, or to discontinue any dose escalation (and discontinue the study).

Safety reasons that could halt dose escalation are discussed in Section 6.2.1.

As needed, details of the responsibilities and organization of the SRC will be provided in a separate document.

9.7 Handling of Missing Data

All data will be handled as available. No specific approaches will be utilized to impute missing data apart from possibly in cases of missing dates, severity or relationship for AEs, where a worst case may be assumed.

Full details of the handling of missing data including the missing individual items in the cognition tests, will be provided in the SAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, patient recruitment advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information, as requested, to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1-year after completion of the study.

10.1.3 Informed Consent Process

- An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the sponsor Study Manager to the investigator. The written

informed consent form is to be prepared in the language(s) of the potential patient population.

- The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The source document must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study if the ICF is revised.
- The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.
- The investigator is also responsible for asking the patient if the patient has a primary care physician and if the patient agrees to have his/her primary care physician informed of the patient's participation in the clinical study unless it is a local requirement. The investigator will then inform the primary care physician. If the patient agrees to such notification, the investigator is to inform the patient's primary care physician of the patient's participation in the clinical study. If the patient does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the patient's medical record.
- If a patient is unable to read, or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written ICF and any other written information to be provided to patients is read and explained to the patient or the patient's legally acceptable representative, and after the patient or the patient's legally acceptable representative has orally consented to the patient's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the patient or the patient's legally acceptable representative, and that informed consent was freely given by the patient or the patient's legally acceptable representative (Refer to ICH GCP guideline, Section 4.8.9).

- Patients who are rescreened are required to sign a new ICF.

10.1.4 Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The investigator must ensure that the patient's confidentiality is maintained for documents submitted to the sponsor.
- For SAEs reported to the sponsor, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).
- Documents that are not submitted to the sponsor (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.
- In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(ies), and the IRB/IEC direct access to review the patient's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.
- The investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study related records, including personal information.

10.1.5 Data Quality Assurance

- All patient data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality, such as Risk Management and Mitigation Strategies and Analytical Risk based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for at least 2 years after the last marketing approval in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug (eg, via notification of the FDA or local regulatory authority), unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from (sponsor's) Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.
- Retention of study documents will be governed by the Clinical Trial Agreement.
- All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

10.1.6 Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Site Trial Binder or other site communication.

10.1.7 Protocol Deviations

There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

The investigator should not deviate from the protocol, except where necessary for patient safety. If other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the Medical/Scientific Monitor to determine the appropriate course of action.

The investigator and study staff should adhere to the time points for all procedures to the extent possible. However, circumstances that result in delays are understandable. If delays are significant (ie, > 10 min for vital signs) or result in a compromised ability to interpret data (ie, ECG delays that prohibit time-matched comparisons), these will be considered protocol deviations.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. However, blood samples not collected within the interval specified for the scheduled sample time below (Table 8) should be recorded in the source documents.

Table 8. Windows for PK Sample Collection

Time Window	Nominal Sampling Time
No more than 0.5 hours pre-dose ± 0.5 minutes	Pre-dose (0 hours) on D1, D8, and D29
± 0.25 hours	End of study drug infusion, 1 and 2 hours after the end of study drug infusion on D1, D8, and D29
± 0.75 hours	4 and 6 hours after the end of study drug infusion on D1, D8, and D29

D = Day

The Significant Protocol Deviation eCRF is to be completed for deviations that are identified by the sponsor before study start

10.1.8 Study and Site Start Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the investigator.
- Discontinuation of further study drug development.

If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator will promptly inform the patient and must ensure appropriate patient therapy and/or follow-up.

10.1.9 Publication Policy

- Data from this study are the property of the sponsor, TrueBinding, Inc. Data may not be disclosed by the investigator(s) to any external source without the permission of TrueBinding, Inc.
- If an investigator wishes to present or publish data in the public domain, the investigator must agree to seek approval from the sponsor before submitting any manuscript or abstract for publication or presentation. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1 Definition of AE

AE Definition
• An adverse event (AE) is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study drug, whether or not considered related to the study drug. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Any new condition detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/serious AE (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequela.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2 Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life threatening The term 'life threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other medically important serious event:

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

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

10.2.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the case report form (CRF).
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- The investigator must assign the following AE attributes:
  - AE diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to study drug or other protocol-required therapies and
  - Action taken.If AE severity changes, record each change as a single event.
- The following should be considered when recoding SAEs:
  - Death is an outcome of an event. The event that results in the death should be recorded and reported on both an SAE and CRF.
  - For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself.

Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study per the NCI CTCAE version 5.0 (see Section 10.2.5). Toxicities that are not specified in NCI CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications).

  An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the severity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- Causality assessments are defined below:
  - Causality assessments that indicate the event is "Not Drug Related":
    - Unrelated: The event is related to an etiology other than the study drug administration (the alternative etiology must be documented in the patient's medical record).
    - Unlikely: The event is unlikely to be related to the study drug and likely to be related to factors other than study drug.
  - Causality assessments that indicate the event is "Drug Related":
    - Possible: There is an association between the event and the administration of study drug and there is a plausible mechanism for the event to be related to the study drug; but there may also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.
    - Probable: There is an association between the event and the administration of study drug and there is a plausible mechanism for the event to be related to the study drug, and the event could not be reasonably explained by known characteristics of the patient's clinical status or an alternative etiology is not apparent.
  - Definite: There is an association between the event and the administration of study drug and there is a plausible mechanism for the event to be related to the study drug and causes other than the study drug have been ruled out and/or the event re-appeared on re-exposure to the study drug.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.4 Reporting of Serious Adverse Events

SAE Reporting to via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Medical/Scientific Monitor by telephone. • Contacts for SAE reporting are noted below.

10.2.5 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0

The NCI CTCAE is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

*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.

Published date of version 5.0: 27 Nov 2017, available here:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

from:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

10.3 Appendix 3: Liver Safety: Suggested Actions and Follow-up Assessments

Phase 1 liver chemistry stopping criteria define liver injury, evaluate liver event etiology, and are considered in dose escalation decisions.

Table 9. Phase 1 Liver Chemistry Stopping Criteria and Follow-up Assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">Alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN)
If ALT ≥ 3 × ULN AND bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or international normalized ratio (INR) > 1.5, report as a serious adverse event (SAE)[a,b]
See additional actions and follow-up assessments below</td></tr>
<tr><th colspan="3">Required Actions and Follow-up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td colspan="2">• Immediately discontinue study drug
• Report the event to the sponsor within 24 hours
• Complete the liver event case report form (CRF), and complete an SAE data collection tool if the event also met the criteria for an SAE[b]
• Perform liver function follow-up assessments
• Monitor the patient until liver function test abnormalities resolve, stabilize, or return to baseline (see MONITORING)
MONITORING:
If ALT ≥ 3 × ULN AND bilirubin ≥ 2 × ULN or INR > 1.5
• Repeat liver function tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver function follow-up assessments within 24 hours.
• Monitor patient twice weekly until liver function test abnormalities resolve, stabilize, or return to baseline.</td><td>• Viral hepatitis serology[c]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
• Fractionate bilirubin, if total bilirubin ≥ 2 × ULN
• Complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE CRF
• Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF
• Record alcohol use on the liver event alcohol intake CRF
If ALT ≥ 3 × ULN AND bilirubin ≥ 2 × ULN or INR > 1.5:</td></tr>
</table>

• A specialist or hepatology consultation is recommended. **If ALT ≥ 3 × ULN AND bilirubin < 2 × ULN and INR ≤ 1.5:** • Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver function follow-up assessments within **24 to 72 hours** • Monitor patients weekly until liver function abnormalities resolve, stabilize, or return to baseline	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in patients with definite or likely acetaminophen use in the preceding week [James et al, 2009]) • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy CRFs

a Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study drug if ALT ≥ 3 × ULN **and** bilirubin ≥ 2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

b All events of ALT ≥ 3 × ULN **and** bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN **and** INR > 1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to patients receiving anticoagulants.

c Includes: Hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

A patient who met liver chemistry stopping criteria cannot restart study drug unless all of the following conditions are met:

- TrueBinding Inc. approval **is granted** (as described below)
- Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval is obtained
- Separate ICF for study drug restart/rechallenge is signed by the patient

If TrueBinding Inc. approval to restart/rechallenge the patient with study drug **is not granted**, then the patient must permanently discontinue study drug and may continue in the study for protocol-specified follow-up assessments.

