IMMUNOBRAIN

Study Title:	**A First in Human Study to Evaluate the Safety, Tolerability and Pharmacokinetics of IBC-Ab002 in Persons with Early Alzheimer's Disease**
Protocol No.:	IBC-01-01
Version Number:	4.0
Version Date:	April 10, 2025
Clinical Phase:	Phase 1
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Eudra CT Number:	2021-006580-19
EU CT Number:	2024-511770-76-00

This clinical study will be conducted in accordance with the Declaration of Helsinki and its updates, current Good Clinical Practice (GCP), the guidelines of International Council for Harmonization (ICH), EU clinical trial regulation No 536/2014, applicable local regulatory laws and requirements, and in compliance with the protocol.

Sponsor's Signature Page

Person(s) authorized to sign the protocol and the protocol amendment(s) for the Sponsor

Sponsor's Medical Expert

Sponsor Representative		
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ImmunoBrain Checkpoint, Inc., Protocol No. IBC-01-01

INVESTIGATOR'S AGREEMENT

I have carefully read the following protocol and agree that it contains all the necessary information for conducting the study safely.

I will conduct the study, which will be carried out in strict accordance with this protocol, and I commit to protect the safety, rights and welfare of the subjects.

I will promptly report to the Institutional Review Board/Ethics Committee (IRB/EC) and to the Sponsor (or designee) all changes in the research activities and all unanticipated problems involving risks to subjects or others as per local regulations.

I will seek IRB/EC approval only at the request of and as agreed upon with the Study Sponsor before any changes or deviations are made in the research study, except when necessary to eliminate hazards to the patients/subjects.

I will conduct this study according to the current GCP guidelines and local applicable clinical trial legislation and will attempt to complete the study within the time designated.

I (and my institution) will permit trial-related monitoring, audits, IRB/EC review, and regulatory inspection(s), providing direct access to source data/documents.

Study Site Principal Investigator's name: _____

Title: _____

Signature: _____

Date (DD/MMM/YYYY): _____

Name of institution: _____

Address of institution: _____

Telephone: _____

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A+ T+ N+	β-amyloid (A), pathological tau (T), and neurodegeneration (N) biomarkers in AD
Aβ	Amyloid beta
ACEc	Amplitude correlation envelope
AChEi	Acetylcholinesterase Inhibitors
AD	Alzheimer's Disease
ADA	Anti-drug Antibody/ies
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Events of Special Interest
A-iADL	Amsterdam iADL (rating scale)
ANOVA	Analysis of Variance
ALT	Alanine Aminotransferase
anti-HBc	Hepatitis B Core Antibody
anti-HBs	Hepatitis B Antibody
anti-HCV	Hepatitis C Virus Antibody
APOE	Apolipoprotein E
APOE e4	Apolipoprotein E e4 allele
ARIA	Amyloid-Related Imaging Abnormalities
ARIA-E	Amyloid-Related Imaging Abnormalities-Edema
ARIA-H	Amyloid-Related Imaging Abnormalities-Hemorrhages
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area Under Curve
BCSFB	Blood-Cerebrospinal Fluid Barrier
BL	Baseline
BNA	Brain Network Analytics
BUN	Blood Urea Nitrogen
C-SSRS	Columbia-Suicide Severity Rating Scale
CBC	Complete Blood Count
CBD	Cannabidiol
CCR-2	C-C Chemokine Receptor Type 2
CDC	Complement-Dependent Cytotoxicity
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Scale Sum of Boxes
CFC	Cognitive-Functional Composite
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CTC	Common Terminology Criteria for Adverse Events
CV%	Percent Coefficient of Variation
DSST	Digit Symbol Substitution Test

EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
EOS	End of Study
ET	Early Termination
Fc	Fragment Crystallizable (region of mAb)
FIH	First in Human
FLAIR	Fluid-Attenuated Inversion Recovery
GCP	Good Clinical Practice
GFAP	Glial Fibrillary Acidic Protein
GGT	Gamma-Glutamyl Transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRE	Gradient Recalled Echo
HbSAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
Hr	Hour
IADL	Instrumental Activities of Daily Living
IBC	ImmunoBrain Checkpoint, Inc.
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICI	Immune Checkpoint Inhibitors
iDMC	Independent Data Monitoring Committee
IFN-γ	Interferon Gamma
IgGk	Immunoglobin G kappa
INR	International Normalized Ratio
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
IV	Intravenous/Intravenously
LDH	Lactate Dehydrogenase
LP	Lumbar Puncture
MABEL	Minimum Anticipated Biological Effect Level
MAD	Multiple Ascending Dose
MCI	Mild Cognitive Impairment
MDM	Monocyte-Derived-Macrophages
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMSE	Mini-Mental State Examination
MOA	Mechanism of Action
MoH	Ministry of Health
MRI	Magnetic Resonance Imaging
mSOC	MEDRA System Organ Class

MSR-1	Macrophage Scavenger Receptor 1
MVPAD	Minimal *in vivo* Pharmacologically Active Dose
NCA	Non-Compartmental Analysis
NCI	National Cancer Institute
NfL	Neurofilament Light Chain
NFTs	Neurofibrillary Tangles
NHP	Nonhuman Primate
NIA-AA	National Institute on Aging and Alzheimer's Association
NOAEL	No-Observed-Adverse-Effect Level
NOD	Non-obese Diabetic (mice)
NPI	Neuropsychiatric Inventory
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PD-1	Program Cell Death Protein 1
PD-L1	Program-Death-Ligand 1
PET	Positron Emission Tomography
PI	Principal Investigator
PK	Pharmacokinetics
PT	Preferred Term; Prothrombin Time
pTau	Phosphorylated Tau
PTT	Partial Thromboplastin Time
QA	Quality Assurance
qEEG	Quantitative Electroencephalography
QT	QT interval
QTc	Corrected QT interval
RO	Receptor Occupancy
RSE	Relative Standard Error
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCD14	Soluble Cluster of Differentiation 14 Protein
SCR	Screening
SDV	Source Data Verification
SMT	Study Monitoring Team
SOC	System Organ Class
SoE	Schedule of Events
sPD-L1	Soluble PD-L1
sTREM2	Soluble Triggering Receptor Expressed on Myeloid Cells 2
SUSAR	Suspected Unexpected Adverse Reaction
$T_{1/2}$	Elimination Half-Life
TEAE	Treatment-Emergent Adverse Event
TIA	Transient Ischemic Attack
Tmax	Time to Reach Maximum Observed Concentration
TMDD	Target Mediated Drug Disposition
TNF-α	Tumor Necrosis Factor Alpha
TSH	Thyroid Stimulating Hormone
Vd	Volume of Distribution
WFI	Water for Injection

WCT	WorldWide Clinical Trials
WHO	World Health Organization
YKL-40	Chitinase-3-like protein 1 (CHI3L1)

1 SYNOPSIS

Study Title	A First in Human Study to Evaluate the Safety, Tolerability and Pharmacokinetics of IBC-Ab002 in Persons with Early Alzheimer's Disease (AD)
Protocol No.	IBC-01-01
Clinical Phase	1
Investigational product (IP)	IBC-Ab002; a human IgGk monoclonal antibody designed to bind to human Program-Death-Ligand 1 (PD-L1).
Study Objectives	**Primary** • To assess safety and tolerability of IBC-Ab002 following single and multiple ascending doses in persons with early AD **Secondary** • To assess the pharmacokinetics of IBC-Ab002 following a single and multiple ascending doses in persons with early AD **Exploratory** • To evaluate the pharmacodynamic effect of single and multiple doses of IBC-Ab002 in persons with early AD • To support the proposed mechanism of action and biological effect of IBC-Ab002 • To evaluate initial effect of IBC-Ab002 on selected efficacy measures in persons with early AD
Study Population	This study will be conducted at approximately 12 centers in United Kingdom, Netherlands and Israel and will enroll at least 40 and up to approximately 60 subjects aged 50-80 years with early AD
Inclusion / Exclusion Criteria	**Inclusion** Subjects must meet all the following inclusion criteria to be eligible to participate in the study: 1. Age range: 50-80 years (inclusive) of age at the Screening visit 2. Diagnosis of early AD based on the NIA-AA Research Framework criteria, regardless of APOE gene status a. Biomarker classification A+T+N+ or A+T+N- based upon Screening CSF profile consistent with AD defined by either of the following criteria: i. CSF Aβ42 < 1000 pg/mL and pTau181 > 19 pg/mL ii. CSF pTau181/Aβ42 ratio > 0.020

b. AD Clinical Stage 3 or 4 based on the National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework criteria

i. Gradual and progressive change in memory function reported by the participant or informant for ≥6 months

ii. Have a Mini-Mental State Examination (MMSE) score at Screening between 20-28 inclusive

iii. Clinical Dementia Rating Scale (CDR) global score at Screening of 0.5 or 1 with memory box score ≥ 0.5

3. Able to speak, read and write the local language fluently
4. With respect to symptomatic treatment for Alzheimer's disease, subjects should either be:

a. Not treated with any approved treatments for AD with a reasonable expectation that, based on the course of illness, need for treatment is not imminent and the patient should not be initiated on treatment for the length of the study, OR

b. Stabilized on an approved medication(s) other than anti-Ab antibodies for the treatment of AD for at least 3 months prior to Baseline. The dose of the AD treatment should remain the same after entering the study

5. Subject has a study partner who spends at least 10 hours/week with the patient, and can attend all visits with the patient, report accurately on the subject's status and ensure compliance with all study requirements
6. Subject and study partner (if necessary) must be willing and able to be admitted at the clinical research site as required by the study protocol
7. Subject and study partner must each independently be able to understand the study requirements and provide informed consent
8. Subject has either received an adequate dosing regimen of an approved SARS-CoV2 vaccine (according to current regional guidelines) at least 3 months prior to the anticipated first dose of study drug, or has recovered from SARS-CoV2, with evidence of persistent SARS-CoV2 serological response at the Screening visit. Nasal swabs or SARS-COVID-2 PCR may be obtained if required by local or institutional regulations
9. Weight between 45 and 120 kg

Exclusion

Subjects will be excluded from study participation if any one of the following exclusion criteria are met:

1. Females who are not postmenopausal at Screening as defined by amenorrhea for at least 12 consecutive months or who have not been sterilized surgically (i.e. bilateral tubal ligation, total hysterectomy, or

	bilateral oophorectomy, all with surgery at least 1 month before Screening) 2. Males who are fertile but refuse to practice double-barrier methods of contraception with female partners of childbearing potential 3. Other than AD, neurologic or medical disorder which may impair cognition including: head trauma, seizure disorder, neurodegenerative disease, hydrocephalus, cerebral / spinal hematoma, inflammatory disease, CNS infection (e.g. encephalitis or meningitis), neoplasm, toxic exposure, metabolic disorder (including hypoxic or hypoglycemic episodes), or endocrine disorder, or any significant medical conditions that, in the opinion of the Investigator, would prohibit their participation in the study 4. As assessed by the central MRI reader, a. Magnetic Resonance Imaging (MRI) evidence of a) more than three lacunar infarcts, b) territorial infarct or macroscopic hemorrhage, or c) deep white matter lesions corresponding to a Fazekas score = 3 b. Presence of any structural lesion that could potentially explain the subject's cognitive impairment or place the subject at risk for AEs during the trial. Examples include but are not limited to: cerebral contusion, encephalomalacia, aneurysm or vascular malformation, infective lesion, intraparenchymal tumor, meningioma or arachnoid cyst larger than 1 cm in longest diameter c. More than 5 Amyloid-Related Imaging Abnormalities-Hemorrhages (ARIA-H) (including microbleeds and areas of leptomeningeal hemosiderosis (LH)), or more than 3 areas of LH. 5. Any contra-indication to undergo MRI, as judged by local PI or radiologist, including but not limited to presence of pacemaker, aneurysm clips, artificial heart valves, ear implants, ventriculoperitoneal shunt, foreign metal objects in the eyes, skin or body or any other circumstance which would contraindicate an MRI scan or impair MRI image quality, or history of claustrophobia or of not tolerating MRI scanning procedures 6. Severe vision or hearing impairment that would prevent the subject from performing psychometric tests or otherwise complying with requirements for study participation and activities 7. History of any of the following neurological, psychiatric or medical conditions: a. History of large vessel stroke b. Transient Ischemic Attack (TIA) documented in the medical record within 12 months of Screening visit

	c. History of head trauma with documented loss of consciousness, evidence of parenchymal brain injury or skull fracture, or neurosurgical procedure which, in the judgement of the Investigator could provide an alternative explanation for the subject's cognitive impairment d. History of myocardial infarction or unstable angina within 12 months of the Screening visit e. History of examination evidence of non-diabetic peripheral neuropathy or myopathy, whether or not of immune or presumed immune origin f. Autoimmune disease (e.g. Systemic Lupus Erythematosus, Multiple Sclerosis, Rheumatoid arthritis, Type 1 diabetes mellitus) g. Immunocompromised systemically due to continuing effects of immunosuppressant medications other than topical steroids h. Current or previous hepatitis B infection [defined as positive test for hepatitis B surface antigen (HbSAg) and/or hepatitis B core antibody (anti-HBc)]. Subjects with immunity to hepatitis B [if due to natural infection defined as negative HbSAg, positive hepatitis B antibody (anti-HBs) and positive anti-HBc; if due to vaccination defined as negative HbSAg, negative anti-HBc and positive anti-HBs] are eligible to participate in the study i. History or positive test at Screening for hepatitis C virus (HCV) antibody j. History or positive test at Screening for human immunodeficiency virus (HIV) k. Diagnosed with cancer with metastatic potential within the last 5 years other than carcinoma *in situ* of the breast or cervix, or squamous cell carcinoma or basal cell carcinoma of the skin that has been completely excised l. Currently meets DSM V criteria for Major depressive disorder and has required initiation of medication or hospitalization within the previous 90 days prior to Screening m. Systolic blood pressure > 160 mm Hg OR diastolic blood pressure > 95 mm Hg on three separate determinations 5 minutes apart, taken at same arm, after the patient feels comfortable and relaxed at the research facility n. Clinically significant orthostatic hypotension o. Presence of hallucinations or delusions suggestive of a diagnosis of Lewy Body Dementia or other non-AD cause for subject's cognitive impairment p. Active infection within 8 days of the first dosing visit

	q. Major surgery within 12 weeks of Screening r. Blood donation of 1 unit or more within 8 weeks prior to the first dose of study medication 8. Any of the following laboratory abnormalities at Screening a. Clinically significant (as determined by a cardiologist or central reader) 12-lead ECG abnormalities b. Screening values for hemoglobin < 12 g/dL for men or < 11 g/dL for women c. Any serum chemistry value (e.g. AST, ALT, Alkaline Phosphatase, total bilirubin etc.) > 1.5x the upper limit of normal on 2 successive determinations less than 2 weeks apart d. eGFR < 50 e. Subjects with a bleeding disorder or at risk for increased or uncontrolled bleeding, including: i. Known bleeding disorder ii. Platelet count < 50,000, INR > 1.5 for subjects who are not on anti-coagulant treatment, or PTT significantly outside the normal range f. Serum vitamin B12 clinically significantly below the lower limit of normal and determined by the PI to contribute to the cognitive impairment 9. Presence of contraindication to lumbar puncture (LP) as judged by local PI, e.g. known X-ray or other evidence of significant lumbar spine abnormalities or history of lumbar surgery with sequalae that would interfere with or pose risks from the procedure; platelet count below 50,000 cells/μL; taking anticoagulant or antiplatelet medications other than aspirin at a dose of ≤ 100 mg/day or clopidogrel (see item 11(h) below) 10. Any other significant medical conditions that, in the opinion of the Investigator, would prohibit participation in the study, including inability to tolerate the MRI scan, LP procedures or IV infusions 11. Taking any of the following medications a. Antipsychotic agents, including pimavanserin not at a stable dose for at least 30 days prior to Screening b. Stimulant medications (e.g., Ritalin, amphetamines) not at a stable dose for at least 30 days prior to Screening c. Antidepressant medications whose dose has not been stable for at least 90 days prior to Screening d. Immunosuppressant medications, including chronic systemic corticosteroids (chronic use of topical steroids is allowed)

	e. Injected or infused antibody therapies, including but not limited to antibodies directed against TNF, anti-IL-6, natalizumab, rituximab and similar agents f. Aducanumab, (aducanumab-avwa) intravenous injection (brand name: Aduhelm™), or any other experimental or approved anti-amyloid antibody g. Insulin h. Anticoagulant or anti-platelet medications including warfarin, heparinoids and direct coagulation factor inhibitors (e.g. apixaban, dabigatran, rivaroxaban) within 90 days of the planned first dose of study drug; *either* aspirin at a dose of ≤ 100 mg/day or clopidogrel at a dose of 75 mg/day, *but not both in combination* is permitted 12. Participation in any other interventional clinical trial, or treatment with any investigational drug or investigational use of an approved therapy, within 30 days or 5 half-lives of such agent, whichever is longer, prior to the first Screening visit 13. Potential subject currently smokes more than 5 cigarettes or equivalent tobacco consumption daily 14. Regular nonmedical use of cannabis or cannabis products unless such products are documented by the manufacturer's label not to contain tetrahydrocannabinol or its derivatives or analogs. 15. History of drug (including cannabis) or alcohol abuse within the last 5 years 16. Positive urine drug test for drugs of abuse at Screening. Potential subjects who test positive for benzodiazepines or opioids in urine drug testing need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications containing benzodiazepines or opioids for a medical condition and not due to drug abuse 17. Potential subjects who answer "yes" to C-SSRS suicidal ideation Type 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening 18. Unwillingness to comply with study requirements or history of noncompliance in prior clinical trials
Primary Endpoints (Safety)	Assessment of safety by determining the number of subjects with any Adverse Events (AE), Serious Adverse Events (SAE) and fatal SAE, clinical laboratory tests, cognitive worsening and electrocardiograms; CSF cell counts, development of new abnormalities on brain MRI (high-res T1, T2*, FLAIR) scans and the Columbia Suicidality Rating Scale (C-SSRS)

Secondary Endpoints	**Pharmacokinetic (PK) Parameters** IBC-Ab002 concentration in serum will be measured by a validated ELISA method: o Serum antibody concentrations o Area under the concentration-time curve from time zero to infinity (AUC_{inf}) o Area under the concentration-time curve from time zero to the time of the last measurable sample (AUC_{last}) o Maximum observed concentration (C_{max}) o Time to reach maximum observed concentration (T_{max}) o Terminal elimination half-life ($T_{1/2}$) o Clearance (CL) o Volume of distribution (Vd) o Concentrations of IBC-Ab002 in CSF at selected time points **Serological Parameters** o Number of subjects with positive serum anti-IBC-Ab002 antibodies (i.e. Anti-drug Antibodies-ADAs)
Exploratory Outcomes	Exploratory biomarker outcomes may include, but may not be limited, to the following: **Blood Pharmacodynamic Measures** o Target engagement o PD-L1 receptor occupancy on blood T lymphocytes o Total Soluble PD-L1 (sPD-L1) concentration in the serum o **Immune-Related** o PD-1+ memory T-cell levels in the blood o CCR2+/MSR1+ monocyte levels in the blood o **Neurodegeneration-related** o Aβ40, Aβ42 o Astroglial Markers: GFAP o Tau isoforms: total Tau, pTau 181, pTau 217 o Neurofilament light chain (NfL) **MoA (Central engagement and pharmacodynamics)** o Cerebrospinal fluid (CSF) o Cytokines/chemokines indicative of immune modulation o Neuroinflammation Markers: sCD14, sTREM2

