NOVARTIS

Novartis Research and Development

ADPT06

Clinical Trial Protocol CADPT06A12201 / NCT04795466

EXploratory PLatform trial on Anti-INflammatory agents in Alzheimer's Disease (EXPLAIN-AD): A randomized, placebo-controlled, multicenter platform study to evaluate the efficacy, safety, tolerability and pharmacokinetics of various anti-inflammatory agents in patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease

Document type:	Amended Protocol Version
EUDRACT number:	2020-003966-38
Version number:	04 (Clean)
Clinical Trial Phase:	IIa
Release date:	15-Sep-2022

Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

Table of contents

Commercially Confidential Information (CCI)

Commercially Confidential Information

List of tables

List of figures

List of abbreviations

AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADL	Activities of daily living
AE	adverse event
Commercially Confidential Information	
ALP	alkaline phosphatase
ALS	Amyotrophic Lateral Sclerosis
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AOSD	Adult Onset Still's Disease
Commercially Confidential Information	
AST	aspartate aminotransferase
AT(N)	Amyloid, tau and neurodegeneration (or neuronal injury)
Aß	Amyloid ß
BUN	blood urea nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale (paper or electronic)
Commercially Confidential Information	
CAPS	Cryopyrin-associated Autoinflammatory Syndrome
CDS	Core Data Sheet (for marketed drugs)
CFT	Category Fluency Test
ChEIs	Cholinesterase inhibitors
CK	Creatinine Kinase
ClinRO	Clinician Reported Outcomes
CMO&PS	Chief Medical Office & Patient Safety
CNS	Central Nervous System
COA	Clinical Outcome Assessments
COWAT	Controlled Oral Word Association Test
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CSR	Clinical study report
CT	Computerized Tomography
CTC	Common Toxicity Criteria
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DDE	Direct Data Entry
DIN	Drug Inducted Nephrotoxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSST	The Digit Symbol Substitution Test

ECG	Electrocardiogram
ECog	Everyday Cognition Scale
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOC	End of Cohort
eSource	Electronic Source
FAS	Full analysis set
FDA	Food and Drug Administration
FMF	Familial Mediterranean Fever
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	hour
HAB	high-affinity binding
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HIDS	Hyperimmunoglobulinemia D syndrome
HIV	human immunodeficiency virus
HRRT	High Resolution Research Tomograph
hsCRP	High-sensitivity C-reactive protein
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

Ig	Immunogenicity
IL	Interleukin
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
MAB	mixed affinity binding

MCI	Mild cognitive impairment
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MKD	Mevalonate Kinase Deficiency
mL	milliliter(s)
MMRM	mixed model with repeated measurements
MMSE	Mini-Mental Status Examination
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis

Commercially Confidential Information

NIA-AA	National Institute on Aging and the Alzheimer's Association
NPI	Neuropsychiatric Inventory
NPI-D	Neuropsychiatric Inventory-Caregiver Distress Scale
NTB	Neuropsychological Test Battery
ObsRO	Observer Reported Outcomes
P-tau	Phosphorylated tau protein

Commercially Confidential Information

PCR	Polymerase chain reaction
PD	pharmacodynamic(s)
PET	Positron Emission Tomography
PK	pharmacokinetic(s)
PPD	purified protein derivative
PT	prothrombin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia’s formula
RA	Rheumatoid arthritis
RAVLT	Rey Auditory Verbal Learning Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	red blood cell(s)
REML	Restricted Maximum Likelihood
RES	reticuloendothelial system
RIP	Respiratory Inductance Plethysmography
RoW	Rest of World
RSI	Reference safety information
s.c.	subcutaneous
SAE	serious adverse event
SBP	Systolic Blood Pressure
sCR	serum creatinine
SD	standard deviation
SJIA	Systemic Juvenile Idiopathic Arthritis
SOC	System organ class

SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
Commercially Confidential Information	
T-tau	Total tau protein
T2DM	Type-2 Diabetes Mellitus
TBL	Total bilirubin
TNF/TNF-α	Tumor Necrosis Factor/Tumor Necrosis Factor-alpha
TRAPS	Tumor Necrosis Factor Receptor-associated Periodic Syndrome
TSH	Thyroid-Stimulating Hormone
Commercially Confidential Information	
ULN	upper limit of normal
UTI	Urinary Tract Infection
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
AT(N) profile	Classifies participants on a syndromal cognitive staging based on the biomarkers Aβ plaques (A), fibrillary tau (T) and neurodegeneration or neuronal injury (N)
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A specific group of participants fulfilling certain criteria. Up to 4 cohorts may be investigated through the duration of the clinical trial program. As noted in the open platform definition, a cohort may contain up to three different investigational agents
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Core EXPLAIN-AD protocol	The first 16 sections of the protocol are the sections of the EXPLAIN protocol that remain constant over the duration of this platform study
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Digital endpoint	Use of wearable sensors to capture objective data throughout a participant's daily life, as compared to subjectively assessing a participant's progress at intermittent appointments
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Early Alzheimer's disease	Mild cognitive impairment due to Alzheimer's Disease and mild Alzheimer's Disease
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol

Enrollment	Point/time of participant entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol). The action of enrolling one or more participants.
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational agent/agent	The drug whose properties are being tested in the study. Also referred to as “Investigational drug/treatment”.
Investigational drug/treatment	The drug whose properties are being tested in the study. Also referred to as “Investigational agent/agent”.
Master Protocol	One overarching protocol designed to answer multiple questions
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). “Participant” terminology is used in the protocol whereas term “Subject” is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Platform trial	A clinical trial studying a range of investigational agents where new investigational agents can be added to the platform trial, in a perpetual manner, at various unspecified time points
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant, corresponding to a specific treatment arm assignment
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A participant who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant

Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Protocol summary

Protocol number	ADPT06A12201
Full Title	EXploratory PLatform trial on Anti-INflammatory agents in Alzheimer's Disease (EXPLAIN-AD): A randomized, placebo-controlled, multicenter platform study to evaluate the efficacy, safety, tolerability and pharmacokinetics of various anti-inflammatory agents in participants with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease
Brief title	Study of the efficacy and safety of various anti-inflammatory agents in participants with mild cognitive impairment due to Alzheimer's disease
Sponsor and Clinical Phase	Novartis Phase IIa
Investigation type	Investigational agent
Study type	Interventional
Purpose and rationale	The purpose of this platform study is to evaluate the effect of anti-inflammatory agents on cognition in early AD. Additionally, the safety and tolerability of these anti-inflammatory agents and the effects on central and peripheral inflammation will be evaluated. The study is designed to safely allow rapid and efficient screening of potentially efficacious agents in participants with early AD.
Primary Objective(s)	To compare the effects of each individual agent vs placebo on cognition in early AD using the Neuropsychological Test Battery (NTB) score at 24 weeks.
Secondary Objectives	To investigate the safety (AEs) and tolerability of each individual agent vs placebo using ECG measurement and findings; adverse events and serious adverse events; laboratory measurements; vital signs; physical examination measurements; and prospective suicidality assessment (ideation and behavior) from the eC-SSRS; To investigate the effects of each individual agent vs placebo in lowering central inflammation using reduction of microglial activation measured by Positron-Emission Tomography CCI (PET CCI) following the initial 12-weeks of treatment in a subset of participants; To explore the effects of each individual agent vs placebo on neuropsychiatric symptoms using the Neuropsychiatric Inventory (NPI-D) total score at 24 weeks and the eNeuropsychiatric At-Home Caregiver assessment score at 12 weeks; To compare the effects of each individual agent vs placebo on function (activities of daily living) using the Everyday Cognition (eCog) scale at 24 weeks; To compare the effects of each individual agent vs placebo on memory and executive function using the NTB memory and executive function composites at 24 weeks; Digit Symbol Substitution Test (DSST) at 24 weeks; and the eCognitive at-home assessment at 12 weeks; To determine the pharmacokinetics of each individual agent using the agent concentration in serum (for biotherapeutic agents) or plasma (for low molecular weight agents) and in cerebrospinal fluid (CSF); and the ratio of agent concentration in CSF to that in serum (for biotherapeutic agents) or plasma (for low molecular weight agents); To determine the total target and immunogenicity of each individual biotherapeutic agent using CCI ; and anti-agent antibodies in serum.