10.3.1 Rechallenge Following Liver Chemistry Events that are Possibly Related to Study Drug

- Following study drug-induced liver injury, rechallenge is associated with 13% mortality across all study drugs in prospective studies (Andrade et al, 2009). Clinical outcomes vary with nearly 50% fatality with halothane readministered within 1 month of the initial injury. However, some interventions seldom result in recurrent liver injury or fatality.
- Risk factors for a fatal rechallenge outcome include:
  - Hypersensitivity with initial liver injury (eg, fever, rash, eosinophilia) (Andrade et al, 2009)
  - Jaundice or bilirubin > 2 × ULN with initial liver injury (direct bilirubin > 35% of total)
  - Ongoing severe liver injury defined by ALT ≥ 3 × ULN AND bilirubin ≥ 2 × ULN (direct bilirubin > 35% of total) OR INR > 1.5
  - SAE or fatality previously observed with rechallenges (Hunt, 2010; Papay et al, 2009)
  - Evidence of drug-related preclinical liability (eg, reactive metabolites, mitochondrial impairment) (Hunt, 2010)
- Rechallenge refers to resuming study drug following drug-induced liver injury (DILI). Because of the risks associated with rechallenge after DILI, this should only be considered if there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit/risk assessment of rechallenge is considered to be favorable.
- Approval by the sponsor for rechallenge with study drug can be considered when:
  - The Principal investigator requests consideration of rechallenge with study drug or a patient who is receiving compelling benefit with study drug that exceeds risk and for whom no effective alternative therapy is available.
  - IRB/IEC approval for rechallenge with study drug has been obtained.

- **If the rechallenge is approved by the sponsor in writing:**
  - The patient must be provided with a clear description of the possible benefits and risks of study drug administration including the possibility of recurrent, more severe liver injury or death.
  - The patient must provide signed informed consent specifically for the rechallenge with study drug. Documentation of informed consent must be recorded in the study file.
  - Study drug must be administered at the dose specified by the sponsor.
  - Patients approved by the sponsor for rechallenge with study drug must return to the clinic twice a week for liver chemistry tests until stable liver chemistry tests have been demonstrated and then standard laboratory monitoring may resume as per protocol.
  - If the patient meets protocol-defined liver chemistry stopping criteria after study drug rechallenge, study drug should be permanently discontinued.
  - The sponsor and the IRB/IEC, must be informed of the outcome for the patient following study drug rechallenge.
  - The sponsor must be notified of any adverse events.

AND/OR

10.3.2 Restart Following Transient Resolving Liver Chemistry Events Not Related to Study Drug

- Restart refers to resuming study drug following liver chemistry events for which there are clear underlying causes (other than DILI) (eg, biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity.
- Approval by the sponsor for study drug restart can be considered when:
  - The investigator requests consideration for study drug restart if liver chemistry events have a clear underlying cause (eg, biliary obstruction, pancreatic events, hypotension, acute viral hepatitis) and liver chemistry tests have improved to normal or are within 1.5 × baseline and ALT < 3 × ULN.
  - Possible DILI has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study drug has an identified genetic marker associated with liver injury (eg, lapatinib, abacavir, and amoxicillin/clavulanate), the presence of the marker should be excluded. If study drug-related liver injury cannot be excluded, the guidance on rechallenge in the previous part of this Appendix will apply.
  - There is no evidence of alcoholic hepatitis.
  - IRB/IEC approval of study drug restart has been obtained.

If restart of study drug is approved by the sponsor in writing:

- The patient must be provided with a clear description of the possible benefits and risks of study drug administration including the possibility of recurrent, more severe liver injury or death.
- The patient must provide signed informed consent specifically for the restart of study drug. Documentation of informed consent must be recorded in the study file.
- Study drug must be administered at the dose specified by the sponsor.
- Patients approved by the sponsor for restart of study drug must return to the clinic twice a week for liver chemistry tests until stable liver chemistry tests have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If the patient meets protocol-defined liver chemistry stopping criteria after study drug restart, study drug should be permanently discontinued.
- The sponsor, and the IRB/IEC, must be informed of the outcome for the patient following study drug restart.
- The sponsor must be notified of any adverse events.