	○ Amyloid Status: Aβ40, Aβ42 ○ Tau Isoforms: total Tau, pTau 181, pTau 217, pTau 231 ○ Neurodegeneration Markers: NfL, neurogranin ○ Astroglial Markers: GFAP, YKL-40 ○ Immune-related cellular markers ○ Quantitative electroencephalography with network analysis (qEEG) ○ MRI: Hi-res T1, T2*/ Gradient Recalled Echo (GRE), FLAIR **Exploratory Clinical Assessments:** ○ MMSE ○ CDR-SB ○ Cognitive-Functional Composite (CFC) (comprised of items from the ADAS-Cog, Letter Fluency Test , DSST, Digit Span Backwards, Category Fluency Test and the Amsterdam-iADL) ○ Neuropsychiatric Inventory (NPI)
Study Design	This is a randomized, double-blind, placebo-controlled first-in-human, Phase 1, safety, tolerability, pharmacokinetic (PK) and preliminary exploratory activity study of escalating multiple IV doses of IBC-Ab002 in persons with early Alzheimer's disease. The study will have both Single- and Multiple-Ascending Dose components. The study will have an adaptive design and will be carried out in two parts. Part A will be comprised of a Single-Ascending-Dose (SAD) study and Part B will continue dosing of Part A subjects as a Multiple-Ascending Dose (MAD) study. Adaptive features may include 1) modification of dosage levels in Parts A and B based upon emerging PK variability and PD data, 2) the ability to add or expand cohorts at the higher dose levels based on emerging safety, PK and PD data. Part A will be preceded by a Screening Period of up to 8 weeks during which subject eligibility will be assessed. A Study Monitoring Team (SMT) will review safety, tolerability and PK data prior to opening new dosing cohorts or initiating dosing in the multiple-dose portion of the study. The SMT will meet at specified intervals to monitor study progress, and, in particular, the emerging safety and tolerability profile of IBC-Ab002. The SMT will consist at least of the Study Director, the Study Principal Investigator, the Study Statistician, Pharmacometrician, Medical Monitor and an Oncologist experienced in checkpoint inhibitor clinical trials. Subjects in five (5) sequential cohorts of 8 subjects each will be assigned in a 3:1 ratio to receive either IBC-Ab002 or matching placebo four (4) times. Part A will be a single-ascending dose study and Part B will be a multiple ascending dose study. The two parts of the study will be intercalated such that subjects will be dosed once every 12 weeks. However, repeated dosing at any dose level will not begin until the anticipated cumulative dose for that cohort has been equaled or exceeded in Part A and/or B of the study, and appropriate safety review of data from all preceding doses in prior subjects has taken place. All

	subjects randomized into Part A of the study will automatically continue into Part B unless dosing is halted at the individual or group level due to safety or other concerns. In an attempt to ensure safety in the study population, a staggered, sentinel dosing paradigm in all dose cohorts will be employed. Two subjects will be dosed initially – one with active study drug and one with placebo, and the remaining subjects in each cohort will begin dosing one week later. Inter-cohort dose escalation will be based on SMT review of safety, tolerability and PK data following at least 28 days (inclusive) of follow-up for each cohort of subjects. The SMT will meet to review safety and PK data as soon as possible after 6 of the 8 subjects in each cohort has completed 8 weeks of observation in Part A of the study. The SMT review will govern the opening of new dose levels in the SAD portion of the study, as well as the initiation of repeated dosing at each dose level in the MAD phase of the study. Once dose-escalation has been completed, the SMT will continue to meet at regular intervals. The SMT will be kept informed in real time of all SAEs reported in the study, and ad-hoc meetings may be called as necessary. Strict individual and study-level dose interruption and stopping rules will be employed to guide the SMT's decisions. At least 40 subjects are expected to be randomized in this study. End of study is defined as the date of last visit of the last subject for last clinical assessment. All subjects will be followed for 3 months following last dosing. Based on emerging safety, tolerability and biomarker data, up to two cohorts may be expanded to include a total of 16 additional subjects, maintaining a 3:1 active: placebo randomization ratio. Up to 2 subjects per dosage level who discontinue participation in the study prior to completion of 30 days' observation in the SAD (Part A) of the study may be replaced. At least 6 subjects must complete the assigned SAD observation period at each dose level before either a) dosing may begin at the next-higher dose level or b) initiation of dosing for the second dose at the same dose level.
Study Duration	The expected duration of participation for each subject will be 48 weeks from the first administration of study drug; and up to 56 weeks in total including the Screening period.
Study Drug Dosage and Administration	IBC-Ab002/placebo will be administered IV. Each subjects will receive 4 dosages of the study drug or placebo throughout the study with an interval of 12 weeks between doses. The assigned doses for the five study cohorts will be as follows: Cohort #1: IBC-Ab002 1 mg/kg or placebo – Single dose (Part A) and then 3 doses Q12W (Part B) Cohort #2: IBC-Ab002 3 mg/kg or placebo - Single dose (Part A) and then 3 doses Q12W (Part B) Cohort #3: IBC-Ab002 7 mg/kg or placebo – Single dose (Part A) and then 3 doses Q12W (Part B)

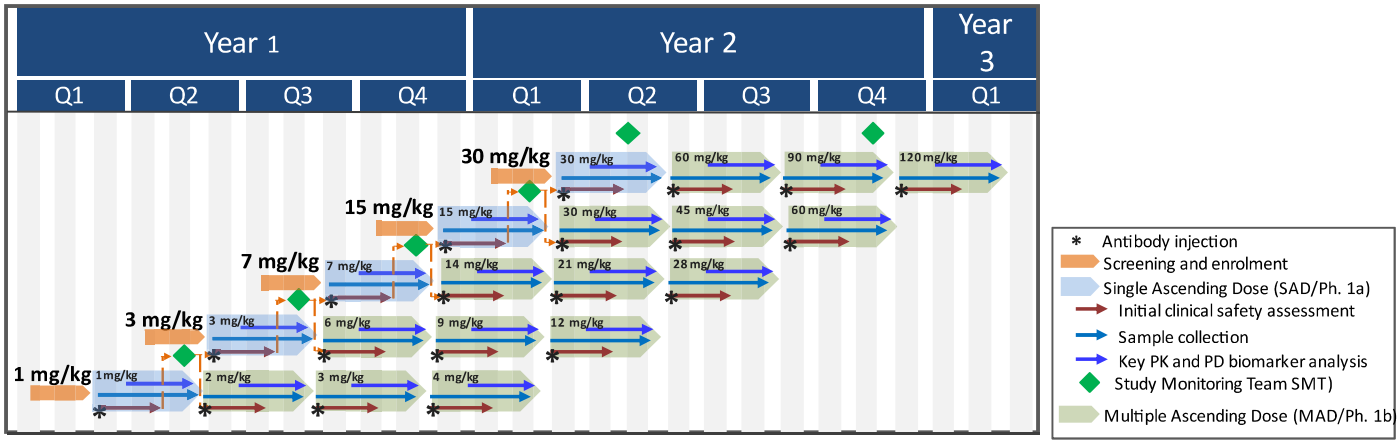
	Cohort #4: IBC-Ab002 15 mg/kg or placebo - Single dose (Part A) and then 3 doses Q12W (Part B) Cohort #5: IBC-Ab002 30 mg/kg or placebo – Single dose (Part A) and then 3 doses Q12W (Part B) IBC-Ab002 is formulated as a lyophilized powder in vials and stored at 2-8°C until reconstitution prior to intravenous (IV) administration. After reconstitution, each vial will contain 5 mL (extractable volume) of IBC-Ab002 at 50 mg/mL, 20 mM histidine, 240 mM sucrose and 0.02 % polysorbate 20. The study drug will be reconstituted in a total volume of 100 mL normal saline by an unblinded pharmacist and will be delivered to the infusion location in covered bags. Study drug will be infused over a period of 2 hours. Study drug administration in Part A of the study may be prolonged by up to 15 minutes but should not be less than 2 hours in duration. For Part B of the study, should safety and tolerability allow, the infusion rate may be shortened to 1 hour. This decision will be at the discretion of the Study Monitoring Team (SMT) and will only be considered after all subjects have received their Part A dosing. Infusion rates may be slowed, or individual infusions may be interrupted for up to ½ hour, at the discretion of the Investigator in the event that infusion reactions are observed, in keeping with local protocols. Subjects assigned to receive placebo will be administered 100 mL of normal saline
Statistical Analysis	Details of the statistical methods to be applied will be given in a Statistical Analysis Plan (SAP). **Sample size justification:** No formal sample size calculation was performed. The study is not expected to achieve statistical power, but rather to provide estimates for safety and PK profiles and a trend for efficacy outcomes. However, with 30 subjects dosed with multiple doses of active study drug, there is chance of ~80% to detect at least 1 relatively rare (≤ 5%) treatment related AE such as thyroid dysfunction or pneumonitis. For more common (~10% - 15%) treatment related AEs such as hepatitis, rash and colitis the chances are at least 95%. **Descriptive Statistics and general information:** All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. For categorical variables summary tables will be provided giving sample size, absolute and relative frequency and 95% Confidence Interval (CI) (if appropriate) for proportions by cohort and treatment group. For continuous variables, summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variation (if appropriate), 25th percentile, median, 75th percentile, minimum, maximum and 95% CI for means of variables (if appropriate) by cohort and treatment group. Cumulative unblinded reviews of all study data may be performed, at the option of the SMT, at the conclusion of Part A (all SAD data + accumulated Part

	B/MAD data) and after all subjects have completed 6 months of follow-up in Part B. The data will be analyzed using the SAS® version 9.4 or higher (SAS Institute, Cary North Carolina). **Primary Endpoints (Safety):** **Adverse Events:** Adverse events will be coded according to coding dictionaries (the most updated version of MedDRA) and presented in tables by MEDRA System Organ Class (mSOC) and Preferred Term (PT) and by cohort and treatment group. A Summary of Adverse Events table will present the number and percent of subjects in each cohort and treatment group with one or more AEs by type of AE (any, serious, drug-related, resulted in death). The number (and percentage) of subjects with incidence of AEs, as well as the severity and relationship to study drug, will be summarized by treatment group, mSOC and PT. **Other Safety Assessments:** Baseline and change from Baseline at each post Baseline evaluation will be presented for laboratory safety assessments and CSF cell counts by cohort and treatment group. Cognitive assessments, electrocardiogram results, development of new abnormalities on brain MRI (high-res T1, T2*, FLAIR) scans and the Baseline version of the Columbia-Suicide Severity Rating Scale (C-SSRS) will be presented at Screening, selected post Baseline evaluation by cohort and treatment group and at the final study visit (EOS/ET). Concomitant medication verbatim terms (as recorded on the CRFs) will be coded to Anatomical Therapeutic Chemical (ATC) Level 2 and 4 using the World Health Organization (WHO) dictionary by cohort and treatment group. **Secondary Endpoints:** **Pharmacokinetic (PK) Parameters:** The secondary objective is to assess the pharmacokinetics of IBC-Ab002 following single and multiple ascending doses of IBC-Ab002 in persons with early AD. Analyses of pharmacokinetic parameters will be performed using Non-Compartmental Analysis (NCA) methods. The goal of the analysis is i) to characterize the IBC-Ab002 PK parameters in the population and ii) to enable selection of doses to take forward in further clinical studies. The sampling strategy is flexible and may be modified in real time as the actual human PK/PD and biomarker data accumulates and the PK and PD parameters are reassessed. Basic PK parameters will be calculated based on measured IBC-Ab002 concentration in serum as specified in the PK analysis plan. Individual PK parameters (as mentioned above) will be listed by cohort and treatment group and summarized in tables presenting sample size (N), mean, standard deviation, standard error, median, minimum and maximum values,

	Coefficient of variation (CV%) and 95% CI for means of variables by cohort and treatment group. Graphical displays will be generated presenting mean concentration by cohort and treatment group as well as individual graphs per subjects. Analyses of pharmacokinetic parameters will be performed using standard pharmacometric methods. **Serological Parameters:** The number and proportion of subjects with positive serum anti-IBC-Ab002 antibodies (ADAs) will be summarized by cohort and treatment group along with 95% CI for proportions. **Exploratory Outcomes:** Our exploratory objective is to evaluate the pharmacodynamic effect of single and multiple doses of IBC-Ab002 in persons with early AD. Both peripheral blood samples for target engagement biomarkers and CSF to evaluate response to AD related biomarkers will be collected. All exploratory outcomes will be summarized by cohort and treatment group. For all variables descriptive summary tables will be provided. **Interim Analysis** A single interim analysis may be conducted after all subjects have completed 12 weeks of observation in Part A of the study.
Study Stopping, Dose Discontinuation and Suspension Rules	**Individual Stopping Rules** Dosing for any individual subject receiving active study drug may not be continued following the occurrence of either a related Serious Adverse Event or a CTCAE v5.0 Grade 3 Adverse Event, unless the SMT agrees that such event was unrelated to study medication. **Study Level Stopping Rules** Dosing at all dose levels will be stopped for all subjects upon the occurrence of a single drug-related death. Upon the occurrence of a single drug related Serious Adverse Event (SAE), two related CTCAE Grade 3 Adverse Events, or 2 irAEs of any type or grade, dosing at all dose levels may be stopped. In this instance, the Study Monitoring Team (SMT) will provide its recommendation to the independent Data Monitoring Committee (iDMC), with whom the final decision will be taken. **Cohort Level Stopping Rules** Regardless of investigator assessment of causality, dosing in any given dose level may be stopped upon the occurrence of 2 SAEs, CTCAE Grade 3 Adverse Events, or other medically significant events that would warrant cessation or interruption of dosing for longer than 4 weeks based on the medical judgement of a Site Investigator. As noted above, the SMT will provide its recommendation to the iDMC, with whom the final decision will be taken.

	Interruptions of individual infusions due to minor infusion reactions that are followed by resumption of dosing with no residual adverse effects to the patient will not be considered significant events. The study director and the SMT may be immediately unblinded in the event of a death, SAE, or CTCAE Grade 3 or 4 Adverse Event deemed related to treatment by a Site Investigator. An independent Data Monitoring Committee (iDMC), consisting of 3 experts in the conduct of AD (2) and Immune Checkpoint (1) clinical trials will meet approximately every 6 months to review the progress of the study and to review the unblinded study data. The iDMC will review and endorse the decisions of the SMT on dose escalation and continuation, and will be informed and consulted regarding any and all safety issues arising during the study. In the event that occurrences meet the study's stopping rules pending the SMT's decision, the iDMC will review the SMT's recommendations and make the final determination on whether to continue or halt the study. The operations and responsibilities of the iDMC will be described in a separate iDMC Charter. If dosing is stopped due to adverse events, a substantial amendment requesting re-start will be submitted for regulatory approval.

2 STUDY SCHEMA



Notes:
SAD = Single Ascending Dose (blue chevrons)
MAD = Multiple Ascending Dose (green chevrons)
Dosage of IBC-Ab002 is expressed in mg/kg

- Active IBC-Ab002 = 6
- Placebo = 2
- Up to two cohorts may be expanded to include a total of up to 16 additional subjects based on emerging safety/tolerability, PK and biomarker data to increase confidence in outcomes, upon consent of the SMT
- Numbers in upper left-hand corner of green and blue chevrons represent cumulative dose of IBC-Ab002

3 SCHEDULE OF EVENTS

Table 3-1: Part A (Screening, Baseline, SAD)

	Screening	Baseline	Dosing		Observation								Early Term.
Visit Number	**SCR**	**BL***	**1****	**2**	**3**(n)	**4**(n)	**5^**	**6 (l)**	**7**	**8^**(n)	**9**	**10**	
Cycle Day	**-56 to -8**	**-8 - to -1**	**1**	**2**	**4**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**29 ± 2**	**43 ± 2**	**57 ± 2**	**84 ± 2**	**ET (f)**
Inpatient Confinement (a, b)			**See Inpatient SoE Table 3-3**										
Informed Consent	√												
Inclusion/Exclusion	√	√											
Medical History	√												
Genetic Sample (APOE status and exploratory pharmacogenetic markers)		√											
Interval Medical History		√			√	√	√	√	√	√	√	√	√
Physical Exam	√	√		√					√			√	√
Neurological Exam	√	√		√					√			√	√
Vital Signs	√	√	√	√	√	√	√		√	√	√	√	√
Weight	√	√									√	√	√
Serum Chemistry, Hematology	√	√				√	√		√		√	√	√
INR	√									√			√
Urinalysis	√					√			√			√	√
Urine Drug Screen	√												
Viral Serologies	√												
SARS-CoV2 PCR (i)	√	√											

	Screening	Baseline	Dosing		Observation								Early Term.
Visit Number	**SCR**	**BL***	**1****	**2**	**3**(n)	**4**(n)	**5^**	**6 (l)**	**7**	**8^**(n)	**9**	**10**	
Cycle Day	**-56 to -8**	**-8 - to -1**	**1**	**2**	**4**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**29 ± 2**	**43 ± 2**	**57 ± 2**	**84 ± 2**	**ET (f)**
12 lead ECG(m)	√		√	√			√		√			√	√
MRI (g)	√									√			√
EEG	√								√		√	√	√
MMSE	√	√					√				√	√	√
CFC (h)		√							√			√	√
CDR-SB	√												√
C-SSRS (j)	√								√		√	√	√
NPI		√										√	√
Blood PK / ADA/ Biomarkers (b,c)	**Refer to Table 3-4: Sampling Times (Part A)**												√
PBMC isolation (c)													√
CSF Sampling (c, d)													√
Concomitant Medications	√	√	√	√	√	√	√	√	√	√	√	√	√
Adverse Events	√	√	√	√	√	√	√	√	√	√	√	√	√
Study Drug Dosing			√									√	

Table 3-2: Part B (MAD)

	Dose 2				Dose 3				Dose 4				EOS	Early Term.
Visit Number	**10/10.1** ***	**11**(n)	**12**(n)	**13**(n)	**14**	**15**^(n)	**16**	**17**(n)	**18**	**19**^(n)	**20**	**21**(n)	**22 (e)**	
Cycle Day	**1**	**8 ± 1**	**29 ± 2**	**57 ± 2**	**1‡**	**8 ± 1**	**29 ± 2**	**57 ± 2**	**1‡**	**8 ± 1**	**29 ± 2**	**57 ± 2**	**84 ± 7**	**ET (f)**
Interval Medical History	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Physical Exam	√		√		√		√		√		√		√	√
Neurological Exam	√		√		√		√		√		√		√	√
Vital Signs	√ (k)	√	√	√	√ (k)	√	√	√	√ (k)	√	√	√	√	√
Weight	√				√				√				√	√
Serum Chemistry, Hematology	√		√	√	√		√	√	√		√	√	√	√
Urinalysis	√				√				√				√	√
INR												√	√ (d)	√
SARS-CoV2 PCR(i)														
12 lead ECG (m)	√		√		√		√		√		√		√	√
MRI (g)													√	√
EEG	√***				√				√				√	√
MMSE	√				√				√				√	√
CFC (h)	√***				√				√				√	√
CDR-SB													√	√
NPI	√***				√				√				√	√
C-SSRS (j)	√		√		√		√	√	√		√	√	√	√
Blood PK / ADA/ Biomarkers (b,c)	**Refer to Table 3-4: Sampling Times (Part B)**													
PBMC isolation (c)														
CSF Sampling (c, d)														

	Dose 2				Dose 3				Dose 4				EOS	Early Term.
Visit Number	**10/10.1** ***	**11**(n)	**12**(n)	**13**(n)	**14**	**15**^(n)	**16**	**17**(n)	**18**	**19**^(n)	**20**	**21**(n)	**22 (e)**	
Cycle Day	**1**	**8 ± 1**	**29 ± 2**	**57 ± 2**	**1‡**	**8 ± 1**	**29 ± 2**	**57 ± 2**	**1‡**	**8 ± 1**	**29 ± 2**	**57 ± 2**	**84 ± 7**	**ET (f)**
Concomitant Medications	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Adverse Events	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Study Drug Dosing	√				√				√					

Notes to Schedule of Events

(a) First (SAD) cycle only

(b) See Table 3-3: Schedule of Inpatient Assessments (SAD Dosing Cycle)

(c) See Table 3-4: Sampling Times

(d) Initial lumbar puncture may be performed any time between the first Screening and Baseline visit after review of MRI and plasma Aβ42:40 ratio and pTau181 results; ***subjects with plasma pTau181 levels < 20.02 pg/mL or exclusionary lesions on MRI scans will not proceed to screening LP*** and will not be eligible for the study. It is recommended that MRI scans should not take place until after results of plasma pTau181 are known. The screening LP may not be done until the MRI has been reviewed and reported to have no exclusionary lesions. The Screening LP will serve as the study baseline. LPs listed under the End-of-Study (EOS) and Early Termination (ET) visits are optional. Study participants will be given the opportunity to opt out of these assessments at the time of the visit. However, if the patient agrees to perform the LP, a coagulation test must be available in advance. The EOS visit assessments may be spread over multiple days to ensure INR results are available.

(e) End of Study (EOS)

(f) Early Termination (ET): In the event a subject discontinues study participation, all assessments should be completed at the earliest possible opportunity, if the subject is willing to comply. The ET visit is thus optional. The LP within the ET visit is also optional; a subject may agree to the ET visit but opt to refuse the LP.

(g) MRI scans will be performed at Screening, Day 43 (Visit 8), and at EOS visits only. MRI should also be performed at ET visits, or in the event of a concerning CNS-related AE (e.g. change in level of consciousness, sudden cognitive decline, seizure, etc.)

(h) Cognitive-Functional Composite (comprised of items from the ADAS-Cog, Letter Fluency Test, DSST, Digit Span Backwards, Category Fluency Test and the Amsterdam-iADL)

(i) SARS-COVID-2 PCR may be obtained if required by local or institutional regulations

(j) C-SSRS Baseline version administered at Screening; Since Last Visit version will be administered at all other scheduled time points

(k) For all doses other than the initial dose, vital signs (Blood pressure, Heart Rate, temperature and respirations) should be taken prior to infusion, at the end of the infusion, and 1h after end of infusion; for the timing of vital sign measurements following the initial dose, refer to Table 3-3

(l) Telephone visit; all assessments to be conducted remotely. Patient presence in clinic not required unless there is an ongoing AE requiring assessment or management

(m) All ECGs will be performed in triplicate and submitted to central reader for review

(n) Should the investigator deem the study participant fully autonomous and perceive no risk in the participant attending the study clinic unaccompanied, the study partner may be reached via telephone to provide updates on Health Status, Side Effect, and Adverse Event Review. The details of this telephone call should be properly documented in the study files.

*Baseline assessments may be performed any time during the week (Days -8 to -1) preceding Day 1. Confirmation of continued eligibility, including results of clinical laboratory tests should be available prior to randomization and dose administration on Day 1.

** Subjects should come to the infusion center/location sufficiently early in the morning so that the study drug infusion should be commenced in order to allow the Hour 6 PK sample can be drawn and processed by the end of the working day.

***Visit 10 (Day 84) may be split into two portions a maximum of 21 days apart if SMT has not had sufficient time to assess data to render a decision regarding dose escalation/continuation. Should this occur, the dosing portion of the visit will be labeled Visit 10.1. EEG, CFC and NPI do not need to be repeated in Visit 10.1.

^ Visit may be conducted at satellite clinic affiliated with the study site if travel is burdensome for the subject, logistics can be arranged, and PI agrees.

‡ Visits 14 and 18, corresponding to Dose 3 and Dose 4 in the MAD part of the study, permit a window of ±7 days relative to the timing of the previous dose.