Study design	This is a randomized, placebo-controlled, participant, and investigator-blinded platform study in participants with MCI due to AD or mild AD who have evidence of peripheral inflammation. Each cohort in the study will undergo the same study evaluations and assessments. Each cohort will include a screening period (Day –60 to Day –8), followed by a baseline period of 7 days (Day –7 to Day -1), a treatment period of 20 weeks (Day 1 to Day 141), and a study completion evaluation (End of Cohort [EOC1]) at minimum 30 days after the last agent administration (Day 171). For agents with longer half-lives, such as monoclonal antibodies, the same study design will be followed; however, an additional post-treatment follow-up visit (EOC2) will occur on Day 281. In addition, a sub-set of these same participants (up to 22 per investigational agent/matching placebo) will undergo PET CCI imaging at baseline and following completion of the first 12 weeks treatment. Alterations in activated microglia and astrocytes due to therapeutic intervention will be measured using a PET CCI . PET imaging in this subset of participants and analysis of CSF and/or serum samples in all participants will provide measures of both central and peripheral inflammation following treatment with an investigational agent. Commercially Confidential Information .
Population	Each cohort will enroll approximately 86 male and female amyloid- and tau-confirmed early AD participants aged between 45 years old and 90 years old with evidence of peripheral inflammation as evidenced by elevated CC levels in serum. I
Key Inclusion criteria	1. Male or female, age ≥ 45 years and ≤ 90 years at the time of signing the informed consent. 2. Participant has a reliable study partner or caregiver (e.g., spouse, sibling, close friend) who, in the investigator's judgement, has frequent, direct contact with the participant at least several days a week, can accompany the participant to all visits, is fluent in and able to read the local language in which study assessments are administered, and is also able to provide information to study investigator/staff. All effort should be made to keep the same study partner throughout the duration of the study. 3. A diagnosis of probable MCI due to AD or mild AD according to the National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria at screening and at least a 6 month decline in cognitive function prior to screening documented in the medical record. 4. Confirmed amyloid and tau positivity via CSF sampling performed at screening. Historical data cannot be used except for potential re-screened participants approved by Sponsor that had CSF sample previously analyzed by Central lab for EXPLAIN-AD study; all participants must have confirmed positivity of (A) CCI . In addition, all participants must have confirmed positivity in **one** of the following Tau markers: (T) CCI as determined by the central laboratory, in order to further classify the participants using the AT(N) profile. 5. Commercially Confidential Information

	6. Mini-Mental State Examination (MMSE) total score of 20 to 24 (inclusive) at screening; OR, MMSE total score of 25 to 30 (inclusive) plus a DSST score at least 0.5 standard deviation (SD) below normative data at point of screening. 7. For participants undergoing PET CCI : Participants with a binding pattern of high affinity binding (HAB) or mixed affinity binding (MAB) CCI -binding profile phenotype can undergo PET CCI imaging in this study. Genotyping will be performed at screening by the Central Laboratory. Those who are low-binding affinity phenotype can continue participation in the cohort, but not undergo the PET CCI .
Key Exclusion criteria	1. Use of an investigational agent or an approved product with the intent to modulate inflammation or modulate the course of AD (e.g., Tau ASOs, gene therapy, amyloid or tau vaccine): • previous use of small molecules is allowed if discontinued for at least five half-lives, or at least 30 days from when the expected pharmacodynamic effect has returned to baseline, whichever is longer • previous use of monoclonal or polyclonal antibodies, or other biologics is allowed if discontinued for at least five half-lives prior to screening. 2. Current medical or neurological condition that in the judgement of the investigator might impact cognition or performance on cognitive assessments, e.g., MCI not due to AD, non-Alzheimer dementia, Huntington's disease, Parkinson's disease, stroke, schizophrenia, bipolar disorder, active major depression, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), active seizure disorder, or history of traumatic brain injury associated with loss of consciousness and ongoing residual transient or permanent neurological signs/symptoms including cognitive deficits, and/or associated with skull fracture. 3. Diagnosis of vascular dementia prior to baseline (e.g.., modified Hachinski Ischaemic Scale score > 6 or those who meet the NINDSAIREN criteria for vascular dementia); 4. At the time of screening for participants undergoing PET CCI , and only if a historical (within 2 years) MRI of the brain is not available: Unable to undergo MRI due to, for example, claustrophobia, or presents absolute contraindications to MRI (e.g. brain aneurysm clip, implanted cardiac pacemaker, pacemaker wires or defibrillator, prosthetic heart valves, cochlear implant, implanted insulin pump, metallic implants, metallic foreign bodies, tattoos (as determined by radiologist)).
Study treatment	A range of investigational agents will be added to each cohort (placebo and active agent) that can enter the platform trial in a perpetual manner and at various unspecified time points.
Efficacy assessments	Assessments of cognition will include the Neuropsychological Test Battery (NTB), the Digit Symbol Substitution Test (DSST), CCI , at-home eCognitive testing; Assessments of neuropsychiatric symptoms and function will include the Neuropsychiatric Inventory - Caregiver Distress Scale, between clinic visit monitoring of changes in mood and neuropsychiatric symptoms, and the Everyday Cognition Scale (eCog - Study partner).