10.4 Appendix 4: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Criteria for Major Neurocognitive Disorder (previously dementia)

- Evidence of significant cognitive decline from a previous level of performance in one or more of the following domains:
- Learning and memory
- Language
- Executive function
- Perceptual-motor
- Social cognition
- The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
  - The deficits do not occur exclusively during the course of a delirium.
  - The disturbance is not better accounted for by another Axis I disorder (eg, Major Depressive Disorder, Schizophrenia).

10.5 Appendix 5: National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA) – Criteria for Diagnosis of Probable Alzheimer's Disease

- Criteria for Diagnosis of Probable Alzheimer's Disease:
  - Dementia established by clinical examination and documented by a standard test of cognitive function (eg, mini-mental state examination, Blessed Dementia Scale, etc.) and confirmed by neuropsychological tests;
  - Significant deficiencies in 2 or more areas of cognition, for example, word comprehension and task-completion ability;
  - Progressive deterioration of memory and other cognitive functions;
  - No loss of consciousness;
  - Onset from age 40 to 90, typically after 65;
  - No other diseases or disorders that could account for the loss of memory and cognition.
- Diagnosis of Probably Alzheimer's Disease is Supported by:
  - Progressive deterioration of specific cognitive functions: language (aphasia), motor skills (apraxia), and perception (agnosia);
  - Impaired activities of daily living and altered patterns of behavior;
  - A family history of similar problems, particularly if confirmed by neurological testing;
  - The following laboratory results:
    - -- Cerebrospinal fluid (lumbar puncture test);
    - -- Normal electroencephalogram test of brain activity;
    - -- Evidence of cerebral atrophy in a series of computed tomography (CT) scans.
- Other Features Consistent with Alzheimer's Disease:
  - Plateaus in the course of illness progression;
  - CT findings normal for the person's age;
  - Associated symptoms including depression, insomnia, incontinence, delusions, hallucinations, weight loss, sex problems, and significant verbal, emotional, and physical outbursts;
  - Other neurological abnormalities, especially in advanced disease, including increased muscle tone and a shuffling gait.
- Features that Decrease the Likelihood of Alzheimer's Disease:
  - Sudden onset;
  - Such early symptoms as seizures, gait problems, and loss of vision and coordination.

10.6 Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table and the rationale for these changes are detailed below.

Amendment 2.0

The rationale for updates to the TB006AD2102 protocol are detailed below.

Overall Rationale for the Amendment

Objectives and Endpoints

1. Updated primary endpoint analysis from "Clinical Dementia Rating scale change from baseline through Day 36" to "Clinical Dementia Rating scale change from baseline through Day 104."

   Rationale: To prioritize the durability of effect through end of patient follow-up as well as the effect at the end of the treatment period.

Study Population

2. Inclusion criteria "6" related to contraceptive use in men has been updated to state that males must agree to use protocol defined contraceptive methods from the first day of dosing through 6 months following the last dose of study drug.

   Rationale: It has been determined that the contraceptive use timeframe of 90 days from last dose of study drug is not effective for this study. This change has been incorporated to bring the protocol document and requirement for male contraception into alignment with the current Investigators Brochure.

3. Change COVID-19 exclusion criterion from 3-month history of positivity to 1-month history of positivity.

   Rationale: Isolation beyond one month presents a minimum risk of spreading the infection and a minimum risk of re-emergence of symptoms that could confound the assessment of the safety profile.

Study Assessments and Procedures

4. Change the dose escalation pattern between dose Groups in Part 1 and between Group 3 in Part 1 to Part 2 from "available safety and PK follow-up 14 days after the last patient receives their last dose in each group" to "available safety and PK follow-up after the last patient in each dose group receives their first dose."

Rationale: The safety and tolerability of single doses up to 5,000 mg is established in the healthy volunteer SAD study (Protocol TB006HV1101). The dose levels used in this study are also used in the SAD study, however in this study the total dose is administered in 5 weekly divided doses. Therefore, projected exposures (both Cmax and AUC) in this study will be lower at each dose level than that at the equivalent doses used in the SAD study. In addition, enrollment will be at a rate (approximately 1 patient/site/month; 4 sites participating in Part 1) that will enable accumulation of a considerable amount of safety and tolerability data when the last patient in enrolled. These data, combined with the safety and tolerability data from the SAD study, provides sufficient information to make informed dose escalation decisions and, although a change from the original protocol, presents a minimum amount of risk to patients.