Table 3-3: Schedule of Inpatient Assessments (SAD Dosing Cycle)

	Day -1	Day 1										Day 2
	Baseline	**Predose**	**0 hr**	**0.25 hr**	**0.5 hr**	**1 hr**	**2 hr**	**3 hr**	**4 hr**	**6 hr**	**10 hr**	**24 ± 2 hr**
Study Drug Administration			→	→	→	→	→					
Vital Signs	√	√			√	√	√	√	√	√	√	√
Weight	√											
Physical Exam	√											√
Neurological Exam	√											√
Serum Chemistry, Hematology	√											
Urinalysis												
PK Sampling (c)	**Refer to Table 3-4: Sampling Times**											
Triplicate 12 lead ECG		√					√			√		√
Adverse Events				√	√	√	√	√	√	√	√	√
Discharge from Inpatient Unit												√

Note: All assessment times are relative to start of infusion. Day 1 assessments should be performed within ±15 minutes of scheduled time. Study drug administration may be prolonged by up to 15 minutes, but should not be less than 2 hours in duration unless SMT has guided that infusion times may be shorter.

Sampling Times for PK and PD Biomarker Testing

Note: The sampling scheme is geared towards increasing the information content of the population collected data. The initial sampling scheme was calculated using the projected PK/PD model derived from preclinical *in vivo* data. The sampling scheme is flexible and may be modified in real time as the actual human PK and biomarker data accumulates and the PK/PD parameters are reassessed.

Table 3-4: Sampling Times

Part A	**Screening**	**Baseline**	**Dose 1**													
Visit Number	**SCR**	**BL***	**1****	**1**	**1**	**1**	**2**	**3**	**4**	**5^**	**6 (l)**	**7**	**8^**	**9**	**10**	
Cycle Day	**-56 to -8**	**-8 to -1**	**D1 Predose**	**D1:0hr** Start of Infusion	**D1:2hr** End of Infusion	**D1:6hr** Post-Infusion	**D2** 24 ±2hr Post-Infusion	**D4** 72 ±2hr Post-Infusion	**D8** ±1 day	**D15** ±1 day	**D22** ±1 day	**D29** ±2 days	**D43** ±2 days	**D57** ±2 days	**D84** ±2 days	**D84** End of Dose
Nominal Study Hour (From start of first Dose)			(any time prior to dose)	0	2	6	24 ± 2	72 ± 2	168 ± 24	336 ± 24	504 ± 24	672 ± 48	1008 ± 48	1344 ± 48	1992 ± 48	1994 ± 48
Serum PK, sPD-L1			√		√	√	√	√	√	√		√	√	√	√	√
ADA			√													
PBMC isolation for RO% and other PD			√				√	√	√	√		√	√	√	√	
Plasma for A/T/N Biomarkers (d)	√		√							√		√	√	√	√	
Serum for Inflammation Biomarkers			√					√	√	√				√	√	
CSF Sampling (d)	√													√		

Part B	Dose 2					Dose 3					Dose 4						Early Term.
Visit Number	**10/10.1*** **		**11^**	**12**	**13**	**14**		**15^**	**16**	**17**	**18**		**19^**	**20**	**21**	**22 EOS (e)**	
Cycle Day	**D1 Pre-Dose**	**D1 End of Dose**	**D8**	**D29**	**D57**	**D1 Pre-Dose**	**D1 End of Dose**	**D8**	**D29**	**D57**	**D1 Pre-Dose**	**D1 End of Dose**	**D8**	**D29**	**D57**	**D84**	**ET (f)**
Serum PK, sPD-L1	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
ADA						√					√					√	√
PBMC Isolation for RO% and other PD	√		√	√		√		√	√		√		√	√		√	√
Plasma for A/T/N Biomarkers	√					√					√					√	√
Serum for Inflammation Biomarkers	√					√					√					√	√
CSF Sampling (d)																√(n)	√

Samples should be obtained within ±2 hours of nominal schedule times on Days 2 and 4 after Dose 1 and immediately prior to start of infusion for doses 2, 3 and 4.

*Notes to Schedule of Events (continued)
(n) Visit 22 and EOS lumbar puncture is optional. Subject must provide separate consent for this procedure

* Baseline assessments may be performed any time during the week (Days -8 to -1) preceding Day 1. Confirmation of continued eligibility, including results of clinical laboratory tests should be available prior to randomization and dose administration on Day 1

** Subjects should come to the infusion center/location sufficiently early in the morning so that the study drug infusion should be commenced in order to allow the Hour 6 PK sample can be drawn and processed by the end of the working day

***Visit 10 (Day 84) may be split into two portions a maximum of 21 days apart if SMT has not had sufficient time to assess data to render a decision regarding dose escalation/continuation. Should this occur, the dosing portion of the visit will be labeled Visit 10.1. EEG, CFC and NPI do not need to be repeated in Visit 10.1.

^ Visit may be conducted at satellite clinic affiliated with the study site if travel is burdensome for the subject, logistics can be arranged, and PI agrees

4 INTRODUCTION

4.1 BACKGROUND

Study IBC-01-01 is a First-in-Human (FIH) clinical trial of the novel anti-PD-L1 monoclonal antibody IBC-Ab002 in subjects with early Alzheimer's disease (AD). The objectives of the study are to gain a preliminary understanding of the safety, tolerability and pharmacokinetics of IBC-Ab002 in the study population. In addition, the study will explore the effects of IBC-Ab002 on pharmacodynamic markers of peripheral immune system activity, biomarkers of AD-related pathology and clinical and electrophysiological measures of brain function.

4.1.1 Definition and epidemiology of Alzheimer's disease

Alzheimer's disease (AD) is the most common type of neurodegenerative dementia. AD is a highly complex, slowly progressive neurodegenerative disease characterized pathologically by the formation and extracellular accumulation of amyloid beta (Aβ) plaques and intracellular aggregations of neurofibrillary tangles (NFTs) composed of hyperphosphorylated microtubule associated protein, Tau (Reviewed in Scheltens et al. 2016). The clinical features of AD include progressive impairment of behavioral and cognitive functions such as memory, comprehension, language, attention, reasoning and judgment.

AD is one of the leading causes of age-related cognitive impairment globally. In the US alone, approximately 5.8 million Americans over the age of 65 have AD, and this number is expected to increase to 7.1 million by 2025 (Alzheimer's Association 2020). In addition, there are approximately 200,000 people aged 65 or below suffering from younger-onset AD (Alzheimer's Association, 2020). In Europe, the prevalence of AD was estimated at 5.05%. The prevalence in men was 3.31% and in women, 7.13% and increased with age. The incidence of AD in Europe was 11.08 per 1000 person-years. Broken down by sex, it was 7.02 per 1000 person-years in men and 13.25 per 1000 person-years in women, in which rates increased with age (Niu et al, 2017).

4.1.2 Symptoms and risk factors

The initial and most common presenting symptom of AD is episodic short-term memory loss with relative sparing of long-term memory and can be elicited in most patients even when not the presenting symptom. Short-term memory impairment is followed by impairment in problem-solving, judgment, executive functioning, lack of motivation and disorganization, leading to problems with multitasking and abstract thinking. In the early stages, impairment in executive functioning ranges from subtle to significant. This is followed by language disorder and impairment of visuospatial skills. Neuropsychiatric symptoms like apathy, social withdrawal, disinhibition, agitation, psychosis, and wandering are also common in the mid to late stages. The end stage of the disease is characterized by a severe amnestic state, loss of control of self-care ability, primitive reflexes, incontinence and total dependence on caregivers (Tang et al, 2019; Zilberzwige & Gazit, 2018; Maccioni et al, 2018). Recent studies (McDade et al 2018; McDade et al, 2018; Jack et al 2013) have shown

that the pathological changes in the brain that underlie AD, including the buildup of amyloid plaques and tau-containing neurofibrillary tangles, begin years, if not decades, before the disease is recognized clinically. The evolution of AD has thus been characterized as passing through several stages, from "preclinical", in which only biomarker changes can be detected, through a stage of mild cognitive impairment or "MCI", in which its victims suffer early memory and behavioral disruptions but display minimal functional impairment in activities of daily living, and finally through Mild, Moderate and Severe stages of the fully manifest clinical disorder. Jack and colleagues have proposed a scheme of biomarker and clinical staging criteria that have found utility in characterizing patients' disease status for the purposes of clinical study (Jack et al, 2018).

Several risk factors have been associated with the development of AD. The most common are increasing age, and presence of Apolipoprotein E (APOE e4) allele (Loeffler, 2021). Other potential risk factors include a history of repeated traumatic head injury, depression, cardiovascular and cerebrovascular disease, higher parental age, smoking, and family history of dementia. On the other hand, higher education, use of estrogen by women, use of anti-inflammatory agents, leisure activities like reading or playing musical instruments, healthy diet and regular aerobic exercise appear to decrease the risk of Alzheimer's disease.

4.1.3 Standard medical management

Acetylcholinesterase inhibitors (AChEi), the mainstay of treatment that are currently approved for early AD have modest effects on symptoms of the disease (Birks 2006; Birks et al, 2015; Birks et al, 2018). The general consensus is that AChEi do not greatly change the course of the disease. However, it has been demonstrated that chronic use may be associated with reduced nursing home placement (Jelic et al, 2016) and a recent review has indicated that AchEi may be associated with reduced risk of dementia progression and death (Xu et al, 2021). Numerous attempts have been made to reverse or at least to modify or attenuate disease progression by targeting Aβ (either soluble Aβ species or amyloid-plaque deposits) (Gallardo & Holtzman, 2017; Sugino et al, 2015). Until recently, such attempts failed to arrest, and at best might modestly slow cognitive decline (Cummings, 2018; Scheltens et al, 2016; Atri, 2019).

In June, 2021, the US FDA approved aducanumab (Aduhelm®), an anti-amyloid antibody, as the first potentially disease-modifying therapy for the treatment of AD. In one of two pivotal clinical trials, aducanumab-treated patients had an average 22% slower rate of disease progression over 18 months as assessed by the Clinical Dementia Rating Sum of Boxes CDR-SB), despite a 71% reduction in the amount of amyloid plaque in the brains of treated patients as determined by PET scans (Aduhelm Prescribing Information, 2021). The modest success of aducanumab may conceivably be due to the fact that multiple factors contribute to disease onset and progression in AD. Therefore, adopting a strategy that addresses multiple aspects of the underlying proteinopathy and enhances mechanisms of brain repair could be more effective than a strategy that is directed towards only a single destructive process such as amyloid accumulation in the brain.

IBC-Ab002 targets the immune system, the exhaustion or deficiency of which are common factors in aging, disease emergence and progression.

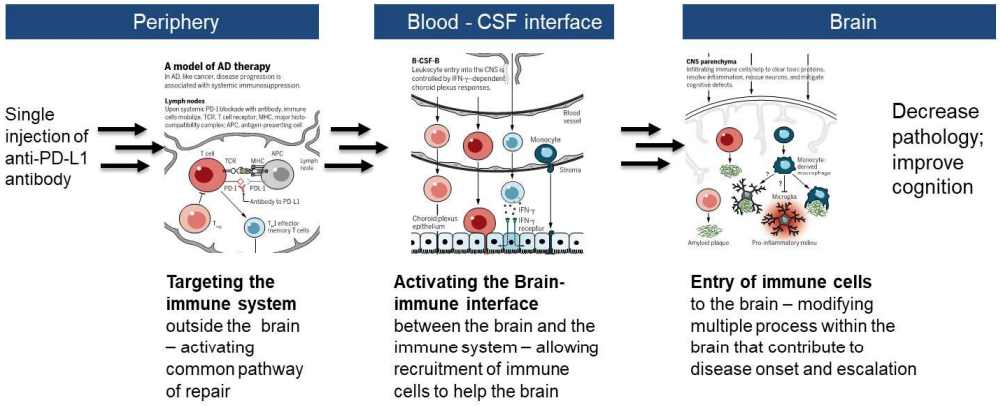
Over the years, several other studies suggested that AD is associated with local inflammation in the brain (Adav & Sze, 2016), and efforts were therefore made to reduce inflammation by systemic administration of steroidal or nonsteroidal anti-inflammatory drugs. Such treatments also failed to affect disease progression (ADAPT-FS Research Group, 2015), leaving the scientific community with the dilemma of what had been missed in the understanding of the disease.

4.2 STUDY RATIONALE

Numerous attempts have been made to arrest the disease, or to slow down its progression by directly targeting its major pathologies - amyloidosis, neurofibrillary tangles, and neuroinflammation (Liu et al, 2019; Selkoe & Hardy, 2016). Most clinical development programs to date have focused on treatments that aimed to directly target the pathological manifestations associated with amyloid beta or aggregated tau; however, despite the successful reduction of amyloid plaque burden in patients, only minimal meaningful effects have been observed on cognitive function (Aisen et al, 2020). Likewise, attempts to target brain inflammation, slowly developed in these diseases, using anti-inflammatory and immunosuppressive drugs have not shown any clinical benefit (Ceyzériat et al, 2020).

IBC-Ab002 represents a novel therapeutic approach for AD. Schwartz et. al (Schwartz et al, 2020) and others (Filiano et al, 2015) have demonstrated the involvement of adaptive and innate immune cells in supporting brain tissue homeostasis, functional plasticity and repair. The brain's borders, including the meninges and the blood-cerebrospinal fluid barrier (BCSFB), were found to play important roles in life-long brain maintenance (Schwartz & Baruch, 2014; Kunis et al, 2015; Tietz & Engelhardt, 2015). It has shown that the choroid plexus epithelium within the BCSFB can provide remote support to the healthy brain, and functions as a selective and well-controlled gateway for immune cells needed for brain repair (Schwartz & Baruch, 2014). The type and number of cells that infiltrate from the periphery into the Central Nervous System (CNS) through this border are tightly regulated by a synergy between stress signals from the brain, such as TNF-α and IFN-γ secreted by circulating $CD4^+$ T cells (Kunis et al, 2013) as depicted in Figure 4-1.

Figure 4-1: Scheme depicting the proposed cascade of events following IBC-Ab002 administration



PD-L1 blockade increases the number of activated memory T cells in the periphery. Memory T cells activate the brain choroid plexus epithelium, allowing selective homing of monocytes to the brain. The homing monocytes remove toxic compounds and modulate the brain's milieu to become less inflammatory. These changes in the brain's milieu are associated with reduced pathology and improved cognitive performance long after the antibody is cleared from the body. Adopted from Schwartz, 2017, with permission.

Studies carried out by Schwartz and by other researchers showed that entry of monocyte-derived macrophages (MDM) into the brain could help modify disease pathology in animal models of Alzheimer's disease (Schwartz & Shechter, 2010; Koronyo et al, 2015). It was further shown that disease severity is augmented in transgenic mouse models of amyloidosis that are bred with T cell-deficient mice (Marsh et al, 2016), demonstrating that peripheral immune cells, though not primary players in AD, have an essential role in AD progression. These discoveries, coupled with existing knowledge that aging, which is the single greatest risk factor for AD, is associated with immune system deviation (suppression/exhaustion (Jagger et al, 2014; Salminen et al, 2019) could explain how an imbalanced relationship between the brain and the immune system contributes to AD progression. Restoring brain-immune system balance, by reducing, in a well-controlled way, systemic immune suppressive mechanisms (Guillot-Sestier et al, 2015; Baruch et al, 2015) was found to be beneficial in reducing disease manifestations in rodent models. Nevertheless, complete and chronic release of systemic immune suppression was found to be ineffective. Thus, it was hypothesized that inflammation-resolving cells must be recruited to the sites of brain pathology, but their homing to the brain requires activation rather than suppression of the peripheral immune system (Schwartz et al, 2020).

The aim of IBC-Ab002 administration is to break age/disease related adaptive immune suppression by blocking the Programmed cell death protein 1 (PD-1)/ Programmed death-ligand 1 (PD-L1) inhibitory immune checkpoint pathway. The PD-1/PD-L1 checkpoint is a crucial immune mechanism that helps in maintaining self-tolerance and has an important role in determining intensity and duration of a physiological immune activity (Qin et al, 2019; Gianchecchi et al, 2013).

4.3 PRECLINICAL EVIDENCE LEADING TO THE DEVELOPMENT OF IBC-AB002

4.3.1 Efficacy

The effects of monoclonal antibodies that block the PD-1/PD-L1 pathway were tested in mouse models of AD and dementia (Baruch et al, 2016; Rosenzweig et al, 2019). Key findings are summarized below and, in more detail, in the Investigator's Brochure. In these studies, even single administrations of monoclonal antibodies specific to PD-1 or PD-L1 were shown to attenuate cognitive loss and brain pathology in mouse models of different AD-related pathologies, i.e. amyloidosis and tauopathy, and was found effective when tested at early as well as late stages of the disease, suggesting that the effect of the treatment is independent of disease etiology or heterogeneity (Rosenzweig et al, 2019). Similarly, treatment of mice carrying the pathogenic P301S mutation (Takeuchi et al, 2011), demonstrated improved cognitive performance and reduced levels of tau pathology. Thus IBC-Ab002 administration could result in amelioration of both amyloid- tau-related aspects of AD pathology.

Based on the evaluation of a several anti-PD-L1 antibodies with different pharmacokinetic properties, the dose response to anti-PD-L1 in preclinical AD animal models was found to be C_{max} dependent but was independent of the duration of antibody exposure. Biomarkers for target engagement and biological activity were identified in the blood of both mice and monkeys treated with the antibody. A PK/PD relationship was also observed and used to model and to predict the PK and effective dose range of IBC-Ab002 in humans.

In summary, the IBC-Ab002 targets immune cells outside the brain and triggers a chain of events that culminate in a series of changes within the brain. IBC-Ab002 administration releases inhibition and facilitates activation of IFN-γ-producing memory T-cells and blood-borne monocytes, allowing recruitment of immune cells to the brain. The trafficking cells contribute to reduction in the inflammatory profile of the brain milieu and removal of toxic protein aggregates, thereby leading to increased survival of neurons and synapses and improved cognitive performance. Altogether, the suggested chain of events requires only transient presence of the antibody; thereafter, it depends on an immune response that is spatially and temporally synchronized. The scheme in Figure 4-1 illustrates the proposed cascade of events evoked by peripheral administration of anti-PD-L1 antibody.

4.3.2 Safety: Known and Potential Risks of IBC-Ab002 Administration

In a 13-week toxicology study conducted in cynomolgus monkeys, the highest IBC-Ab002 dose of 300 mg/kg administered weekly was tolerated, and no dose-related adverse effects were detected (See Investigator Brochure for details).

The most concerning AEs observed in association with administration of immune checkpoint-inhibiting antibodies to humans in the clinic have been immune-related Adverse Events (irAEs). The cumulative incidence over the treatment duration of individual classes of irAEs in clinical trials of anti-PD-1 and anti-PD-L1 (most reviews do not discriminate between the two) ranges from 1% for colitis, 1-3% for pneumonitis, 2% for renal irAEs, 1-6% for hepatitis, up to 10% for dermatological

irAEs and up to 14% for hypothyroidism (Ramos-Casals et al, 2020). In general, safety profiles of anti-PD-L1 antibodies, as revealed in Phase 1 studies, have been predictive of those seen in later stages of development, although full elaboration of the safety/tolerability profile of these agents was most robust in studies with the largest cohorts (Costa et al, 2017). The timing of onset of irAEs varies greatly; however, onset after a single dose is relatively uncommon (Ramos-Casals et al, 2020). Reported severity of these AEs has ranged from mild to fatal. Management approaches have ranged from discontinuation or withdrawal of the therapeutic antibody to use of steroid medication in certain cases (Brahmer et al 2018).

There is limited data in the literature regarding the relationship between exposure, clearance and irAE incidence, since the dosing regimens for oncology indications are designed to provide continuous exposure. Of note, for avelumab, which has the most rapid clearance rate of anti-PD-L1 antibodies currently in clinical use, a weak correlation was noted between $C_{trough,ss}$ and irAEs, with an increase in the odds ratio for irAE occurrence of 1.019 per μg/mL of serum trough concentration. This observation is important with respect to IBC-Ab002 and the planned Q12 week dosing paradigm, as we expect C_{trough} to be zero between doses. For atezolizumab (CDER, FDA, TECENTRIQ (atezolizumab), 2016a) there appears to be a weak association between AUC_{ss} and incidence of Adverse Events of Special Interest (AESI) which include irAEs. However, according to FDA's review, this relationship was not expected to be clinically meaningful. With respect to IBC-Ab002, we estimate that for the proposed dosing regimen, IBC-Ab002 levels in serum will be undetectable throughout most of the inter-dose interval. $C_{average}$ levels will thus be significantly lower than that which was observed with atezolizumab and avelumab which may reduce the risk of irAEs even further (CDER, FDA, BAVENCIO (avelumab), 2017). irAEs will be considered Adverse Events of Special Interest (AESI) in the IBC-Ab002 clinical development program.

The prevalence of irAEs with Immune Checkpoint Inhibitors (ICI) therapy for oncologic indications is considerably less than the reported incidence of Amyloid-Related Imaging Abnormalities (ARIA) seen with certain anti-amyloid antibodies (Sevigny et al, 2016).

irAEs must be taken seriously and they will be monitored closely in our clinical trial. Our preclinical data has led us to suspect that the occurrence of irAEs may be related to the sustained exposure to antibody generated in current cancer treatment regimens. Our therapeutic hypothesis stipulates that modification of the AD disease process will require only periodic exposure to immune checkpoint suppression. Thus, as described below, IBC has taken two additional steps to mitigate the risk of irAEs in our AD population:

1. Modifications to the Fc domain of the antibody to both minimize Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity (CDC) risks and to shorten the antibody's circulating half-life
2. Dosing of IBC-Ab002 at 12-week intervals to provide discontinuous PD-L1 blockade with the aim of reducing propensity to induce irAEs

The combination of these two factors (short half-life, and infrequent administration) could potentially reduce the risk of irAEs; nevertheless, our clinical trial program is designed to closely monitor safety risk:benefit in this regard.