Pharmacodynamic assessments	For biotherapeutic agents, serum and CSF samples will be evaluated for total CCI concentration CCI as a PD marker for CCI .
Pharmacokinetic assessments	Agent concentrations will be assessed in serum (for biotherapeutic agents) or plasma (for low molecular weight agents) and CSF for all agent treated participants.
Key safety assessments	Physical examination; vital signs; laboratory evaluations; electrocardiogram (ECG); pregnancy and assessments of fertility; eC-SSRS.
Other assessments	Commercially Confidential Information
Data analysis	The study research hypothesis is that each investigated anti-inflammatory agent provides an improvement over placebo in NTB response at 24 weeks. The change from baseline in NTB total z-score will be analyzed using a restricted maximum likelihood (REML)-based mixed model with repeated measurements (MMRM), using FAS dataset. The model will include fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline and baseline-by-visit interaction. The model will also adjust for several important baseline prognostic factors, such as age and MMSE score. Unstructured covariance will be used to model within-participant errors, with Kenward-Roger approximation to estimate denominator degrees of freedom. If the unstructured covariance causes model convergence issues, then other simpler covariance structures will be considered. Least squares mean, the associated 2-sided 90% confidence interval and the p-value will be obtained for each treatment at each visit. The primary comparison will be the contrast between active treatment and placebo at 24 weeks. Both cohort-wise and combined cohort analysis (i.e. pooling placebo data across different cohorts) will be performed.
Key words	Alzheimer's disease; mild cognitive impairment; inflammation; cognition; PET CCI

1 Introduction

1.1 Background

Alzheimer's disease (AD)

Alzheimer's disease (AD) is a terminal neurodegenerative disorder characterized by progressive loss of cognitive function and independence. AD is the most common cause of dementia affecting approximately 50 million people worldwide (Prince et al 2015). With a rising proportion of older adults, it has been estimated that this number may double every 20 years (Prince et al 2015).

AD is associated with a long prodromal phase and a slow, insidious disease progression. While cognitive symptoms may start out as mild memory and executive functioning anomalies, with time, almost all cognitive domains become compromised. This steady cognitive decline slowly renders the individual incapable of carrying out basic activities of daily living and ultimately leads to complete reliance and placement in a nursing home or other long-term care facility.

The long duration of illness before death contributes significantly to the tremendous caregiver and societal burden associated with AD.

As such, AD remains one of the highest unmet medical and societal needs. With a 99.6% trial failure rate and no available treatment to slow, stop or prevent the disease, today's drug development in AD needs more innovative trial designs, endpoints, novel biomarkers and therapeutic targets. Although recent efforts have largely focused on discovering disease-modifying treatments, there continues to be a high-unmet need for improved symptomatic treatment of AD.

Accumulating evidence points towards neuroinflammation as a key mechanism in the pathogenesis of AD. In vitro and in vivo models suggest that misfolded and aggregated proteins trigger an innate immune response and increase the levels of inflammatory mediators in the brain, which contribute to disease severity and progression. Several genes involved in glial clearance of misfolded proteins and inflammatory reaction have been associated with increased risk of AD. In addition, in the absence of neuroinflammation, clinical symptoms of dementia do not occur in individuals with high plaque load and high Braak stages of neurofibrillary tangles (Perez-Nievas et al 2013). Moreover, apolipoprotein E4 (ApoE4) positive individuals with chronic low-grade inflammation have been found to be at a significantly higher risk of AD and an earlier disease onset compared with ApoE4 carriers without chronic inflammation (Tao et al 2018). Numerous studies suggest that chronic systemic inflammatory conditions such as periodontitis (Teixeira et al 2017), rheumatoid arthritis (Chou et al 2016) and sleep apnea (Polsek et al 2018) are likely to affect the immunological processes of the brain and further promote AD progression. In addition, an anti-Tumor Necrosis Factor (TNF) compound, etanercept, was associated with lowered risk of AD among rheumatoid arthritis participants (Chou et al 2016). Finally, asthma drugs have been shown to reduce levels of amyloid beta (Aß) in rodent models (Hori et al 2015), as well as modulate microglia activation and apoptosis (Zhang et al 2018; Wang et al 2014).

The EXPLAIN-AD study (EXploratory PLatform trial on Anti-INflammatory agents in Alzheimer's Disease) is designed to measure the efficacy and safety of various anti-inflammatory agents in participants with mild cognitive impairment (MCI) due to AD and mild AD.