5. Urine alcohol and drug screening test were separated on the Schedule of Activities.

   Rationale: This is a procedural change. The urine alcohol test will be performed by the local laboratory.

6. Increase frequency of MMSE and Clinical Dementia Rating scale assessments.

   Rationale: To assess for efficacy at an early timepoint (during the treatment period).

   Note: The Clinical Dementia Rating scale was erroneously scheduled at weekly intervals during the treatment period. This was corrected.

7. Added “hemoglobin” to laboratory assessments in Table 5, Protocol-required Clinical Safety Laboratory Assessments.

   Rationale: Omission was an oversight in original protocol.

8. In the Suicide Ideation and Behavior Risk Monitoring portion of the study and the C-SSRS assessment. The C-SSRS assessment is provided to subjects through 2 versions, the “Lifetime” version at screening and then the “Since Last Visit” version on all remaining visits according to the Schedule of Events. The C-SSRS version provided at screening has been updated from the “Lifetime” version to the “Past 6 months” version.

   Rationale: Asking patients to recall a “lifetime” occurrence in this patient population is not necessary or relevant in a mild to severe AD patient population.

9. Changed the Lumbar Puncture procedure to “optional”.

   Rationale: Acquisition of CSF data (TB006 concentrations, CSF biomarkers) is not germane to the assessment of TB006 efficacy and tends to discourage AD patients from participating. Nonetheless, acquisition of partial data will be informative for subsequent drug development.

10. Added MRI and PET scan on Day 36. Allowed procedures window of ± 3 days for MRI/PET.

    Rationale: To assess the effect at an earlier timepoint. Procedure window allows flexibility for patient and study staff.

Administrative Changes

11. Removed Prinicpal Investigator name on Investigator agreement page.

    Rationale: This study is multi-site study, removing the Principal Investigator name allows, thus removing the the name on the page will change per site.

Summary of Changes:

Section # and Name	Description of Change	Brief Rationale
Title Page	• Updated Title page to align with protocol version	• Administrative update
Investigator Agreement	• Removed "[redacted]" and replaced with "Principal Investigator"	• This is a multi-site study thus there will be more than one investigator
Section 1.1, Synopsis, Objectives and Endpoints - Part 2	• Updated primary endpoint Change from baseline on the Clinical Dementia Rating scale – Sum of Boxes total score from "through Day 36" to "through Day 104". • Updated secondary endpoint Change from baseline on the Clinical Dementia Rating scale – Sum of Boxes total score from "through Day 104" to "through Day 36"	• Endpoints were updated to prioritize not only the efficacy of treatment at the end of dosing but the durability of effect through end of patient follow-up

Section 1.1, Synopsis, Overall Design	• Revised sentence relating to review of safety, PK, and tolerablility data to include that safety, tolerability and PK data would be reviewed after the 2,100 mg and 5,000 mg single dose, respectively, had been administered"	• To provide additional clarity on when safety data would be reviewed
Section 1.2, Schema, Figure 1 and Figure 2	• Updated schema to include new dosing regimen for the MAD study	• To align with the new dosing regimen
Section 1.3, Schedule of Activities	**Table 1** • Added an MMSE assessment at Day 15 visit • Added a Clinical Dementia Rating scale at Day 15 visit • Lumber puncture was updated to "optional"	• Updated MMSE and Clinical Dementia Rating scale in the Schedule of Activities tables to assess and detect efficacy at an early timepoint • Acquisition of CSF data (TB006 concentrations, CSF biomarkers) is not germane to the assessment of TB006 efficacy and tends to discourage AD patients from participating
	Table 2 • Added an MMSE assessment at Day 15 visit • Removed a Clinical Dementia Rating scale assessment at the Day 8 visit and the Day 22 visit **Table 1 and 2** • Separated out the urine alcohol tests from the drug screening tests • Added an additional assessment for MRI and PET at Day 36 and added a	• To evaluate to assess and detect efficacy at an early timepoint • The Clinical Dementia Rating scale was erroneously scheduled at weekly intervals during the treatment period • Tests will be performed by different laboratories and are separate tests. Updated for clarity • To assess efficacy at an earlier timepoint and expanding the

	window for the assessment of ± 3 days	procedure window "alllows" flexibility for patient and study staff
Section 3, Objectives and Endpoints	• In Part 2, updated primary endpoint Change from baseline on the Clinical Dementia Rating scale – Sum of Boxes total score from "through Day 36" to "through Day 104" • In Part 2, updated secondary endpoint Change from baseline on the Clinical Dementia Rating scale – Sum of Boxes total score from "through Day 104" to "through Day 36"	• Endpoints were updated to prioritize not only the efficacy of treatment at the end of dosing but the durability of effect through end of patient follow-up
	• [redacted] • [redacted] • [redacted]	• [redacted]