Of particular note, anti-PD-L1 antibodies bearing mutations in the heavy chain that resulted in shortening of circulating half-life were just as effective as native antibodies in preclinical AD mouse models. However, shortening the antibody half-life reduced the propensity of the anti-PD-L1 antibody to induce autoimmune reactions in mice. To assess potential of IBC-Ab002 to elicit irAEs, IBC used non-obese diabetic (NOD) mice, which spontaneously develop type 1 autoimmune diabetes. In this model, administration of an unmodified anti-PD-L1 antibody hastened the onset of autoimmune diabetes. This effect was dramatically reduced when the Fc-domain of the antibody was modified with specific amino acid substitutions that shortened half-life. These studies led to the development of IBC-Ab002, a fully human monoclonal antibody with high affinity to human and non-human primate PD-L1 but low affinity to PD-L1 of rodents.

Further with respect to the potential safety profile of IBC-Ab002 in the clinic, it has been reported that commercially available anti-PD-L1 monoclonal antibodies, with similar *ex vivo* activity to IBC-Ab002, were shown to be well-tolerated in rodents, monkeys and humans and have not reached no-observed-adverse-effect level (NOAEL) in GLP toxicology studies.

In addition, irAEs observed in humans in association with commercially available anti-PD-L1 monoclonal antibodies do not appear to have been detected in primate toxicology studies according to available reports. Thus, nonclinical toxicology studies of IBC-Ab002, even in cynomolgus monkeys, may not be predictive of the full safety profile in humans (Ochoa de Olza et al, 2018).

Of note, the current standard of care for an oncology indication with chronic atezolizumab, with a dose of 1200 mg total (approximately 17 mg/kg) Q3W (a total cumulative dose of 5.5 mg/kg/week) translates into a 20-fold higher exposure, in terms of AUC, to what is expected with the IBC-Ab002 at the highest dose (30 mg/kg, Q12W) in the planned FIH study. Furthermore, IBC estimates that the atezolizumab dose of 17 mg/kg, if given in the same frequency (Q12W) as in the planned FIH study, will impose 4-fold higher exposure compared to what is expected with IBC-Ab002.

4.3.3 Summary: Known and Potential Benefits and Risks of IBC-Ab002 Administration

Whereas benefits and risks for individual subjects in this clinical trial cannot be predicted, the following statements may apply: 1) Based upon available preclinical data, IBC-Ab002 has the potential to improve, stabilize or slow the progression of cognitive deficits in persons with AD. However, the magnitude of benefit, if any, cannot be predicted at this time, and larger, longer trials than IBC-01-01 will be required to achieve definitive determination of efficacy. 2) Administration of Immune Checkpoint antibodies carries with it a known risk of precipitating irAEs, with an incidence ranging between 0.1 and 15% depending on the type of reaction. However, IBC-Ab002 has been engineered, and the dosing regimen being used in this study has been devised, with the aim of reducing irAE risk while maintaining

efficacy. The risk of irAEs following ICI administration, even in oncology clinical trials, is less than the 35% risk of ARIA-E reported in clinical trials of the recently approved anti-amyloid antibody, Aducanumab (ADUHELM Prescribing Information, 2021).

The sponsor will notify the Member States concerned through the EU portal of all unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions. Such notification will be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

5 STUDY OBJECTIVES AND ENDPOINTS

The objectives of the study and the corresponding endpoints and outcome measures are:

Endpoints	Outcome Measures
Primary:	
• To assess safety and tolerability of IBC-Ab002 following single and multiple ascending doses in persons with early AD	• Assessment of safety by determining the number of subjects with any Adverse Events (AE), Serious Adverse Events (SAE) and fatal SAE, clinical laboratory tests, cognitive worsening and electrocardiograms; CSF cell counts, development of new abnormalities on brain MRI (high-res T1, T2*, FLAIR) scans and the Columbia Suicidality Severity Rating Scale (C-SSRS)
Secondary:	
• To assess the pharmacokinetics of IBC-Ab002 following a single and multiple ascending doses in persons with early AD	• **Pharmacokinetic Parameters** IBC-Ab002 concentration in serum will be measured by a validated ELISA method o Serum antibody concentrations o Area under the concentration-time curve from time zero to infinity (AUC_{inf}) o Area under the concentration-time curve from time zero to the time of the last measurable sample (AUC_{last}) o Maximum observed concentration (C_{max}) o Time to reach maximum observed concentration (T_{max}) o Terminal elimination half-life ($T_{1/2}$) o Clearance (CL) o Volume of distribution (Vd) o Concentrations of IBC-Ab002 in CSF at selected time points **Serological Parameters**

	Number of subjects with positive serum anti-IBC-Ab002 antibodies (i.e. Anti-drug Antibodies-ADAs)
Exploratory:	
• To evaluate the pharmacodynamic effect of single and multiple doses of IBC-Ab002 in persons with early AD • To support the proposed mechanism of action and biological effect of IBC-Ab002 • To evaluate initial effect of IBC-Ab002 on selected efficacy measures in persons with early AD	Exploratory biomarker outcomes may include, but may not be limited, to the following: **Blood Pharmacodynamic Measures** o Target engagement o PD-L1 receptor occupancy on blood T lymphocytes o Total Soluble PD-L1 (sPD-L1) concentration in the serum o **Immune-Related** o PD-1+ memory T-cell levels in the blood o CCR2+/MSR1+ monocyte levels in the blood o **Neurodegeneration-related** o Aβ40, Aβ42 o Astroglial Markers: GFAP o Tau isoforms: total Tau, pTau 181, pTau 217 o Neurofilament light chain (NfL) **MoA (Central engagement and pharmacodynamics)** o Cerebrospinal fluid (CSF) o Cytokines/chemokines indicative of immune modulation o Neuroinflammation Markers: sCD14, sTREM2 o Amyloid Status: Aβ40, Aβ42 o Tau Isoforms: total Tau, pTau 181, pTau 217, pTau 231 o Neurodegeneration Markers: NfL, neurogranin o Astroglial Markers: GFAP, YKL-40 o Immune-related cellular markers o Quantitative electroencephalography with network analysis (qEEG) o MRI: Hi-res T1, T2*/ Gradient Recalled Echo (GRE), FLAIR **Exploratory Clinical Assessments:** o MMSE o CDR-SB

	o Cognitive-Functional Composite (CFC) (comprised of items from the ADAS-Cog, Letter Fluency Test, DSST, Digit Span Backwards, Category Fluency Test and the Amsterdam-iADL) o Neuropsychiatric Inventory (NPI)

6 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled first-in-human, Phase 1, safety, tolerability, pharmacokinetic (PK) and preliminary exploratory activity study of escalating multiple IV doses of IBC-Ab002 in persons with early Alzheimer's disease. The study will have both Single- and Multiple-Ascending Dose components.

The study will have an adaptive design and will be carried out in two parts. Part A will be comprised of a Single-Ascending-Dose (SAD) study and Part B will continue dosing of Part A subjects as a Multiple-Ascending Dose (MAD) study. Adaptive features may include 1) modification of dosage levels in Parts A and B based upon emerging PK variability and PD data, 2) the ability to add or expand cohorts at the higher dose levels based on emerging safety, PK and PD data. Part A will be preceded by a Screening Period of up to 8 weeks during which subject eligibility will be assessed.

A Study Monitoring Team (SMT) will review safety, tolerability and PK data prior to opening new dosing cohorts or initiating dosing in the multiple-dose portion of the study. The SMT will meet at specified intervals to monitor study progress, and, in particular, the emerging safety and tolerability profile of IBC-Ab002. The SMT will consist at least of the Study Director, the Study Principal Investigator, the Study Statistician, Pharmacometrician, Medical Monitor and an Oncologist experienced in checkpoint inhibitor clinical trials. In addition to the SMT, an Independent Data Monitoring Committee (iDMC), consisting entirely of outside experts experienced in AD and Immune Checkpoint clinical trials, will meet at regular intervals to review the emerging study data and the recommendations of the SMT.

Subjects in five (5) sequential cohorts of 8 subjects each will be assigned in a 3:1 ratio to receive either IBC-Ab002 or matching placebo four (4) times. Part A will be a single-ascending dose study and Part B will be a multiple-ascending dose study. The two parts of the study will be intercalated such that subjects will be dosed once every 12 weeks. However, repeated dosing at any dose level will not begin until the anticipated cumulative dose for that cohort has been equaled or exceeded in Part A and/or B of the study, and appropriate safety review of data from all preceding doses in prior subjects has taken place. All subjects randomized into Part A of the study will automatically continue into Part B unless dosing is halted at the individual or group level due to safety or other concerns. The starting dose is projected to be 1 mg/kg, with subsequent dosage levels of 3, 7, 15 and 30 mg/kg.

To ensure safety in the study population, a staggered, sentinel dosing paradigm in all dose cohorts will be employed. Two subjects will be dosed initially – one with active study drug and one with placebo and the remaining subjects in each cohort will begin dosing one week later.

Inter-cohort dose escalation will be based on SMT review of safety, tolerability and PK data following at least 28 days (inclusive) of follow-up for each cohort of subjects. The SMT will meet to review safety and PK data as soon as possible after 6 of the 8 subjects in each cohort have completed 8 weeks of observation in Part A of the study. Every attempt will be made to ensure that the first Part B dose for subjects in each continuing cohort is administered approximately 12 weeks after subjects have received their Part A dose. However, it is recognized that logistical considerations may impair sites' abilities to schedule the first Part B dose at precisely a 12-week interval. Therefore, up to 3 additional weeks may be allowed between the Part A dose and the first Part B dose for each subject.

The SMT review will govern the opening of new dose levels in the SAD portion of the study, as well as the initiation of repeated dosing at each dose level in the MAD phase of the study. Once dose-escalation has been completed, the SMT will continue to meet at regular intervals. The SMT will be kept informed in real time of all SAEs reported in the study and ad-hoc meetings may be called as necessary. Strict individual and study-level dose interruption and stopping rules will be employed to guide the SMT's decisions.

At least 40 subjects are expected to be randomized in this study. End of study is defined as the date of last visit of the last subject for last clinical assessment. All subjects will be followed for 3 months following last dosing. Based on emerging safety, tolerability and biomarker data, up to two cohorts may be expanded to include a total of 16 additional subjects, maintaining a 3:1 active: placebo randomization ratio.

Up to 2 subjects per dosage level who discontinue participation in the study prior to completion of 30 days' observation in the SAD (Part A) of the study may be replaced. At least 6 subjects must complete the assigned SAD observation period at each dose level before either a) dosing may begin at the next-higher dose level or b) initiation of dosing for the second dose at the same dose level.

6.1 TRIAL TREATMENT(S), DOSAGE AND DOSAGE REGIMEN

Each dose of IBC-Ab002/placebo will be administered IV in an appropriately equipped infusion facility. Each subject will receive 4 dosages of the study drug or placebo throughout the study with an interval of 12 weeks between doses.

The nominal dose levels assigned for the five cohorts planned for the study will be as follows:

- Cohort #1: IBC-Ab002 1 mg/kg or placebo - Single dose (Part A) and then 3 doses Q12W (Part B)
- Cohort #2: IBC-Ab002 3 mg/kg or placebo - Single dose (Part A) and then 3 doses Q12W (Part B)
- Cohort #3: IBC-Ab002 7 mg/kg or placebo - Single dose (Part A) and then 3 doses Q12W (Part B)
- Cohort #4: IBC-Ab002 15 mg/kg or placebo - Single dose (Part A) and then 3 doses Q12W (Part B)

- Cohort #5: IBC-Ab002 30 mg/kg or placebo - Single dose (Part A) and then 3 doses Q12W (Part B)

Study drug will be infused over a period of 2 hours. Study drug administration in Part A of the study may be prolonged by up to 15 minutes but should not be less than 2 hours in duration. For Part B of the study, should safety and tolerability allow, the infusion rate may be shortened to 1 hour. This decision will be at the discretion of the Study Monitoring Team (SMT) and will only be considered after all subjects have received their Part A dosing. Infusion rates may be slowed, or individual infusions may be interrupted for up to ½ hour, at the discretion of the Investigator in the event that infusion reactions are observed, in keeping with local protocols.

Subjects assigned to receive placebo will be administered 100 mL of normal saline.

6.2 RATIONALE FOR CHOICE OF STARTING AND SUBSEQUENT DOSE LEVELS

The proposed starting dose for IBC-Ab002 in the FIH clinical trial is 1 mg/kg. This dose has been selected based upon the following considerations. PK/PD parameters were estimated previously from preclinical mouse and monkey PK/PD data. PK/PD analysis of the *in vitro* receptor occupancy (RO) in mouse, Nonhuman Primate (NHP) and human T cells was employed to estimate the Minimum Anticipated Biological Effect Level (MABEL) (Yang et al, 2015). The resulting estimates, which are very consistent across the three species, suggest an EC_{20} in the range of 0.01 µg/mL. This corresponds to C_{max} levels expected to be observed following administration of single IBC-Ab002 doses lower than 0.01 mg/kg, 1000-fold lower than the predicted efficacious dose levels, which are in the range of 10 - 30 mg/kg and ~ 30,000-fold lower than the estimated NOAEL of 300 mg/kg (the Human Equivalent Dose (HED) to 300 mg/kg NOAEL reached in NHP preliminary toxicity study). To minimize the potential ethical hazard of exposing subjects to such very low doses, we proceeded to estimate the minimal *in vivo* pharmacologically active dose (MVPAD) to guide the dosage planning. Specifically, from the translational PK/PD model we estimated an *in vivo* RO EC_{10} of ~ 2 µg/mL. This corresponds to C_{max} levels that would be generated by doses in the range of 0.1 mg/kg, or 100x below the anticipated minimal pharmacologically active dose level of 10 mg/kg. Given that 1) the affinity of variable region of IBC-Ab002 for its target is similar to that of already-approved anti-PD-L1 antibodies and 2) as previously discussed, the circulating half-life of IBC-Ab002, and hence overall exposure to antibody, is much lower than that of other anti-PD-L1 antibodies, our assumption (based on observations in the mouse AD models and assuming that PD effects are similar across species) is that the efficacious dose levels will be between 10 and 30 mg/kg. As a result of these calculations, and in light of the clinical experience with approved anti-PD-L1 antibodies in cancer treatment, we are proposing our starting dose as 1 mg/kg and anticipating not needing to exceed 30 mg/kg to achieve maximum efficacy in our clinical study.

The planned human dose range of 1-30 mg/kg falls within the equivalent of the efficacious dose and exposure range predicted by our transgenic mouse efficacy studies on the basis of translating PD effects on PD-L1 receptor occupancy and T cell activation. Subsequent dosages will be increased in two approximately half-log steps (3 and 7 mg/kg), followed by two approximate doublings (15 and 30 mg/kg).

The maximum dose of 30 mg/kg is 10-fold below the maximum dose of 300 mg/kg in the study-enabling GLP toxicology study.

More detail regarding the methods employed for selecting the starting dose and maximum dose levels for the study can be found in the Investigator's Brochure.

6.3 JUSTIFICATION FOR USE OF PLACEBO

IBC-01-01 is a placebo-controlled clinical trial. The use of placebo and associated blinding of study drug assignment is justified for both safety and efficacy reasons to ensure adequate assessment of the risk:benefit profile of IBC-Ab002 administration. With respect to safety, subjects with Alzheimer's disease are subject to numerous comorbidities and incident illnesses. The use of placebo will aid in the estimation of adverse event rates and the true safety profile of the drug. With respect to efficacy, blinding and the use of placebo is necessary in order to ensure the fidelity and accuracy of clinical outcome assessments. Standard-of-care treatment will be maintained for participants in study IBC-01-01. Study participants will be allowed to continue taking standard-of-care medications (e.g., acetylcholinesterase inhibitors) if they have been on a stable dose for at least 3 months prior to study entry. Antidepressant medications will also be allowed. Thus, the term "placebo" in the context of study IBC-01-01 refers only to the study medication, and not treatment for AD in general.

6.4 DOSE ESCALATION AND REPEATED DOSING

6.4.1 SAD and MAD Study Components

This is a randomized, double-blind, placebo-controlled first-in-human, Phase 1, safety, tolerability, pharmacokinetic (PK) and preliminary exploratory activity study of escalating multiple IV doses of IBC-Ab002 in persons with early Alzheimer's disease. The study will have both Single- and Multiple-Ascending Dose components.

The study will have an adaptive design and will be carried out in two parts. Part A will be comprised of a Single-Ascending Dose (SAD) study and Part B will continue dosing of Part A subjects as a Multiple-Ascending Dose (MAD) study. Adaptive features may include 1) modification of dosage levels in Parts A and B based upon emerging PK variability and PD data, 2) the ability to add or expand cohorts at the higher dose levels based on emerging safety, PK and PD data.

Subjects in five (5) sequential cohorts of 8 subjects each will be assigned in a 3:1 ratio to receive either IBC-Ab002 or matching placebo four (4) times. Part A will be a single-ascending dose study and Part B will be a multiple ascending dose study. The two parts of the study will be intercalated such that subjects will be dosed once every 12 weeks. However, repeated dosing at any dose level will not begin until the anticipated cumulative dose for that cohort has been equaled or exceeded in Part A and/or B of the study, and appropriate safety review of data from all preceding doses in prior subjects has taken place. All subjects randomized into Part A of the study will automatically continue into Part B unless dosing is halted at the individual or group level due to safety or other concerns. The starting dose is projected to be 1 mg/kg, with subsequent dosage levels of 3, 7, 15 and 30 mg/kg.

6.4.2 Staggered Dosing Within Each Cohort

In order to attempt to ensure safety in the study population, a staggered, sentinel dosing paradigm in all dose cohorts will be employed. Two subjects will be dosed initially – one with active study drug and one with placebo, and the remaining subjects in each cohort will begin dosing one week later.

6.4.3 Study Monitoring Team

A Study Monitoring Team (SMT) will review safety, tolerability and PK data prior to opening new dosing cohorts or initiating dosing in the multiple-dose portion of the study. The SMT will meet at specified intervals to monitor study progress and, in particular, the emerging safety and tolerability profile of IBC-Ab002. The SMT will consist at least of the Study Director, the Study Principal Investigator, the Study Statistician, Pharmacometrician, Medical Monitor and an Oncologist experienced in checkpoint inhibitor clinical trials. The level of blinding/unblinding of reviewed data will be specified in a separate SMT Guidelines document.

Inter-cohort dose escalation will be based on SMT review of safety, tolerability and PK data following at least 28 days (inclusive) of follow-up for each cohort of subjects. The SMT will meet to review safety and PK data as soon as possible after 6 of the 8 subjects in each cohort have completed 8 weeks of observation in Part A of the study. The SMT review will govern the opening of new dose levels in the SAD portion of the study, as well as the initiation of repeated dosing at each dose level in the MAD phase of the study. Once dose-escalation has been completed, the SMT will continue to meet at regular intervals. The SMT will be kept informed in real time of all SAEs reported in the study, and ad-hoc meetings may be called as necessary. Strict individual and study-level dose interruption and stopping rules will be employed to guide the SMT's decisions.

6.4.4 Independent Data Monitoring Committee (iDMC)

In addition to the SMT, an independent Data Monitoring Committee (iDMC), consisting of 3 experts in the conduct of AD (2) and Immune Checkpoint (1) clinical trials will meet approximately every 6 months to review the progress of the study and to review the unblinded study data. The iDMC will review and endorse the decisions of the SMT on dose escalation and continuation, and will be informed and consulted regarding any and all safety issues arising during the study. In the event that occurrences meet the study's stopping rules pending the SMT's decision, the iDMC will review the SMT's recommendations and make the final determination on whether to continue or halt the study. The operations and responsibilities of the iDMC will be described in a separate iDMC Charter.

7 STUDY OUTCOME MEASURES

A listing of the activities to be carried out on each of the study visits is listed in Section 3, Schedule of Events.

7.1 PRIMARY OUTCOME: SAFETY ASSESSMENT

7.1.1 Adverse Events

Adverse Events (AEs) and Serious Adverse Events (SAEs) will be continuously assessed throughout the study, without reference to the level of possible or probable relatedness, from the time the subject signs the ICF until 3 months after cessation of IBC-Ab002. AEs and SAEs which occur beginning with the administration of the first dose of IBC-Ab002 will be labelled as "treatment emergent" AEs (TEAEs). AEs and SAEs that occur between signing of informed consent and administration of the first dose of study drug will also be recorded. Any abnormal findings, assessed by the Investigator as clinically significant, should be recorded in source documents and the eCRF (e.g. adverse event, medical history).

All AEs, including abnormal results of laboratory investigations, will be defined and graded according to the NCI Common Toxicity Criteria (NCI CTCAE v5.0). They should be reviewed and updated at each subsequent clinical and telephone visit and during any additional phone contact (if applicable) with the subject.

7.1.2 Safety Laboratory Evaluations

Blood, urine and CSF samples will be collected at Screening (i.e. *for CSF, initial lumbar puncture may be performed any time between the first Screening and Baseline visit*) and at visits indicated on the Schedule of Events. Samples for safety, PK and biomarker analysis will be analyzed by central laboratories as specified in the relevant procedures manual. Amounts of blood and CSF to be taken at each time point for PK, ADA and biomarker analysis will be specified in the relevant procedures manual.

Kits for collection of all laboratory specimens will be provided by the Sponsor.

Clinically significant laboratory abnormalities emerging or worsening during the study will be reported as AEs. The following tests will be performed in a central laboratory in accordance with quality laboratory standards at times indicated on the Schedule of Events:

- Hematology, including differential and platelet counts
- Clinical chemistry tests: serum glucose, electrolytes, BUN, creatinine, liver function test battery [ALT, AST, Alkaline Phosphatase, GGT, LDH; Albumin and total protein], serum amylase, bilirubin, cholesterol and triglycerides, uric acid, thyroid function tests (T3, T4, TSH)
- Coagulation panel: INR and PTT
- Viral serology
- Urinalysis

The following tests will be performed at the local laboratories in the participating clinical sites in accordance with quality laboratory standards:

- CSF glucose, protein and total cell counts
- Urine Pregnancy tests (if required)

Any acute, non-scheduled laboratory examinations required for the assessment of adverse events and their resolution for which immediate interpretation of results is required to ensure patient safety and optimize medical management will be carried out as needed.

Clinical laboratory assessments drawn to aid in the evaluation of AEs occurring during the study may be analyzed in local or hospital laboratories affiliated with the clinical site. All such non-scheduled laboratory results must be retained in the subject's study file and updated in the relevant sections of the eCRF. The sites must obtain all local laboratory certifications and accreditations before the study initiation and provide signed certifications by the laboratory directors to the Sponsor.

7.1.3 Vital Signs

Vital signs include temperature, peripheral arterial blood pressure, heart rate, and respiratory rate, all of which will be obtained in a sitting position after the subject has rested for 5 minutes.

7.1.4 ECG with QT parameters

Triplicate ECG recordings will be obtained at specified time points. Provisional interpretation will be done by appropriate clinical staff members in each clinical site. All ECGs will be read and interpreted by a central reader. Intervals and peak durations, including PR, QRS and QT/QTc intervals, will be assessed centrally and will be averaged across the three recordings at each time point. The central reading will be the interpretation of record for the study.

7.1.5 Physical and Neurological Examination

Physical and neurological examinations will be performed at Baseline and as required to report changes related to AEs and documented by the Investigator or a qualified designee.

7.1.6 Magnetic Resonance Imaging

MRI imaging will be performed according to standard methods at Screening, at Day 43 and EOS/ET visit, or in the event of a concerning CNS-related AE (e.g. change in level of consciousness, sudden cognitive decline, seizure, etc.). MRI imaging will support both safety and bioeffect objectives of the study. As a safety biomarker, MRI scans will be reviewed both locally and centrally to detect evidence, if any, of potentially adverse changes following IBC-Ab002 administration such as inflammation or evidence of edema, macro- or micro-hemorrhage. High-resolution T1, T2*/GRE and FLAIR images will be obtained.

The MRI imaging protocol will be designed to meet the requirements set forward by Jack (Jack et al, 2008). Standardization of scan acquisition parameters, quality control, archiving of images, eligibility reads, central reading for safety and exploratory bioeffect analyses will be conducted by an experienced contract research organization. Details of study MRI procedures will be presented in the Study Imaging Charter.

The central reading performed by the imaging CRO will be the interpretation of record for the study.

7.1.7 Columbia Suicide Severity Rating Scale (C-SSRS)

Regulatory authorities recommend the use of a suicidality assessment instrument as part of the safety assessment of experimental therapeutic agents for neurological disorders. The C-SSRS is a validated questionnaire the proves a series of questions to enquire about the presence of suicidal ideation and/or behavior (Posner et al, 2011) The Baseline version of the C-SSRS will be administered prior to the first dose of study drug in order to assess lifetime history of suicidality prior to study entry. At selected post-Baseline clinic visits the Since Last Visit version of the scale will be used.

7.2 SECONDARY OUTCOMES

7.2.1 Pharmacokinetic Parameter Assessment

Defining the pharmacokinetic behavior of IBC-Ab002 is a key objective of the study. Derived pharmacokinetic parameter estimates will be incorporated into our existing PK/PD model to refine dose and dose-interval selection for future Phase 2 and Phase 3 clinical trials and to design the population pharmacokinetic sampling regimen for these studies. Blood samples will be obtained at designated time points as defined in the relevant procedures manual and depicted in the Schedule of Events. The sampling schedule aims to optimize the sampling time points while keeping the number of samples comparable to the sampling schemes deployed in FIH trials of other monoclonal antibodies. Specifically for PK we plan 11 sampling points per subject in the first dosing interval with up to 27 sampling points per subject to cover the entire treatment duration of four dose administrations. The sampling strategy is flexible and may be modified in real time as the actual human PK/PD and biomarker data accumulates and the PK and PD parameters are reassessed.

Serum will be collected from whole blood, aliquoted and kept frozen until analysis in a central laboratory. The following PK parameters will be calculated using NCA methods from the measured IBC-Ab002 concentration in serum:

- Serum antibody concentrations
- Area under the concentration-time curve from time zero to infinity (AUC_{inf})
- Area under the concentration-time curve from time zero to the time of the last measurable sample (AUC_{last})
- Maximum observed concentration (C_{max})
- Time to reach maximum observed concentration (T_{max})
- Terminal elimination half-life ($T_{1/2}$)
- Clearance (CL)
- Volume of distribution (Vd)
- Concentrations of IBC-Ab002 in CSF at selected time points

To increase the chances of properly assessing the PK and PD parameters in the population of subjects across the dose levels, we support our sampling scheme with the D-optimality approach which is geared towards increasing the information content of the population collected data by minimizing the determinant of the inverse population Fisher information matrix (i.e. minimizing the "variance" of the parameter estimates). The initial sampling scheme was calculated using the projected PK/PD model derived from preclinical *in vivo* data and supplemented with literature data about similar anti-PD-L1 compounds. The chances to properly assess the PK and PD parameters are proportional both to the number of cycles that will be administered as well as the number of samples. The standard metric for the parameter estimation precision is the relative standard error (RSE) which has to be at most 50% and desirably less if a parameter is to be considered reliable.

7.2.2 Anti-Drug Antibody (ADA) Assessment

Blood samples will be obtained at designated time points. Serum will be collected from whole blood, aliquoted and kept frozen until analysis in a central laboratory. Detection of Anti-IBC-Ab002 Antibody (ADA) in human serum will be performed using a validated Meso Scale Discovery (MSD)-based assay for ADA detection.

7.3 EXPLORATORY OUTCOMES

7.3.1 Biomarkers

A battery of fluid- and cell-based biomarkers will be assessed in blood and CSF during the course of the study. These exploratory outcomes may include, but may not be limited to the following blood-based, CSF and electrophysiological measures, which are categorized as follows:

- **To support the proposed mechanism of action and biological effect of IBC-Ab002**, including target engagement, we will measure PD-L1 receptor occupancy on blood T lymphocytes and Total Soluble PD-L1 (sPD-L1) concentration in the serum.
- **To assess the proximal pharmacodynamic effects of IBC-AB002 on the peripheral immune system**, we will evaluate several immune-related cellular and humoral markers, including the following cell populations: PD-1+ memory T-cells levels; CD38+ T cells; CCR2+/MSR1+ monocyte levels. In addition, levels of cytokines (IL-1β, IL-4, IL-6, IL-10, IL-12p35, IL-12p40, TNFα, TGFβ) and chemokines (IL-8, Eotaxin 3, CCl2/MCP-1, Beta-Trace protein, CXCl-12) indicative of immune modulation. Changes reported in blood and CSF cytokines in AD have been reviewed by Swardfager (Swardfager et al, 2010), Shen (Shen et al, 2018) and by Taipa et al (Taipa et al, 2019).
- **To assess changes in immune activity in the CNS compartment following IBC-Ab002 administration**, we will evaluate cytokines and chemokines indicative of immune modulation as described above, protein markers reflective of microglial activity in the brain, including sCD14, YKL-40 and sTREM2; 24-OH cholesterol and sAPOE as makers of choroid plexus

activation. Changes in CSF levels of 24-OH cholesterol, sAPOE and Beta-Trace Protein will be monitored as potential indices of changes in the status of the blood-brain interface in the choroid plexus and leptominenges. Finally, immunophenotyping of cells in the CSF will be performed by single-cell nuc-seq to evaluate changes in CSF lymphocyte and monocyte populations.

- **To evaluate the pharmacodynamic effect of single and multiple doses of IBC-Ab002 on markers of neurodegeneration in persons with early AD**, we will evaluate a number of protein biomarkers in blood, plasma and CSF. The field of blood and CSF biomarkers in AD clinical trials has recently been reviewed by Leuzy (Leuzy et al, 2021). To detect changes in disease-related pathology, manifestation of disease modification and support Phase 2 study design, we will assess levels of Aβ peptides and total and phosphorylated tau. Decreases in CSF Aβ 1-42 and its ratio to Aβ 1-40 is a well-known hallmark of AD (reviewed in Olsson et al, 2016). Elevations in total and phosphorylated tau isoforms are accepted biomarker changes associated with AD. Recent clinical trials of anti-amyloid antibodies have demonstrated reductions, primarily in p-tau 181, in AD and prodromal AD even in the absence of meaningful cognitive improvement. Recently, CSF p-tau 217 has emerged as being more sensitive than p-tau 181, the previous standard (Barthélemy et al, 2020), and highly correlative with PET imaging (Janilidze et al, 2020). CSF Aβ, total tau and p-tau 181 levels will be assessed by validated Elecsys® assay. P-tau 217 will be assessed with a qualified ELISA assay. Neurogranin and NfL are accepted biomarkers associated with AD. NfL is a general neurodegeneration marker and not specifically related to AD pathophysiology, however CSF NfL levels do correlate with cognitive impairment in AD and other neurodegenerative disorders (Olsson et al, 2019) and may thus provide information on overall brain health. Furthermore, the correlation between CSF and blood levels of NfL is very high (Lewczuk et al, 2018), Thus total CSF tau, p-tau 217 and NfL will be the three main CSF biomarkers of interest for our study. In addition, increases in CSF neurogranin, a synaptic protein, have been reported in AD, with a negative correlation to cognitive function (Sanfilippo et al, 2016). We will also assess CSF neurogranin as a potential marker of synaptic integrity. Tau isoforms, including total Tau, pTau 181 and pTau 217, YKL-40 (Craig-Schapiro et al, 2010) and GFAP (Fukuyama et al, 2001) are presumed markers of astroglial activity. Soluble TREM-2 (sTREM2) is the cleaved portion of a cell-surface receptor that is present on CNS microglia and macrophages in CSF in AD and in neuroinflammatory conditions such as multiple sclerosis (Piccio et al, 2008; Suarez-Calvet et al, 2016). CD14 (Yin et al, 2009) is another microglia/macrophage cell surface receptor thought to be involved in the pathobiology of AD, a soluble fragment of which is found to be elevated in the CSF of AD patients.

  Additional blood and CSF biomarkers may be explored. For example, Baseline levels of T cells expressing CD38, an ectoenzyme involved in purine metabolism and which has been implicated in AD and a number of neurodegenerative disorders (Guerreiro et al, 2020). CD38 expression on tumor-infiltrating lymphocytes has been shown to be predictive of anti-PD-L1 response in hepatocellular carcinoma (Ng et al, 2020). CD38 levels may

thus be looked at for their ability to predict anti-PD-L1 response in the present study.

Sample acquisition times for blood and CSF biomarkers are listed in the Schedule of Events. Samples will be aliquoted at the time of LP. One aliquot will be sent to the local clinical laboratory for cell count, protein and glucose levels. The remainder of the aliquots will be sent to the Central Laboratory for biomarker analysis. Methods for sample collection, handling and shipment to central laboratories for measurement are provided in the relevant procedures manual.

Collection of CSF at Visit 22 (End of Study, EOS) or Early Termination (ET) visits will be optional. Subjects will be allowed to either opt out of or agree to undergo this procedure at the time of signing the Informed Consent Document to participate in the study, and will be asked to reaffirm or alter their choice at the time of the EOS or ET visit.

7.3.2 Clinical Outcomes

The following clinical outcome measures will be monitored at specified time points during the study. Details of all cognitive assessment procedures will be presented in the relevant procedures manual.

- **Cognitive assessments**
  - Cognitive-Functional Composite (CFC): The CFC (Jutten et al, 2017a; Jutten et al, 2017b; Jutten et al, 2019) comprises existing cognitive tests focusing on the domains that are known to be vulnerable to decline in incipient AD, specifically episodic memory, working memory and executive functioning. The CFC incorporates elements of the ADAS-Cog (Rosen et al, 1984), and Letter Fluency Test. To amplify its clinical relevance, the CFC encompasses an everyday functioning questionnaire focusing on instrumental activities of daily living (Amsterdam-iADL, Sikkes et al, 2012). IADL are activities that require the use of multiple cognitive processes and include activities such as cooking, driving and managing finances. The Amsterdam IADL Questionnaire is a 70-item informant-based computerized questionnaire aimed at detecting early impairments in IADL in MCI and dementia, incorporating cognitively complex everyday activities, such as the use of computers and other common technologies. The original version of the A-iADL-Q has been carefully validated, as has a reduced version of 30 items (Jutten et al, 2017); both versions demonstrate appropriate psychometric properties regarding validity, reliability and diagnostic accuracy. The entire CFC battery takes 20-25 minutes to complete. A trained rater administers the cognitive tests to the subject while, at the same time, the subjects' study partner/informant completes the IADL questionnaire. Recently the CFC has been shown to be sensitive to longitudinal change (Jutten et al, 2020).
    - The individual components of the CFC are as follows:

- Reverse score of the ADAS-Cog Word Recognition Total, so that higher scores represent better cognitive functioning
- Reverse score of the ADAS-Cog Orientation Total, so that higher scores represent better cognitive functioning
- Reverse score of the ADAS-Cog Word Recall Total, so that higher scores represent better cognitive functioning
- Letter Fluency Test: Total number of accepted words in 3 minutes (DAT/FAS)
- Category Fluency Test: Total number of accepted animals in 1 minute
- Digit-Symbol Substitution Test: Number of correct symbols in 90 seconds
- Digit Span Backwards: Total score
- The total score of the Amsterdam IADL Questionnaire

  - Clinical Dementia Rating Sum of Boxes: The Clinical Dementia Rating (CDR) is a well-validated instrument that has been in use for more than 30 years in clinical trials in AD and MCI (Hughes et al, 1982; Morris, 1993). The CDR assesses three domains of cognition (memory, orientation, judgment or problem solving) and three domains of function (community affairs, home or hobbies, personal care) using structured interviews of the study subject and a companion or informant carried out by a trained rater and scored using a standard methodology. The scores for the six domains (range from 0 to 3) tested can be summed as the CDR Sum of Boxes or CDR-SB; an algorithm is used for integrating the information obtained into an overall score, termed here the CDR Global score. It has an advantage for trials lasting a year or more in that it does not require the rater to remember remote details of the subject's Baseline performance or to make an assessment of the subject's clinical change from Baseline. It faithfully tracks the clinical course of early AD (Coley et al, 2011; Cedarbaum et al, 2013).
  - Neuropsychiatric Inventory: The NPI (Cummings et al 1994) is a by-now standard, validated rating scale for assessment of behavioral abnormalities used in many AD clinical trials. The NPI assesses presence, severity and caregiver distress related to 12 domains of behavior. The 12-item version of the scale will be used.

- **EEG**

  The Electroencephalogram (EEG) reflects neuronal and synaptic activity in the brain. Recent developments in EEG analysis have provided improved understanding of changes in network activity in the brain associated with

cognitive decline (Babiloni 2020). We will explore the effects of IBC-Ab002 using resting state quantitative EEG (qEEG) Details of EEG recording and analysis procedures will be provided in the relevant procedures manual.

Standard EEG recording will be performed, including 5 minutes of data collection in the resting state with eyes closed. EEG changes over the course of AD have been well-characterized. Although the EEG may be normal in the very earliest stages of the disease, as the disease progresses there is a gradual increase in slow-wave activity, characterized initially by an increase in spectral power in the theta (4-6 Hz) band and a decrease of activity in the fast beta band (13-30 Hz). Eventually alpha (6-13 Hz) activity also begins to decrease, and in the end-stage of the disease, the EEG is dominated by activity in the delta (0.5-4 Hz) and theta (4-8 Hz) range. The key resting state outcome measure is termed "relative theta power" (Poli et al 2013; Gouw et al, 2017). Global and regional relative power in alpha, beta, and delta bands will also be assessed. Finally, network connectivity analysis will be performed specifically the corrected Amplitude Correlation Envelope (ACEc; Hipp et al, 2012). This quantifies the interregional synchronization, as a measure of communication between brain regions. In AD, functional connectivity is expected to gradually decrease.

- **MRI imaging** will be performed at Screening, at Day 43 and EOS/ET visit, or in the event of a concerning CNS-related AE (e.g. change in level of consciousness, sudden cognitive decline, seizure, etc). MRI imaging will support both safety and bioeffect objectives of the study: As an exploratory bioeffect marker: MRI assessments may be used to seek alterations in the rate of progression of brain volume loss. The MRI imaging protocol will be designed to meet the requirements set forward by Jack (Jack et al, 2008). Standardization of scan acquisition parameters, quality control, archiving of images, eligibility reads, central reading for safety and exploratory bioeffect analyses will be conducted by an experienced contract research organization. Details of study MRI procedures will be presented in the relevant procedures manual and the Study Imaging Charter.

7.3.3 Additional Baseline Biological Measures

- **Apolipoprotein E Genotyping:** Apolipoprotein E (APOE) genotyping is a mandatory part of this study. This data will be used to attempt to assess whether or not APOE genotype is predictive of response to or adverse effects arising from IBC-Ab002 administration. Blood sampling for APOE genotyping will be performed at the Baseline visit. Neither subjects nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results.
- **Whole Blood Samples for Pharmacogenetic Research:** A whole blood sample will be collected for pharmacogenetic analysis at the Baseline visit where local regulations permit. These samples will be used to investigate whether genetic variants related to AD risk factors, pathological markers,

immune function or other potential modifying factors affect response to IBC-Ab002 therapy. Pharmacogenetic samples will be de-identified in such a way that genetic information relating to individual study subjects will not be traceable by study site personnel. Such pharmacogenetic data may be archived for future use by pooling with data from other studies of IBC-Ab002 or for other internal research purposes at IBC. Data from subjects who prospectively agree, and who reside in countries where sharing of genetic data is permitted, may be shared with external investigators who agree to follow appropriate procedures to guarantee the privacy of individual subjects' genetic data.

7.4 TIMING OF STUDY ASSESSMENTS BY VISIT

Visit-by-visit listings of the study assessments and activities are shown in the Schedule of Events. Detailed recommendations for the order of assessments and activities within each study visit are provided in Appendix A: Recommended Order of Assessments at Each Visit

8 SELECTION AND ENROLLMENT OF SUBJECTS

8.1 SUBJECT INCLUSION CRITERIA

Subjects must meet all the following inclusion criteria to be eligible to participate in the study:

1. Age range: 50-80 years (inclusive) of age at the Screening visit
2. Diagnosis of early AD based on the NIA-AA Research Framework criteria, regardless of APOE gene status:
    a. Biomarker classification A+T+N+ or A+T+N- based upon a Screening CSF profile consistent with AD defined by either of the following criteria:
        1. CSF Aβ42 < 1000 pg/mL and pTau181 > 19 pg/mL
        2. CSF pTau181/Aβ42 ratio > 0.020
    b. AD Clinical Stage 3 or 4 based on the National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework criteria
        i. Gradual and progressive change in memory function reported by the participant or informant for ≥6 months
        ii. Have a Mini-Mental State Examination (MMSE) score at Screening between 20-28 inclusive
        iii. Clinical Dementia Rating Scale (CDR) global score of 0.5 or 1 with memory box score ≥0.5
3. Able to speak, read and write the local language fluently
4. With respect to symptomatic treatment for Alzheimer's disease, subjects should either be:
    a. Not treated with any approved treatments for AD with a reasonable expectation that, based on the course of illness, need for treatment is not

imminent and the subject should not be initiated on treatment for the length of the study, OR

b. Stabilized on an approved medication(s) other than anti-Ab antibodies for the treatment of AD for at least 3 months prior to Baseline. The dose of the AD treatment should remain the same after entering the study

5. Subject has a study partner who spends at least 10 hours/week with the subject, and can attend all visits with the subject, report accurately on the subject's status, and ensure compliance with all study requirements
6. Subject and study partner (if necessary) must be willing and able to be admitted at the clinical research site as required by the study protocol
7. Subject and study partner must each independently be able to understand the study requirements and provide informed consent
8. Subject has either received an adequate dosing regimen of an approved SARS-CoV2 vaccine (according to current regional guidelines) at least 3 months prior to the anticipated first dose of study drug, or has recovered from SARS-CoV2, with evidence of persistent SARS-CoV2 serological response at the Screening visit. Nasal swabs for SARS-COVID-2 PCR may be obtained if required by local or institutional regulations.
9. Weight between 45 and 120 kg

8.2 SUBJECT EXCLUSION CRITERIA

Subjects will be excluded from study participation if any one of the following exclusion criteria are met:

1. Females who are not postmenopausal at Screening as defined by amenorrhea for at least 12 consecutive months or who have not been sterilized surgically (i.e. bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before Screening)
2. Males who are fertile but refuse to practice double-barrier methods of contraception with female partners of childbearing potential.
3. Other than AD, neurologic or medical disorder which may impair cognition including: head trauma, seizure disorder, neurodegenerative disease, hydrocephalus, cerebral / spinal hematoma, inflammatory disease, CNS infection (e.g. encephalitis or meningitis), neoplasm, toxic exposure, metabolic disorder (including hypoxic or hypoglycemic episodes), or endocrine disorder, or any significant medical conditions that, in the opinion of the Investigator, would prohibit their participation in the study
4. As assessed by the central MRI reader,
    a. Magnetic Resonance Imaging (MRI) evidence of a) more than three lacunar infarcts, b) territorial infarct or macroscopic hemorrhage, or c) deep white matter lesions corresponding to a Fazekas score = 3
    b. Presence of any structural lesion that could potentially explain the subject's cognitive impairment, or place the subject at risk for AEs during the trial. Examples include but are not limited to: cerebral contusion, encephalomalacia, aneurysm or vascular malformation, infective lesion,

intraparenchymal tumor, meningioma or arachnoid cyst larger than 1 cm in longest diameter

c. More than 5 Amyloid-Related Imaging Abnormalities-Hemorrhages (ARIA-H) (including microbleeds and areas of leptomeningeal hemosiderosis (LH)), or more than 3 areas of LH.