Section 4.1, Overall Design	• Edited sentence to add that text was referring to Part 1 • Dose escalation decisions were changed from using available safety and PK follow-up "14 days after the last patient receives their last dose in each group" to "available safety and PK follow-up after the last patient in each dose group receives their first dose" • Revised to state that Part 2 would comment "after the last patient in Part 1 had received their first dose" instead of "at least 14 days after the last patient in Part 1 received their first dose"	• Administrative change for clarity • Sufficient data from the SAD study provides sufficient information to make informed dose escalation decisions and, although a change from the original protocol, presents a minimum amount of risk to patients
Section 4.2, Scientific Rationale for Study Design	• Updated dosing escalation	• To align with overall study design
Section 4.4, End of Study	• Revised the term "End of Study" to "End of Study (End of Trial)	• Administrative change for clarity
Section 5.1, Inclusion Criteria	• Male contraceptive use was updated contraceptive use from the first day of dose through 90 days after dosing to 6 months after dosing	• This change has been incorporated to bring the protocol document and requirement for male contraception into alignment with the current Investigators Brochure
Section 5.2, Exclusion Criteria	• Updated recent history of a positive COVID-19 test from 3 months to 1 month • Defined the abbreviation of "qw" to weekly and removed abbreviation	• Isolation beyond 1 month presents minimal risk of spreading infection • Minor edit for readability

Section 8.2.4, Clinical Safety Laboratory Assessments	• Added "hemoglobin" to Table 5	• Omission was an oversight in the original protocol
Section 8.2.5, Suicide Ideation and Behavior Risk Monitoring	• Replaced the "Lifetime" version of the C-SSRS with the "Past 6 months" version of the C-SSRS	• To more align the protocol document with the appropriate assessments for the patient population
Section 8.5, Pharmacokinetics	• Lumbar puncture was updated to "optional"	• Acquisition of CSF data is not germane to the study. Partial information will be informative for subsequent drug development
Section 8.6.2, Lumbar Puncture	• Assessment was changed to "optional"	• Acquisition of CSF data is not germane to the study. Partial information will be informative for subsequent drug development
Section 9.1, Statistical Hypotheses	• Updated the primary endpoint in Part 2 from change from baseline Clinical Dementia Rating Scale – Sum of Boxes score "at Day 36" to "through Day 104" • Update also applied to the null hypothesis.	• To align with updates to objectives and endpoints in Section 3
Section 9.2, Sample Size Determination	• Updated the primary efficacy endpoint for change from baseline Clinical Dementia Rating Scale – Sum of Boxes at "Day 36" to "Day 104"	• To align with updates to objectives and endpoints in Section 3

Section 9.4.5, Part 2 Primary and Secondary Endpoints	• Updated the primary efficacy endpoint in Part 2 from Clinical Dementia Rating Scale – Sum of Boxes change from baseline "at Day 36" to "through Day 104" • Updated the key secondary efficacy endpoint to the change from baseline on the Clinical Dementia Rating Scale – Sum of Boxes "through Day 104" to "through Day 36"	• To align with updates to objectives and endpoints in Section 3
Section 9.4.6, Part 2 Exploratory Endpoints	• Revised sentence to include Day 36 as well as Day 64 and text for analyses were changed from Analysis of Covariance to MMRM and added the additional comparisons including "with treatment group visit, and treatment group by visit interaction as fixed effects"	• To align with changes to the endpoints in the objectives and endpoints table
Section 9.6, Safety Review Committee	• Revised the text to indicate that the SRC will review after the "last patient in each group has received their first dose" to align with the new dosing regimen	• To align with changes to dose escalation decisions in the Overall Study Design

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