5. Any contra-indication to undergo MRI, as judged by local PI or radiologist, including but not limited to presence of pacemaker, aneurysm clips, artificial heart valves, ear implants, ventriculoperitoneal shunt, foreign metal objects in the eyes, skin or body or any other circumstance which would contraindicate an MRI scan or impair MRI image quality, or history of claustrophobia or of not tolerating MRI scanning procedures.
6. Severe vision or hearing impairment that would prevent the subject from performing psychometric tests or otherwise complying with requirements for study participation and activities.
7. History of any of the following neurological, psychiatric or medical conditions:
    a. History of large vessel stroke
    b. Transient Ischemic Attack (TIA) documented in the medical record within 12 months of Screening visit
    c. History of head trauma with documented loss of consciousness, evidence of parenchymal brain injury or skull fracture, or neurosurgical procedure which, in the judgement of the Investigator could provide an alternative explanation for the subject's cognitive impairment
    d. History of myocardial infarction or unstable angina within 12 months of the Screening visit
    e. History of examination evidence of non-diabetic peripheral neuropathy or myopathy, whether or not of immune or presumed immune origin
    f. Autoimmune disease (e.g., Systemic Lupus Erythematosus, Multiple Sclerosis, Rheumatoid arthritis, Type 1 diabetes mellitus)
    g. Immunocompromised systemically due to continuing effects of immunosuppressant medications other than topical steroids
    h. Current or previous hepatitis B infection (defined as positive test for hepatitis B surface antigen (HbSAg) and/or hepatitis B core antibody (anti-HBc). Subjects with immunity to hepatitis B (if due to natural infection defined as negative HbSAg, positive hepatitis B antibody [anti-HBs] and positive anti-HBc; if due to vaccination defined as negative HbSAg, negative anti-HBc and positive anti-HBs) are eligible to participate in the study
    i. History or positive test at Screening for hepatitis C virus (HCV) antibody
    j. History or positive test at Screening for human immunodeficiency virus (HIV)
    k. Diagnosed with cancer with metastatic potential within the last 5 years other than carcinoma *in situ* of the breast or cervix, or squamous cell

carcinoma or basal cell carcinoma of the skin that has been completely excised

l. Currently meets DSM V criteria for Major depressive disorder and has required initiation of medication or hospitalization within the previous 90 days prior to Screening

m. Systolic blood pressure > 160 mm Hg OR diastolic blood pressure > 95 mm Hg on three separate determinations 5 minutes apart, taken at same arm, after the patient feels comfortable and relaxed at the research facility

n. Clinically significant orthostatic hypotension

o. Presence of hallucinations or delusions suggestive of a diagnosis of Lewy Body Dementia or other non-AD cause for subject's cognitive impairment

p. Active infection within 8 days of the first dosing visit

q. Major surgery within 12 weeks of Screening

r. Blood donation of 1 unit or more within 8 weeks prior to the first dose of study medication

8. Any of the following laboratory abnormalities at Screening

a. Clinically significant (as determined by a cardiologist or central reader) 12-lead ECG abnormalities

b. Screening values for hemoglobin < 12 g/dL for men or < 11 g/dL for women

c. Any serum chemistry value (e.g. AST, ALT, Alkaline Phosphatase, Creatine Kinase (CK), total bilirubin etc. > 1.5x the upper limit of normal on 2 successive determinations less than 2 weeks apart

d. eGFR < 50

e. Subjects with a bleeding disorder or at risk for increased or uncontrolled bleeding, including:

i. Known bleeding disorder
ii. Platelet count < 50,000, INR > 1.5 for subjects who are not on anti-coagulant treatment, or PTT significantly outside the normal range

f. Serum vitamin B12 clinically significantly below the lower limit of normal and determined by the PI to contribute to the cognitive impairment

9. Presence of contraindication to lumbar puncture (LP) as judged by local PI, e.g. known X-ray or other evidence of significant lumbar spine abnormalities or history of lumbar surgery with sequelae that would interfere with or pose risks from the procedure; platelet count below 50,000 cells/µL; taking anticoagulant or antiplatelet medications other than aspirin at a dose of ≤ 100 mg/day or clopidogrel (see item 11(h) below)

10. Any other significant medical conditions that, in the opinion of the Investigator, would prohibit participation in the study, including inability to tolerate the MRI scan, LP procedures or IV infusions.
11. Taking any of the following medications
    a. Antipsychotic agents, including pimavanserin not at a stable dose for at least 30 days prior to Screening.
    b. Stimulant medications (e.g., Ritalin, amphetamines) not at a stable dose for at least 30 days prior to Screening
    c. Antidepressant medications whose dose has not been stable for at least 90 days prior to Screening.
    d. Immunosuppressant medications, including chronic systemic corticosteroids (chronic use of topical steroids is allowed)
    e. Injected or infused antibody therapies, including but not limited to antibodies directed against TNF, anti-IL-6, natalizumab, rituximab and similar agents.
    f. Aducanumab, (aducanumab-avwa) intravenous injection (brand name: Aduhelm™), or any other experimental or approved anti-amyloid antibody.
    g. Insulin
    h. Anticoagulant or anti-platelet medications including warfarin, heparinoids and direct coagulation factor inhibitors (e.g. apixaban, dabigatran, rivaroxaban) within 90 days of the planned first dose of study drug; *either* aspirin at a dose of ≤ 100 mg/day or clopidogrel at a dose of 75 mg/day, *but not both in combination* is permitted
12. Participation in any other interventional clinical trial, or treatment with any investigational drug or investigational use of an approved therapy, within 30 days or 5 half-lives of such agent, whichever is longer, prior to the first Screening visit
13. Subject currently smokes more than 5 cigarettes or equivalent tobacco consumption daily
14. Regular nonmedical use of cannabis or cannabis products unless such products are documented by the manufacturer's label not to contain tetrahydrocannabinol or its derivatives or analogs
15. History of drug (including cannabis) or alcohol abuse within the last 5 years.
16. Positive urine drug test for drugs of abuse at Screening. Subjects who test positive for benzodiazepines or opioids in urine drug testing need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications containing benzodiazepines or opioids for a medical condition and not due to drug abuse.
17. Potential subjects who answer "yes" to C-SSRS suicidal ideation Type 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at

Screening, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

18. Unwillingness to comply with study requirements or history of noncompliance in prior clinical trials

8.3 RECRUITMENT, SCREENING AND RANDOMIZATION PROCEDURES

Prospective study subjects may be identified at any time following site activation. However, entry into the study will occur only at the Screening visit for each SAD dose level cohort.

Screening activities for individual subjects should commence no more than 56 days (8 weeks) prior to the anticipated first dosing day. It is recommended that all eligibility assessments be completed within a 48-day (6 week) time frame in order to allow for the final baseline assessments to take place within 8 days of the planned dosing visit. The recommended order of Screening activities is as follows:

1. Review of Inclusion/Exclusion Criteria
2. Signing informed consent – after presentation of the study by the site PI and/or qualified staff member
3. Medical History, general physical and neurological examinations
4. C-SSRS
5. Cognitive assessments
    - CDR-SB
    - MMSE
6. Triplicate ECG
7. Clinical laboratory evaluations:

    The following tests will be performed in a central laboratory in accordance with quality laboratory standards at times indicated on the Schedule of Events:

    - Hematology, including differential and platelet counts
    - Clinical chemistry tests: serum glucose, electrolytes, BUN, creatinine, liver function test battery [ALT, AST, Alkaline Phosphatase, GGT, LDH; Albumin and total protein], serum amylase, bilirubin, cholesterol and triglycerides, uric acid, thyroid function tests (T3, T4, TSH), Vitamin B12
    - Coagulation panel: INR and PTT
    - Serology (HBV, HCV, HIV)
    - Plasma Aβ42:40 ratio, plasma pTau 181 (results to be returned within 8 days).
        - ***If a subject's plasma biomarker profile is not consistent with the presence of brain amyloidosis, as indicated by a plasma pTau181 level < 20.02 pg/mL, the subject should not proceed to Lumbar Puncture for CSF Sampling.***

- Urinalysis
- SARS-CoV-2 PCR (only if required by local or institutional regulations)

8. Brain MRI

   Subjects with plasma pTau181 levels < 20.02 pg/mL or exclusionary lesions on MRI scans will not proceed to screening LP. Therefore, it is recommended that MRI scans should not take place until after results of plasma pTau181 are known (approximately 8 days from receipt of the samples in the testing laboratory).

9. Lumbar Puncture (within 4 weeks of planned dosing). LP should only be performed if
   - All clinical inclusion/exclusion criteria have been met
   - no space-occupying or other exclusionary lesions are observed on screening MRI scan; and
   - if subject's plasma biomarker profile is consistent with the presence of brain amyloidosis as indicated by a plasma pTau181 level > 20.02 pg/mL

   The following tests will be performed at the local laboratories in the participating clinical sites in accordance with quality laboratory standards:

   - CSF glucose, protein and total cell counts

10. Assessment of Eligibility
11. Other Pre-Baseline Study activities, including the following, may be performed any time prior to dosing:
    - NPI
    - EEG
12. Entry into interactive randomization system following confirmation of continued eligibility at Baseline

Subjects who are successfully screened but who are not able to enter the study due to completion of enrollment in any individual cohort will be given priority to enter the next available dose group. At a minimum, the following assessments must be repeated during the abbreviated Re-Screening visit prior to randomization in the subsequent cohort:

1. Interval medical history, including review of concomitant medications
2. Physical and neurological examination
3. Clinical laboratory tests
   a. CBC with differential
   b. Clinical Chemistry Panel
   c. Coagulation Panel

d. Urinalysis

8.4 RECRUITMENT, SCREENING AND REPLACEMENT OF SUBJECTS

8.4.1 Subject Recruitment

Recruitment for Cohort 1 may begin at each site once regulatory and IRB/EC and other institutional approvals have been obtained. For Cohorts 2-5, recruitment may begin as soon as the last subject has been randomized into the previous cohort and the SMT has reviewed the data and approved progression to the next cohort. The time from signing informed consent to randomization should not exceed 8 weeks.

8.4.2 Randomization of Subjects

Eligibility to enter the study will be determined algorithmically based upon entry into the EDC system. Once a subject qualifies for randomization into the study, he/she will be assigned to either active or placebo within the study Interactive Response Technology (IRT) system. If the subject is assigned to receive active IBC-Ab002, the appropriate number of vials to meet the subject's dosing requirements will be shipped to the site pharmacy in advance of the scheduled dosing day.

8.4.3 Rescreening

Prospective subjects who qualify for study entry but who qualify for enrollment after eight subjects have already been consented for a given cohort and the subsequent cohort is not yet open for recruitment, may undergo abbreviated rescreening in order to qualify for the next dose level group and will be given priority to enter the study if they continue to meet all study entry criteria. The abbreviated rescreening procedures will consist of interval history and physical examination, all Screening clinical laboratory tests other than viral serologies, and a thorough review of all inclusion/exclusion criteria. If abbreviated re-screening and Baseline occur within a 1-week span, safety lab tests do not need to be repeated.

8.4.4 Replacement of Subjects

If a subject discontinues or is discontinued for any reason during the Screening period, sites will be allowed to screen additional subjects until such time as the site has met the recruitment cap according to the IRB/EC approval. The recruitment goal for this study is to obtain 100% retention, or 100% active subjects. Up to 2 subjects not completing Part A of the study may be replaced in each cohort in order to meet the recruitment goals of the trial, unless such dropouts/discontinuations were due to AEs meeting any of the criteria listed in the Stopping Rules listed in Section 9.

9 DOSE INTERRUPTION AND STOPPING RULES

Individual Stopping Rules

Dosing for any individual subject receiving active study drug may not be continued following the occurrence of either a related Serious Adverse Event or a CTCAE v5.0

Grade 3 Adverse Event, unless the SMT agrees that such event was unrelated to study medication.

Study Level Stopping Rules

Dosing at all dose levels will be stopped for all subjects upon the occurrence of a single drug-related death. Upon the occurrence of a single drug related Serious Adverse Event (SAE), two related CTCAE Grade 3 Adverse Events, or 2 irAEs of any type or grade, dosing at all dose levels may be stopped. In this instance, the Study Monitoring Team (SMT) will provide its recommendation to the independent Data Monitoring Committee (iDMC), with whom the final decision will be taken.

Cohort Level Stopping Rules

Regardless of investigator assessment of causality, dosing in any given dose level may be stopped upon the occurrence of 2 SAEs, CTCAE Grade 3 Adverse Events, or other medically significant events that would warrant cessation or interruption of dosing for longer than 4 weeks based on the medical judgement of a Site Investigator. As noted above, the SMT will provide its recommendation to the iDMC, with whom the final decision will be taken.

Interruptions of individual infusions due to minor infusion reactions that are followed by resumption of dosing with no residual adverse effects to the patient will not be considered significant events.

The study director and the SMT may be immediately unblinded in the event of a death, SAE, or CTCAE Grade 3 or 4 Adverse Event deemed related to treatment by a Site Investigator. An independent Data Monitoring Committee (iDMC), consisting of 3 experts in the conduct of AD (2) and Immune Checkpoint (1) clinical trials will meet approximately every 6 months to review the progress of the study and to review the unblinded study data. The iDMC will review and endorse the decisions of the SMT on dose escalation and continuation, and will be informed and consulted regarding any and all safety issues arising during the study. In the event that occurrences meet the study's stopping rules pending the SMT's decision, the iDMC will review the SMT's recommendations and make the final determination on whether to continue or halt the study. The operations and responsibilities of the iDMC will be described in a separate iDMC Charter. If dosing is stopped due to adverse events, a substantial amendment requesting re-start will be submitted for regulatory approval.

9.1 SUBJECT WITHDRAWAL CRITERIA

Subject may continue on protocol treatment at the discretion of the Investigator. Subjects who either voluntarily or involuntarily withdraw prematurely from the study must undergo the final EOS follow-up procedures for safety purposes. Data from subjects who leave the study will be analyzed up to the date of their discontinuation. Subjects will be withdrawn from the study under the following conditions:

1) Death (complete AE form and SAE report)

2) Subject withdraws consent
3) Request of primary care physician or Investigator to withdraw the subject
4) Sponsor requests subject to be withdrawn
5) Failure to return or lost to follow-up

9.2 END OF STUDY DEFINITION

At least 40 subjects are expected to be randomized in this study. Based on emerging safety, tolerability and biomarker data, up to two cohorts may be expanded to include a total of 16 additional subjects, maintaining a 3:1 active:placebo randomization ratio. End of study is defined as 90 days following the date of last visit of the last subject for last clinical assessment. Study close-out will not take place until all samples have been assayed, the data has been quality-reviewed, and the study database has been locked.

9.3 EARLY TERMINATION OF THE STUDY

The study may be prematurely terminated if, in the opinion of the Sponsor, there is sufficient reasonable cause. Circumstances that may warrant early termination of the study may include, but are not limited to:

- Recommendation of the SMT that there is unexpected, significant or unacceptable risk to the study subjects, including risk of worsening cognition
- Unsatisfactory enrollment
- Actions taken by regulatory authorities
- Discontinuation of the development of IBC-Ab002 for any reason

In the event of premature study discontinuation, the Sponsor will promptly inform the Investigators, participating institutions and relevant regulatory authorities of the termination and the reasons the study was stopped.

9.4 TERMINATION OF INDIVIDUAL SUBJECT DOSING IN THE EVENT OF RAPID DISEASE PROGRESSION

The following procedures will be followed in the event that a study participant is deemed by the Principal Investigator at the site to be incapable of providing informed consent to continue participation in the study. If a subject's cognitive status has declined sufficiently so that he/she is no longer competent to provide informed consent, such occurrence will be considered an adverse event. Study drug dosing for that subject will be discontinued, and further actions may be taken as stipulated in Protocol Section 9 above.

If at all possible, it is recommended that the subject continue to be followed until the end of the study observe for worsening, resolution of the event or an alternate explanation for its occurrence. In such an event, consent for the subject's continued participation will need to be obtained from a legal representative to continue clinical and safety assessments of the affected subject without repeating invasive procedures such as lumbar puncture unless information to be obtained from such procedures is deemed by the Investigator to be important to understanding the etiology of the sudden cognitive decline and/or for the management of the subject's medical

condition. A separate Legal Representative Informed Consent form will be required to permit continued observation of the subject under such circumstances.

In the event study drug dosing is discontinued due to abrupt and severe cognitive worsening, subjects who continue to be followed will undergo the following limited set of study procedures at the times set according the Protocol SOE, and contingent upon the signing of a separate informed consent form by the subject's legal representative:

• Interval History, with AE and ConMed reporting

• Clinical Chemistry and Hematology labs

• Vital Signs, including weight

• MMSE

• Amsterdam Cognitive-Functional Composite (if subject is unable to participate, study partner may complete the i-ADL portion only)

• NPI

• Any additional procedures deemed necessary by the site Investigator that might be required to appropriately evaluate, monitor and/or treat the subject’s medical condition

10 TREATMENT OF SUBJECTS

10.1 STUDY DRUGS

10.1.1 Description of Study Drugs

Each vial containing IBC-Ab002 will be labeled in accordance with requirements of local law and legislation. Labels will indicate that the vial contains active IBC-Ab002 study drug, vial and lot number. The Sponsor will not provide placebo solution.

IBC-Ab002 is formulated as a lyophilized powder in vials and stored at 2-8°C until reconstitution prior to intravenous (IV) administration. After reconstitution with 5 mL of Water for Injection (WFI), each vial will contain 5 mL (nominal extractable volume) of a dosage solution containing 50 mg/mL IBC-Ab002, 20 mM histidine, 240 mM sucrose and 0.02 % polysorbate 20, pH 6.0. The reconstituted lyophilized study drug will be further diluted in a total volume of 100 mL normal saline by an unblinded pharmacist and will be delivered to the infusion location in covered bags.

Subjects assigned to receive placebo will be administered 100 mL of normal saline to which nothing has been added.

All vials containing active IBC-Ab002 received in the study centers must be stored under the specified conditions in a secure area accessible only to the Investigator and designated site personnel in each site. All investigational products should be stored and inventoried according to applicable government regulations and study procedures. The lyophilized IBC-Ab002 should be stored at -2-8°C. Any deviation from this storage temperature should be reported to the Sponsor as a protocol deviation immediately. Simultaneously, the affected vials of study drug must be

placed in quarantine until the Sponsor approves its continued use or instructs the site to return or destroy the affected vials.

The Sponsor will be responsible for ensuring that IBC-Ab002 is manufactured in accordance with applicable current Good Manufacturing Practice (GMP) regulations and local requirements.

10.1.2 Labeling of Investigational Product

Vials containing IP will be labeled according to the requirements of local law and legislation and will be placed on each vial in accordance with local and international regulations.

Labels will indicate that the vial contains active IBC-Ab002 study drug, vial and lot number. The Sponsor will not provide placebo solution. The unblinded pharmacist at each site will provide saline solution to add to the IV administration bag. The infusion bag label should list the subject identification number and the date of the infusion, and the designation "IBC-01-01 Study Drug/Placebo". No information should be displayed to indicate the contents of the IV bag. Additional information to ensure that the study drug is being administered to the correct study subject may also be displayed if required by local institutional procedures or regulations.

10.1.3 Blinding of study drug

Study drug will be provided in individual vials, each bearing a unique number. The unblinded pharmacist will record the vial numbers used to prepare each subject's dose in the pharmacy log. No investigational product will be shipped for subjects assigned to receive placebo. Bags and administration set tubing must be labeled only with the subject's study number and date of dosing, and must be covered with an opaque covering to mask any potential color differences to the site staff. No information regarding the contents of the dose may be shared with personnel other than those authorized to view unblinded dose information within the investigational pharmacy.

10.1.4 Accountability and Compliance

Vials of study drug will be received at the designated pharmacy and will re-constituted by the Study Pharmacist according to detailed procedures outlined in the Pharmacy Manual at the time of scheduled study drug administrations. A drug accountability log will be used at each study center to maintain accurate records of investigational product inventory at the center (date and quantity received, dates of administration to the subjects, dates when used/unused/damaged vials returned to the Sponsor/Depot). Accountability will also be recorded within the IRT system in order to track all vials received and dispensed by the Pharmacy.

The Study Pharmacist or a designated staff member will be responsible for maintaining accurate records of the quantity and dates of all investigational product supplies received, administered and returned. The quantity of investigational product lost, missing or destroyed must also be accounted for and documented. At the end of the study, reconciling the delivery records with those of usage and returned stocks must be possible. The site study staff in each site must account for any discrepancies.

Unused vials of IBC-Ab002 remaining at the site that were not administered during the course of the study will be disposed of according to instructions to be provided by the Sponsor in the Study Pharmacy Manual.

10.2 PREVIOUS MEDICATIONS/THERAPIES

All prior treatments received by the subject within 30 days of the Screening visit will be recorded on the subject's eCRF including the name of the treatment, total daily dose, and the start and stop dates.

Any medications (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study must be approved by the Investigator.

All approved concomitant medications taken by the subject must be recorded on the eCRF, along with the start and stop dates as well as daily dose.

10.2.1 Allowed Previous Medications/Therapies

Any medication that is not specified in Section 10.2.2 is permitted.

If subjects are taking approved medications (acetylcholinesterase inhibitors) for the treatment of AD, they must be on a stable dose for at least 3 months prior to Baseline. The dose of the AD treatment should remain the same after entering the study.

Taking either aspirin at a dose of ≤ 100 mg/day or clopidogrel at a dose of 75 mg/day, *but not both in combination* is permitted.

Vaccines of any kind (including COVID) should only be administered between days 28 and 57 of each dose cycle so that it is done no sooner than 28 days before or after a dose of study drug.

10.2.2 Disallowed Previous Medications/Therapies

a. Antipsychotic agents, including pimavanserin, not at a stable dose for at least 30 days prior to Screening

b. Stimulant medications not at a stable dose for at least 30 days prior to Screening

c. Antidepressant medications whose dose has not been stable for at least 90 days prior to Screening

d. Immunosuppressant medications, including chronic corticosteroids

e. Injected or infused antibody therapies, including but not limited to antibodies directed against TNF, anti-IL-6, natalizumab, rituximab and similar agents

f. Aducanumab, (aducanumab-avwa) intravenous injection (brand name: Aduhelm™), or any other experimental or approved anti-amyloid antibody

g. Insulin

h. Anticoagulant or anti-platelet medications including warfarin, heparinoids and direct coagulation factor inhibitors (e.g. apixaban, dabigatran, rivaroxaban) within 90 days of the planned first dose of study drug; *either* aspirin at a dose

of ≤ 100 mg/day or clopidogrel at a dose of 75 mg/day, *but not both in combination* is permitted

i. Regular use of cannabis or cannabis products, including non-prescription products containing cannabidiol (CBD)

j. Treatment with any investigational drug or investigational use of an approved therapy within 30 days (or 5 half-lives of such agent) prior to the first Screening visit is not permitted.

10.3 CONCOMITANT MEDICATIONS/THERAPIES DURING STUDY

10.3.1 Allowed Concomitant Medications/Therapies during Study

Permitted medications as listed in Section 10.2.1 are allowed to be taken during the study.

10.3.2 Disallowed Concomitant Medications/Therapies during Study

Disallowed medications as listed in Section 10.2.2 are not allowed to be taken during the study.

11 SAFETY REPORTING

All subjects will be assessed regularly for potential adverse events (AEs) occurring at any time after the subject signs the informed consent, until the EOS/ET visit. Each time the subject is seen or contacted by the investigator or the study staff, be it at the study clinic, hospital, or over the telephone, the investigator will determine whether any AE has occurred by evaluating the subject. AEs may be directly observed, reported spontaneously by the subject, or by questioning the subject at each contact. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. All AEs, regardless of grade or relationship to the study drug, will be reported. and will be assigned a severity grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0

Illnesses that are present at the time informed consent is given are to be regarded as concomitant illnesses and recorded in the medical history. Investigators should document all significant illnesses that the subject has experienced prior to Screening as prior illnesses. Illnesses first occurring or detected during the study and / or worsening of a pre-existing illness during the study are to be documented as AEs.

11.1 TERMINOLOGY

An *Adverse Event (AE)* is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the occurrence is considered drug related. An AE (may also be referred to as an adverse experience) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the

medicinal (investigational or marketed) product and from any route of administration, formulation, or dose, including an overdose.

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

- results in death
- is life-threatening, (NOTE: 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 which hypothetically might have caused death if it were more severe.)
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- results in a congenital anomaly/birth defect

If either the Sponsor or Investigator believes that an event is serious, the event must be considered serious and be evaluated by the Sponsor for expedited reporting.

A *suspected adverse reaction* means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

11.2 ASSESSMENT OF CAUSAL RELATIONSHIP

The following categories and definitions for assessing the causal relationship of an event to the investigational product(s) are provided as a guide to be used for evaluating adverse events reported in this study to determine "suspected adverse reactions" that require expedited reporting to regulatory agencies if they are unexpected, as detailed in Table 11-1.

Table 11-1: Relationship of Study Medication to Adverse Events

Definitely related	An adverse event occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible. The event must be definite pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary and feasible.
Probably related	An adverse event with a reasonable time sequence to administration, and which cannot be explained by concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal. Re-challenge information is not required to fulfil this definition. (Note: there are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists, (e.g. bone marrow suppression, fixed-drug eruptions, and tardive dyskinesias)
Possibly related	An adverse event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Not related	An adverse event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying diseases provide plausible explanations.

11.1 ADVERSE EVENT GRADING AND CODING

Severity of adverse events will be graded according to the revised National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0 as outlined in **this table.**

Table 11-2.

In this table, 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, as defined by NCI CTCAE. In the event the CTCAE does not provide appropriate severity descriptors for an individual AE, the Investigator at the clinical site will assign a severity grade according to the criteria shown in this table.

Table 11-2: NCI CTCAE Grading System

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
3	Severe or medically significant but not immediately life-threatening	Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences	Urgent intervention indicated
5	Fatal	Death related to AE

AEs will be coded, grouped, and tabulated according to the current Medical Dictionary for Regulatory Activities (MedDRA) preferred terms by body system organ class.

11.2 HANDLING OF SERIOUS ADVERSE EVENTS (SAES)

Adverse events classified as serious must be recorded in the SAE section of the eCRF and require expeditious handling and reporting to the CRO as well as the Sponsor in order to comply with regulatory requirements. All SAEs must be reported using the Serious Adverse Event Report form via the eCRF system. **The completed SAE report form with supporting documentation must be completed in the eCRF system within 24 hours of the study site personnel's initial**

notification/awareness of the event. All telephone/internet communications regarding SAE must be followed by a written report. Supporting documentation must be submitted to the Sponsor, to local IRB/EC and to the national regulatory authorities if required.

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (e.g. hospital discharge summaries, additional lab and test results, autopsy reports, etc.), should be collected subsequently, if not available at the time of the initial report, and immediately sent to CRO and Sponsor using the same procedure as the initial SAE report. Information on the SAE must be in sufficient detail to allow for a complete medical assessment of the case and independent determination of causality. At a minimum such information should include: the Patient ID, verbatim event term(s), Investigator's assessment of causality, and reporter contact information.

For ease of analysis, worldwide standardization and regulatory reporting, the CRO or Sponsor representative will code each reported adverse event or symptom into its corresponding preferred term and body system/organ class according to the current MedDRA version. The Principal Investigator will be responsible for assessing severity based on the intensity of the event as it presented using the criteria listed in Section 11.1 above. All SAE reports will be sent electronically to the CRO and Sponsor via the eCRF system.

If the eCRF system is not available, the site staff will complete the back-up paper SAE Report Form and e-mail it within 24 hours to the following address: drugsafety@worldwide.com.

In cases where the email system is unavailable, site staff will transmit the back-up paper SAE Report Form by fax to: Worldwide PV +44 208 043 4813

As required, all Investigators will be notified of all AE reports that are determined to be serious, unexpected, and related to the investigational product. The notification will be in the form of a Safety Update (Dear Doctor Letter).

All suspected unexpected serious adverse reactions (SUSARs) to IBC-Ab002 will be the subject of expedited reporting. SUSARs will be submitted according to local regulatory requirements, including submission to EudraVigilance in accordance with EU CTR No 536/2014.

A SUSAR that is fatal or life-threatening will be reported to the relevant competent authorities and EC as soon as possible but no later than 7 days after the sponsor becomes aware of such a case. All other SUSARs will be reported to the relevant competent authorities and EC within 15 days after the sponsor becomes aware of such a case.

11.3 ADVERSE EVENTS OF SPECIAL INTEREST (AESIS)

All confirmed and suspected irAEs (See Section 4.3) will be considered AESIs.

11.4 LABORATORY TEST ABNORMALITIES

All new abnormal laboratory findings and those abnormal at Baseline that change significantly (i.e. by at least one toxicity grade as defined in the NCI CTCAE v5.0) are considered AEs. Abnormal laboratory values that are considered by the Investigator not to be clinically significant (e.g. minimally out of range values with no accompanying signs or symptoms) need not be recorded as AEs. Laboratory AEs not listed in the NCI CTCAE v5.0 will be considered as grade 1 (mild) if there is no clinical effect or intervention. Laboratory values outside the normal range for certain parameters will not be considered AEs if they are generally not considered as indicating an abnormality. If there is a clinical sequela or intervention, the laboratory abnormality is to be graded according to the criteria used for clinical AEs, described above.

11.5 OTHER SAFETY CONSIDERATIONS

All AEs must be recorded and followed until resolution or for at least 30 days after discontinuation of the study medication, whichever comes first. Any clinically significant changes noted during interim or final physical examinations, electrocardiograms, radiological assessments, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded on the AE section of the eCRF.

11.6 EMERGENCY UNBLINDING DUE TO ADVERSE EVENTS

In the event a Site Investigator requires unblinding of a subject treatment assignment for the purposes of managing the subject's medical care, the investigator may immediately access the emergency unblinding feature of the IRT system to obtain the subject's treatment assignment. However, it is requested that the Investigator attempt to contact the Study Medical Monitor and/or the Study Director before requesting emergency unblinding information from the IRT system if time permits or if there is any uncertainty around the decision to unblind or concerning the management of the subject's medical condition as related to the pharmacological actions of IBC-Ab002. Detailed procedures for unblinding individual subjects and protection of the overall study blind will be detailed in the Study Unblinding Plan.

12 STATISTICAL METHODOLOGY

Details of the statistical methods to be applied will be given in a Statistical Analysis Plan.

12.1 SAMPLE SIZE JUSTIFICATION

No formal sample size calculation was performed. The study is not expected to achieve statistical power, but rather to provide estimates for safety and PK profiles and a trend for efficacy outcomes. However, with 30 patients dosed with multiple doses of active study drug, there is chance of ~80% to detect at least 1 relatively rare (≤ 5%) treatment related AE such as thyroid dysfunction or pneumonitis. For more common (~10% - 15%) treatment related AEs such as hepatitis, rash and colitis the chances are at least 95%.

12.2 ANALYSIS POPULATIONS

Modified Intent to Treat (mITT) **Population:** All subjects who received at least one dose of study medication and had at least one post-Baseline biomarker or clinical assessment.

Safety Population: All subjects who received at least one dose of study medication.

PK Population: All subjects who received at least one dose of study medication and had at least one post-Baseline PK assessment.

Per Protocol Population: All subjects who received all doses of study medication, completed all post-Baseline assessments, and were not considered protocol violators.

12.3 DESCRIPTIVE STATISTICS AND GENERAL INFORMATION

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. For categorical variables, summary tables will be provided giving sample size, absolute and relative frequency and 95% Confidence Interval (CI) (if appropriate) for proportions by cohort and treatment group. For continuous variables, summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variation (if appropriate), 25th percentile, median, 75th percentile, minimum, maximum and 95% CI for means of variables (if appropriate) by cohort and treatment group.

Cumulative unblinded reviews of all study data may be performed, at the option of the SMT, at the conclusion of Part A (all SAD data + accumulated Part B/MAD data) and after all subjects have completed 6 months of follow-up in Part B. The data will be analyzed using the SAS® version 9.4 or higher (SAS Institute, Cary North Carolina).

12.4 ANALYSIS OF PRIMARY ENDPOINT (SAFETY)

12.4.1 Adverse Events

Adverse events will be coded according to coding dictionaries (the most updated version of MedDRA) and presented in tables by mSOC and Preferred Term (PT) and by cohort and treatment group. A Summary of Adverse Events table will present the number and percent of patients in each cohort and treatment group with one or more AEs by type of AE (any, serious, drug-related, resulted in death). The number (%) of subjects with incidence of AEs, as well as the severity and relationship to study drug, will be summarized by treatment group, mSOC and PT.

Clinically significant laboratory abnormalities will be reported as AEs. The incidence for each AE will be provided as the total number of subjects that experienced the AE, as well as the percentage of the population that this represents. If an AE is reported more than once during treatment for a given subject, the greatest severity and the worst-case attribution will be presented in the summary tables.

12.4.2 Other Safety Assessments

Additional safety parameters will include physical examination, neurological examination, vital signs, clinical laboratory results, 12 lead ECG, emergence of any

new abnormalities on brain MRI scans (high-res T1, T2*, FLAIR), cognitive assessments and the Columbia Suicidality Rating Scale, all of which will be summarized in appropriate tables by dosing group and time points.

For continuous variables, Baseline and change from Baseline at each post Baseline evaluation will be presented for laboratory safety assessments and CSF cell counts by cohort and treatment group.

Concomitant medication verbatim terms (as recorded on the CRFs) will be coded to Anatomical Therapeutic Chemical (ATC) Level 2 and 4 using the World Health Organization (WHO) dictionary by cohort and treatment group.

12.5 ANALYSIS OF SECONDARY ENDPOINTS

12.5.1 Pharmacokinetic (PK) Parameters

The secondary objective is to assess the pharmacokinetics of IBC-Ab002 following single and multiple ascending doses of IBC-Ab002 in persons with early AD. Analyses of pharmacokinetic parameters will be performed using NCA methods. The goal of the analysis is i) to characterize the IBC-Ab002 PK parameters in the population and ii) to enable selection of doses to take forward in further clinical studies. The following PK parameters will be calculated using NCA methods based on measured IBC-Ab002 concentration in serum:

- Serum antibody concentrations
- Area under the concentration-time curve from time zero to infinity (AUCinf)
- Area under the concentration-time curve from time zero to the time of the last measurable sample (AUClast)
- Maximum observed concentration (Cmax)
- Time to reach maximum observed concentration (Tmax)
- Terminal elimination half-life (T1/2)
- Clearance (CL)
- Volume of distribution (Vd)
- Concentrations of IBC-Ab002 in CSF at selected time points

Individual PK parameters (as mentioned above) will be listed by cohort and treatment group and summarized in tables presenting sample size (N), mean, standard deviation, standard error, median, minimum and maximum values, Coefficient of variation (CV%) and 95% CI for means of variables by cohort and treatment group.

Graphical displays will be generated presenting mean and individual concentration by cohort and treatment group in both linear and semi log scales, as well as individual graphs per subject. Additional analyses of pharmacokinetic parameters will be performed using standard pharmacometric methods. Additional analyses of pharmacokinetic parameters will be performed using standard pharmacometric methods. The goal of the additional analysis is i) to characterize the IBC-Ab002 PK parameters in the population ii) Explore potential effect of ADA on exposure iii) Enable selection of doses to take forward in further clinical studies. The results of

the pharmacometric analysis will be reported elsewhere pending the collection of full PK data set.

Following the first cycle we anticipate generating a reasonable estimation of the population primary PK parameters (CL, Vcentral, etc,) with relative standard error RSE ~35%. Target-mediated drug disposition TMDD (Vm, Km) parameters that can be expected in IBC-Ab002 elimination will be more difficult to assess with one cycle only. However, we expect that the TMDD parameters may be reasonably well captured with three cycles (or more) of treatment (RSE ≤ 50%).

12.5.2 Serological Parameters

The number and proportion of subjects with positive serum anti-IBC-Ab002 antibodies (ADAs) will be summarized by cohort and treatment group along with 95% CI (confidence interval) for proportions.

12.6 ANALYSIS OF EXPLORATORY ENDPOINTS

Our exploratory objective is to evaluate the pharmacodynamic effect of single and multiple doses of IBC-Ab002 in persons with early AD. Both peripheral blood samples for target engagement biomarkers and CSF to evaluate response to AD related biomarkers will be collected. Following the first cycle we anticipate generating only a potential estimation of the population receptor occupancy parameters (IC_{50} for example) with relative standard error (RSE) ~55%. We expect higher accuracy with subsequent cycles with IC_{50} RSE ≤ 25% with ≤ 3 cycles of treatment or more. All exploratory outcomes will be summarized by cohort and treatment group. For categorical variables, summary tables will be provided giving sample size, absolute and relative frequency and 95% CI (if appropriate) for proportions. For continuous variables, summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variation (if appropriate), 25^{th} percentile, median, 75^{th} percentile, minimum, maximum and 95% CI for means of variables (if appropriate).

Due to their invasive nature, the CSF analyses are of necessity limited in number, and therefore analyses are aimed to be primarily descriptive. Inferential testing, when performed, will be for the purposes of guiding the evaluation of relative impact of IBC-Ab002 on the various outcomes and to enable projections of effect sizes to be anticipated in future clinical trials.

12.6.1 Dose-Response

Linear Regression modeling will be applied on efficacy parameters of all treatment groups (6 for each cohort), with cohort as independent variable, for testing the significance (p for trend) of the dose escalating response. If the p for trend is not found significant (no significant trend between cohort's treatment groups), then a comparative pooled analysis between all treatment groups (30 subjects) and all control groups (10 subjects) will be performed on PK and efficacy parameters to increase the study power. In the absence of nominal statistical significance, we plan to incorporate the weight of biomarker evidence, based on estimates of effect size but not statistical significance, into go/no go decision making for advancement of

the program. The final study data will be used to augment the existing PK/PD model which in turn will inform the optimal dose and dose-frequency for Phase 2 testing.

12.6.2 Inferential Testing

As noted above, inferential testing, when performed, will be for the purposes of guiding the evaluation of relative impact of IBC-Ab002 on the various outcomes, and to enable projections of effect sizes to be anticipated in future clinical trials. If and when inferential statistical tests are applied, the resulting p-values will be used to provide guidance as to the relative magnitude of effect of observed differences. All tests will be two-tailed, and a p-value of 5% or less will be considered nominally significant. Comparisons may be made between active and placebo-treated subjects within a dose cohort in the conduct of each SMT review. For summarizing study results at the end of Part A and at the end of Part B, hypothesis testing will also compare subjects in each treatment group to the pooled placebo group.

For continuous variables, including secondary outcomes and all exploratory parameters, the Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the differences within each cohort and within the pooled placebo group.

One-way Analysis of Variance (ANOVA) model will be applied for analyzing the differences of relative change (absolute and percent) between the pooled placebo group and each treatment cohort.

Fisher's Exact test will be applied for testing the statistical significance of the difference in adverse events rates between treatment groups for each cohort and, at the conclusion of the study, between treated subjects in each cohort and the pooled placebo group.

12.7 INTERIM ANALYSIS

A single interim analysis will be performed after all subjects have completed the SAD portion of the study. Dosing of all subjects will continue during the time the analysis is being conducted. The purposes of the analysis will be 1) to summarize all safety, PK and biomarker data in order to inform decisions regarding potential Phase 2 study design and dose selection and 2) to inform a decision regarding expansion of one or more cohorts in the current study to obtain additional safety and bioeffect data on a larger sample of subjects. No futility analysis will be conducted.

Details of interim analyses will be specified in the Statistical Analysis Plan.

13 REGULATORY AND ETHICAL ISSUES

13.1 COMPLIANCE WITH REGULATIONS APPLICABLE TO CLINICAL TRIALS

The study will be conducted according to the laws, regulations, and administrative provisions relating to the implementation of ICH Good Clinical Practice (GCP) in the conduct of clinical trials on medicinal products for human use.

This clinical trial will be registered, at a minimum, on the “ClinicalTrials.gov” clinical trial registry website, EU Clinical Trials Register and the Israeli MoH

clinical trial registry and on other relevant public websites according to national regulations in each participating country.

13.2 INFORMED CONSENT

The principles of Informed Consent, conducted in accordance with Declaration of Helsinki and its updates, current Good Clinical Practice (GCP), the provisions of ICH (International Council on Harmonization), EU Directives and local regulations of all countries and territories in which this clinical trial is being conducted will be strictly followed. A subject is not allowed to enter a clinical study until he/she has been properly informed, has been given time to contemplate participation and has freely given his/her consent by signing and dating the Institutional Review Board/Ethics Committee/ (IRB/EC) approved informed consent form. This must be done prior to performing any study related procedures.

The proposed protocol, consent form and any other subject-facing documents must be submitted to the IRB/EC, together with the relevant study documents and must be approved prior to study start. Initial study ICFs and any ICF updates mandated by protocol amendments or important safety updates may not be presented to participants until EC favorable opinion is received and where required the approval from the Competent Authority.

Copies of all fully signed and dated ICFs will be given to the subject and the original will be maintained at the site.

13.3 SUBJECT CONFIDENTIALITY

Subjects will be assigned a unique identifier and will not be identified by name in the eCRF, study related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or Investigator(s) will be redacted according to applicable laws and regulations.

Subjects must be informed that his/her personal study related data will be used by the Sponsor in accordance with local data protection laws and regulations, as well as institutional policies. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study related data may be examined by the Sponsor, auditors or other authorized personnel appointed by the Sponsor, by appropriate Institutional Review Board members and by inspectors from regulatory authorities.

13.4 INVESTIGATOR(S) QUALIFICATIONS, RESPONSIBILITIES AND AGREEMENTS

The Investigator's qualifications, responsibilities and agreements are listed below:

- The Investigator(s) should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the IRB/EC, and/or the regulatory authority(ies)

- The Investigator(s) should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the Sponsor
- The Investigator(s) should be aware of, and should comply with, GCP and the applicable regulatory requirements
- The Investigator(s)/institution(s) should permit monitoring and auditing by the Sponsor and inspection by the appropriate regulatory authority(ies)
- The Investigator(s) should maintain a list of appropriately qualified persons to whom the Investigator has delegated significant trial-related duties

13.5 INSTITUTIONAL REVIEW BOARD (IRB) / ETHICS COMMITTEE (EC) AND REGULATORY AGENCIES

The study must have unconditional approval in writing by the appropriate authorities and / or Institutional Review Board/Ethics Committee (IRB/EC) of each participating institution. Approval is required for the study protocol, Investigator's Brochure, protocol amendments, ICFs, subject information sheets and advertising materials, in accordance with local regulations. No study drug will be shipped to a site until written IRB / EC authorization has been received by the Sponsor or its representative.

Any amendments to the protocol or subsequent changes to the informed consent form and/or Investigator's Brochure which is approved by the Sponsor must also be approved by the IRB/EC and documentation of this approval must be provided to the Sponsor. Records of the IRB/EC review and approval of all documents pertaining to this study must be kept on file by the Investigator and are subject to the Sponsor's audit and/or regulatory authority inspection during or after completion of the study.

Serious adverse events (SAEs) must also be reported to the IRB/EC by the Investigator or the Sponsor according to local regulations.

The Investigators must submit periodic status reports to their IRB/ECs as required, as well as notification of completion of the study and a final report where applicable.

13.6 PROTOCOL AMENDMENTS

Protocol amendments must be prepared by the Sponsor or designee and approved by IRB/ECs and regulatory agencies if applicable prior to implementation.

The Investigator should not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/EC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects

13.7 LIABILITY AND INSURANCE (IF APPLICABLE)

A Certificate of Clinical Trials Insurance will be provided to the study centers by the Sponsor.

14 DOCUMENTATION

14.1 DATA COLLECTION AND HANDLING

All trial data will be recorded in the appropriate sections of the eCRFs.

All primary laboratory, imaging and cognitive testing results must be kept in each subject's study file to enable source data verification of relevant sections of the Electronic Case Report Form (eCRF).

14.1.1 Data Collection

The Sponsor will provide the study sites with secure access to and sufficient training on the Electronic Data Capture (EDC) application to permit study site personnel to enter or correct information in the eCRFs on the subjects for which they are responsible. Subjects will be identified in the EDC system beginning with the Screening visit by a unique study identifier. Sites will be identified by a 3-digit site code followed by a unique personal identifier. Patient numbers will not include any information that could result in identification of the subject by parties outside the study.

An eCRF will be completed for each subject who provides informed consent, whether eventually randomized to receive study drug or not. For subjects who fail during the Screening process, the EDC will capture only limited information, including the date consent was given, basic demographic information, reason for screen failure, and any AEs or SAEs recorded during the Screening period.

It is the Investigator's responsibility to ensure the accuracy, completeness, clarity and timeliness of the data reported in the subject's eCRF. Source documentation supporting the CRF data will indicate the subject's participation in the study and will document the dates and details of study procedures, AEs, other observations, and subject status.

The Investigator, or designated representative, will complete the eCRF in a timely manner as detailed in the relevant procedures manual.

The Investigator will provide source data/ documents of all the information entered in the eCRFs, including any changes made to the eCRFs, to endorse the final submitted data for the subjects for whom the Investigator is responsible.

The Sponsor will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a CD or other electronic media, in PDF format, will be placed in the Investigator Site File at end of study.

A log will be kept at the study site to record all screen failures and the reason for exclusion of the subjects.

14.1.2 Discrepancy Handling

The study eCRFs/database will be reviewed for any discrepancies and missing data which will be resolved before data lock.

14.1.3 Data Correction/Queries

The study eCRFs/database will be reviewed for any data correction/queries and missing data. All queries will be resolved before database lock.

14.2 MAINTENANCE AND RETENTION OF RECORDS

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations, after the end of the study. At a minimum, unless notified otherwise by the Sponsor, study records must be retained for at least 2 years from the last marketing authorization submission or at least 25 years, whichever is greater, or at least 2 years after notification by the Sponsor of termination of all clinical development programs in all indications for IBC-Ab002.

Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing, and they must receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including, but not limited to, archival arrangements at an offsite facility or transfer of ownership if the Investigator leaves the site. If the site closes during this time period, the Investigator / site must transfer the data to an appropriate data repository designated by the Sponsor.

14.3 DATA PRIVACY PROTECTIONS

Each site will be responsible for maintaining arrangements to comply with the applicable rules on the protection of personal data; in particular, each site must have organizational and technical arrangements that will be implemented to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and processed personal data.

Each site will ensure confidentiality of records and personal data of subjects in accordance with GCP principles. Therefore, any information that could aid in the identification of subjects on an individual basis must not be provided to the Sponsor or the Sponsor's representatives. In the event that such information is inadvertently transferred to the Sponsor or one of the Sponsor's representatives, any such documents must be deleted or destroyed, and the sender will be notified and asked to delete these files from its servers. The sender will be requested to resend the files with the identifying information removed or obscured.

15 QUALITY ASSURANCE

During and/or after completion of the study, quality assurance officers named by the Sponsor or the regulatory authorities may wish to perform onsite audits/inspections.

The purpose of these audits/inspections is to determine whether the study is being conducted and monitored in compliance with the protocol and recognized GCP guidelines and local regulations. Such audits, if necessary, will be pre-arranged with the site and conducted within a reasonable time frame. The Investigator will be expected to cooperate with any audit/inspection and to provide assistance and documentation (including source documentation) as requested.

16 STUDY MONITORING

16.1 CLINICAL SITE MONITORING

Clinical site monitoring is conducted by the study site monitor to ensure that the rights and well-being of trial subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Clinical site monitoring for this study will be performed by representatives of Worldwide Clinical Trials (WCT), the CRO designated by the Sponsor for oversight of this clinical trial.

Monitoring will be performed according to ICH–GCP guidelines, CRO SOPs and according to the Clinical Monitoring Plan for this study. 100% Source Data Verification (SDV) of data related to eligibility (inclusion and exclusion criteria), medical history, prior and concomitant medication, adverse events, laboratory safety, efficacy and endpoints and protocol deviations will be performed.

The study monitors will also review the progress of the study with the Investigator and other site personnel on a regular basis. Sufficient time must be allowed by the site personnel for the monitor to review eCRFs and relevant source documents. The coordinator and/or Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits will be made available by the Investigator.

16.2 PRIMARY SOURCE DOCUMENTS

The Investigator must maintain primary source documents to support eCRF data entries. These original documents, data, and records, which are considered “source data”, may include but are not limited to:

- hospital records
- clinical and office charts
- laboratory notes
- memoranda
- paper copies of data collection forms completed by the subject (if any)
- pharmacy dispensing records
- recorded data from automated instruments
- copies or transcriptions certified after verification as being accurate copies,
- microfiches, photographic negatives, microfilm, or magnetic media
- x-rays, imaging results (CT, MRI, CT-PET, US)
- subject files
- records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial

The Investigator must also retain all subject specific electronic files as well as any printouts/reports of tests/ procedures performed as a requirement of the study.

16.3 eCRF

Data will be collected on the eCRF to document eligibility, safety and efficacy parameters, compliance with treatment schedules and parameters necessary to evaluate the study endpoints.

The applicable eCRF sections will be completed on site by the authorized study member for each visit. All eCRF entries must be based on source documents.

16.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the subjects, the Investigator, or the trial site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. All deviations from the protocol must be addressed in the subject's source documents. All protocol deviations will be reported to the IRB/IECs (and/or regulatory authorities where required) and entered in the Protocol Deviations Log.

Details and specific instructions regarding classification and reporting of protocol deviations will be provided in the relevant procedures manual.

17 USE OF INFORMATION AND PUBLICATION

17.1 Confidential Information

In addition to the confidentiality and publication restrictions pursuant to the agreement which will be signed with the Sponsor or designee, all information that by its nature can be identified as confidential including information which has not been previously published concerning the test product and the Sponsor, including but not limited to subject applications, manufacturing process, basic scientific data, etc., is considered confidential and remains the sole and exclusive property of the Sponsor. The Investigator or qualified designee agrees to use this information only and strictly in connection with this study and must not use it for other purposes without the prior written permission from the Sponsor.

17.2 Publications connected to the clinical trial

The Sponsor has full ownership of the data collected in the Database of the study.

By signing the clinical study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. The authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol. In the event that the Sponsor chooses to publish the data from this study a copy of the manuscript will be provided to all site Investigators for review in advance of the expected date of submission to the intended publisher.

Authorship of the primary study manuscript will be determined by a writing group consisting of representatives of the Sponsor and the individual sites.

Should an individual Investigator wish to publish or present some or all of the results of this study, the Investigator agrees to 1) provide the Sponsor with a manuscript/presentation for review at least 60 days prior to submission for publication/presentation; 2) withhold submission of any such publication until after the main study manuscript has been published; 3) grant the Sponsor access to all analyses generated in the development of the study manuscript; 4) submit the manuscript for review to the Sponsor and the remaining site Investigators prior to publication.

The Sponsor retains the right to delete from the manuscript/presentation information that is confidential or proprietary and to object to a suggested publication and/or its timing at the Sponsor's sole discretion.

In addition, if requested by the Sponsor, the Investigator shall withhold publication/presentation to allow for filing a patent application or taking such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

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APPENDIX A: RECOMMENDED ORDER OF ASSESSMENTS AT EACH VISIT

Please refer to footnotes from Schedule of Events tables

Visit number	Description	Cycle Day	Description of visit activities
Part A (Screening Baseline SAD)			
SCR	Screening	-56 to -8	Informed consent signature Inclusion/exclusion Medical history AE assessment Concomitant Medications Vital signs Weight Physical exam Neurological exam MMSE CDR-SB C-SSRS Laboratory tests - Serum Chemistry, Hematology, viral serologies, COVID PCR and INR Urinalysis Urine Drug Screen Triplicate 12-lead ECG MRI scan – can be done on separate day, but must be obtained and results reviewed prior to LP. Note: MRI should not be scheduled to take place until after results of plasma pTau181 levels are known CSF sampling – may be performed any time within 4 weeks of anticipated first dose, only after MRI results and results of plasma Aβ42:40 ratio and pTau 181 tests have been reviewed EEG/ – may be done on separate day once eligibility is confirmed
BL	Baseline	-8 - -1	* *Baseline assessments may be performed any time during the week (Days -8 to -1) preceding Day 1. Confirmation of continued eligibility, including results of clinical laboratory tests should be available prior to randomization and dose administration on Day 1.* Interval medical history (from last visit) Physical exam Neurological exam Inclusion/exclusion

Visit number	Description	Cycle Day	Description of visit activities
			Genetic sample (APOE and exploratory pharmacogenetic markers) AE assessment Concomitant Medications Vital signs Weight Laboratory tests -Serum Chemistry, Hematology COVID PCR (if required locally) MMSE Cognitive Functional Composite NPI
1	Inpatient Day 1	1	*** Subjects should come to the infusion center/location sufficiently early in the morning so that the study drug infusion should be commenced in order to allow the Hour 6 PK sample can be drawn and processed by the end of the working day* *Admission procedures for the required overnight stay may be completed earlier, or during the period of observation following the completion of dose administration* AE assessment Concomitant Medications Vital signs Triplicate 12 lead ECG Obtain Pre-Dose Laboratory and biomarker tests (may be drawn from IV line before starting infusion): Serum PK, sPD-L1 ADA PBMC isolation Plasma for A/T/N Biomarkers Serum for Inflammation Biomarkers Administer Dose Vital signs: prior to IV insertion, 0.5 hr, 1 hr, 2hr, 3hr, 4hr, 6hr and 10hr after starting infusion Serum PK: At end of infusion (2hr) 6 hours post-infusion Triplicate 12 lead ECG At end of infusion (2hr)

Visit number	Description	Cycle Day	Description of visit activities
			6 hours post-infusion Overnight Inpatient Confinement
2	Inpatient Day 2	2	Physical exam Neurological exam AE assessment Concomitant Medications Vital signs 24hr + 2hr from start of infusion Triplicate 12-lead ECG Serum PK 24hr + 2hr from start of infusion PBMC isolation 24hr + 2hr from start of infusion Discharge from inpatient unit
3	Observation	4	Interval medical history AE assessment Concomitant Medications Vital signs Serum PK, sPD-L1 PBMC isolation Serum for Inflammation Biomarkers
4	Observation	8 ± 1	Interval medical history AE assessment Concomitant Medications Vital signs Serum Chemistry, Hematology Urinalysis Serum PK, sPD-L1 PBMC isolation Serum for Inflammation Biomarkers
5	Observation	15 ± 1	^ *Visit may be conducted at satellite clinic affiliated with the study site if travel is burdensome for the subject, logistics can be arranged, and PI agrees* Interval medical history AE assessment Concomitant Medications Vital signs Serum Chemistry, Hematology Triplicate 12-lead ECG MMSE Serum PK, sPD-L1 PBMC isolation Plasma for A/T/N Biomarkers Serum for Inflammation Biomarkers

Visit number	Description	Cycle Day	Description of visit activities
6	Observation	22 ± 1	*Telephone visit; all assessments to be conducted remotely. Patient presence in clinic not required unless there is an ongoing AE that requires assessment or management* Interval medical history AE assessment Concomitant Medications
7	Observation	29 ± 2	Interval medical history AE assessment Concomitant Medications Vital signs Physical exam Neurological exam Cognitive Functional Composite Serum Chemistry, Hematology Urinalysis Serum PK, sPD-L1 PBMC isolation Plasma for A/T/N Biomarkers Triplicate 12-lead ECG EEG/ C-SSRS
8	Observation	43 ± 2	^ *Visit may be conducted at satellite clinic affiliated with the study site if travel is burdensome for the subject, logistics can be arranged, and PI agrees* Interval medical history AE assessment Concomitant Medications Vital signs Serum PK, sPD-L1 PBMC isolation Plasma for A/T/N Biomarkers INR MRI- may be done ± 2 days from time of scheduled visit
9	Observation	57 ± 2	Interval medical history AE assessment Concomitant Medications Vital signs MMSE C-SSRS Serum Chemistry, Hematology Serum PK, sPD-L1

Visit number	Description	Cycle Day	Description of visit activities
			PBMC isolation Plasma for A/T/N Biomarkers Serum for Inflammation Biomarkers EEG/ CSF sampling
10	Observation	84 ± 2 Conduct same assessments at early termination (ET) visits	***Visit 10 (Day 84) may be split into two portions a maximum of 21 days apart if SMT has not had sufficient time to assess data to render a decision regarding dose escalation/continuation. Should this occur, the dosing portion of the visit will be labeled Visit 10.1. EEG, CFC and NPI do not need to be repeated in Visit 10.1.* Interval medical history AE assessment Concomitant Medications Vital signs Weight Physical exam Neurological exam EEG/ MMSE Cognitive Functional Composite NPI C-SSRS *<u>If Dose 2 is administered:</u>* Triplicate 12 Lead ECG prior to dose Obtain Pre-Dose Laboratory and biomarker tests (Samples may be drawn from IV line before starting infusion): Serum Chemistry, Hematology Urinalysis Serum PK, sPD-L1 PBMC isolation Plasma for A/T/N Biomarkers Serum for Inflammation Biomarkers Administer Dose Vital Signs at end of infusion and 1h after end of infusion Serum for PK to be drawn at end of infusion. (Sample may not be taken from infusion IV line)

Visit number	Description	Cycle Day	Description of visit activities
			If Dose 2 is not to be administered due to delay in SMT Feedback, only the following laboratory and biomarker assessments are to be performed: Triplicate 12-lead ECG Serum Chemistry, Hematology Urinalysis PBMC isolation Plasma for A/T/N Biomarkers Serum for Inflammation Biomarkers
Part B (MAD)			
10.1	Dose 2 Dosing (only if Dose 2 was postponed due to delayed feedback from SMT)	1	***Visit 10 (Day 84) may be split into two portions a maximum of 21 days apart if SMT has not had sufficient time to assess data to render a decision regarding dose escalation/continuation. Should this occur, the dosing portion of the visit will be labeled Visit 10.1. EEG, CFC and NPI do not need to be repeated in Visit 10.1.* Interval Medical History AE assessment Concomitant Medications Vital signs (pre-dose) Weight Physical exam Neurological exam MMSE C-SSRS Triplicate 12 Lead ECG prior to Dose Obtain Pre-Dose Laboratory and biomarker tests (Samples may be drawn from IV line before starting infusion): Serum Chemistry, Hematology Urinalysis Serum PK, sPD-L1 PBMC isolation Plasma for A/T/N Biomarkers Serum for Inflammation Biomarkers Administer Dose Vital Signs at end of infusion and 1h after end of infusion Serum for PK will be drawn at end of infusion. (Sample may not be taken from infusion IV line)

Visit number	Description	Cycle Day	Description of visit activities
11	Dose 2 Observation	8 ± 1	^ *Visit may be conducted at satellite clinic affiliated with the study site if travel is burdensome for the subject, logistics can be arranged, and PI agrees* Interval Medical History AE assessment Concomitant Medications Vital signs Serum PK, sPD-L1 PBMC isolation
12	Dose 2 Observation	29 ± 2	Interval Medical History AE assessment Concomitant Medications Vital signs Physical exam Neurological exam Triplicate 12-lead ECG C-SSRS Serum Chemistry, Hematology Serum PK, sPD-L1 PBMC isolation
13	Dose 2 Observation	57 ± 2	Interval Medical History AE assessment Concomitant Medications Vital signs Serum Chemistry, Hematology Serum PK, sPD-L1
14	Dose 3 Dosing	1	Interval Medical History AE assessment Concomitant Medications Vital signs (pre-dose) Weight Physical exam Neurological exam EEG/ MMSE C-SSRS Triplicate 12 Lead ECG prior to dose Obtain Pre-Dose Laboratory and biomarker tests (Samples may be drawn from IV line before starting infusion): Serum Chemistry, Hematology Urinalysis Serum PK

Visit number	Description	Cycle Day	Description of visit activities
			ADA PBMC isolation Plasma for A/T/N Biomarkers Serum for Inflammation Biomarkers Administer Dose Vital Signs at end of infusion and 1h after end of infusion Serum for PK to be drawn at end of infusion. (Sample may not be taken from infusion IV line)
15	Dose 3 Observation	8 ± 2	^ *Visit may be conducted at satellite clinic affiliated with the study site if travel is burdensome for the subject, logistics can be arranged, and PI agrees* Interval Medical History AE assessment Concomitant Medications Vital signs Serum PK, sPD-L1 PBMC isolation
16	Dose 3 Observation	29 ± 2	Interval Medical History AE assessment Concomitant Medications Vital signs Physical exam Neurological exam Triplicate 12-lead ECG C-SSRS Serum Chemistry, Hematology Serum PK, sPD-L1 PBMC isolation
17	Dose 3 Observation	57 ± 2	Interval Medical History AE assessment Concomitant Medications Vital signs Serum Chemistry, Hematology Serum PK, sPD-L1 C-SSRS
18	Dose 4 Dosing	1	Interval Medical History AE assessment Concomitant Medications Vital signs (pre-dose) Weight Physical exam

Visit number	Description	Cycle Day	Description of visit activities
			Neurological exam EEG/ MMSE C-SSRS Triplicate 12 Lead ECG prior to dose Obtain Pre-Dose Laboratory and biomarker tests (Samples may be drawn from IV line before starting infusion): Serum Chemistry, Hematology Urinalysis Serum PK ADA PBMC isolation Plasma for A/T/N Biomarkers Serum for Inflammation Biomarkers Administer Dose Vital Signs at end of infusion and 1h after end of infusion Serum for PK to be drawn at end of infusion. (Sample may not be taken from infusion IV line)
19	Dose 4 Observation	8 ± 2	^ *Visit may be conducted at satellite clinic affiliated with the study site if travel is burdensome for the subject, logistics can be arranged, and PI agrees* Interval Medical History AE assessment Concomitant Medications Vital signs Serum PK, sPD-L1 PBMC isolation
20	Dose 4 Observation	29 ± 2	Interval Medical History AE assessment Concomitant Medications Vital signs Physical exam Neurological exam Triplicate 12-lead ECGMMSE C-SSRS Serum Chemistry, Hematology Serum PK, sPD-L1 PBMC isolation
21	Dose 4	57 ± 2	Interval Medical History AE assessment

Visit number	Description	Cycle Day	Description of visit activities
	Observation		Concomitant Medications Vital signs Serum Chemistry, Hematology Serum PK, sPD-L1 INR C-SSRS
22	EOS/ET	84 ± 7_EOS Conduct same assessments at early termination (ET) visits	Interval medical history AE assessment Concomitant Medications Vital signs Weight Physical exam Neurological exam Triplicate 12-lead ECG MRI- may be done on different day EEG/ MMSE Cognitive Functional Composite CDR-SB NPI C-SSRS Serum Chemistry, Hematology Urinalysis INR (if LP is performed, review results prior to LP Procedure) Serum PK, sPD-L1 ADA PBMC isolation Plasma for A/T/N Biomarkers Serum for Inflammation Biomarkers CSF sampling (Optional; subject must provide separate consent for this procedure)