Commercially Confidential Information

1.2 Purpose

The purpose of this platform study is to evaluate the effect of anti-inflammatory agents on cognition in early AD. Additionally, the safety and tolerability of these anti-inflammatory agents and the effects on central and peripheral inflammation will be evaluated.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To compare the effects of each individual agent vs. placebo on cognition in early AD	• The Neuropsychological Test Battery (NTB) score at 24 weeks
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To investigate the safety (AEs) and tolerability of each individual agent vs placebo	• ECG measurements and findings; • Adverse events and serious adverse events; • Laboratory measurements; • Vital signs; • Prospective suicidality assessment (ideation and behavior) from electronic Columbia Suicide Severity Rating Scale (eC-SSRS).

Objective(s)	Endpoint(s)
• To investigate the effects of each individual agent vs placebo in lowering central inflammation	• Reduction of microglial activation measured by Positron-Emission Tomography CCI (PET CCI) following the initial 12-weeks of treatment in a subset of participants
• To explore the effects of each individual agent vs placebo on neuropsychiatric symptoms	• The Neuropsychiatric Inventory (NPI-D) total score at 24 weeks • eNeuropsychiatric At-Home Caregiver assessment score at 12 weeks
• To compare the effects of each individual agent vs placebo on function (activities of daily living) • To compare the effects of each individual agent vs placebo on memory and executive function	• The Everyday Cognition (ECog) scale at 24 weeks • The NTB memory and executive function composites at 24 weeks • DSST at 24 weeks • eCognitive at-home assessment at 12 weeks
• To determine the pharmacokinetics of each individual agent	• Agent concentration in serum (for biotherapeutic agents) or plasma (for low molecular weight agents) and in cerebrospinal fluid (CSF) • Ratio of agent concentration in CSF to that in serum (for biotherapeutic agents) or plasma (for low molecular weight agents)
• To determine the total target and immunogenicity of each individual biotherapeutic agent	• Commercially Confidential Information • Anti-agent antibodies in serum (when applicable)

Commercially Confidential Information

Commercially Confidential Information

3 Study design

This is a randomized, placebo-controlled, participant- and investigator-blinded platform study in participants with MCI due to AD or mild AD who have evidence of peripheral inflammation.

The EXPLAIN-AD study uses a platform type design to investigate "multiple targeted therapies in the context of a single disease in a perpetual manner" (Woodcock and LaVange 2017).

Commercially Confidential Information

For each completed cohort, the data analysis will be performed upon final database lock for the cohort, and the results will be reported upon completion of each cohort in an end of cohort report.

Each cohort in the study will undergo the same study evaluations and assessments. Each cohort will include a screening period (Day -60 to Day -8), followed by a baseline period of 7 days (Day -7 to Day -1), a treatment period of 20 weeks (Day 1 to Day 141), and a study completion evaluation [End of Cohort (EOC1)] approximately 30 days after the last agent administration (Day 171). For agents with longer half-lives, such as monoclonal antibodies, the same study design will be followed; however, an additional post-treatment follow-up visit (EOC2) will occur on Day 281.

Participants who meet the eligibility criteria at screening will have baseline assessments performed. All baseline safety evaluation results must be available prior to randomization. All participants will undergo assessments of cognition, neuropsychiatric symptoms and function (activities of daily living) at various time points throughout the duration of the trial.

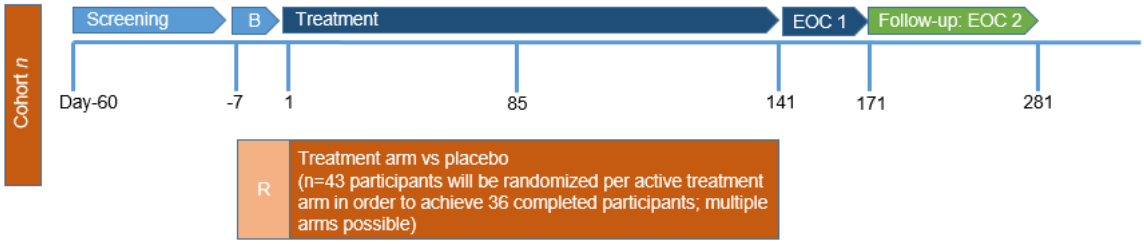
Moreover, all participants will undergo CSF sampling at screening and following completion of 12 weeks treatment. In addition, blood samples will be collected throughout the study (see Table 8-1 assessment schedule and Section 17 agent-specific sample collection table).

In addition, a sub-set of these same participants (up to 22 per investigational agent/matching placebo) will undergo PET CCI imaging at baseline and following completion of the first 12 weeks treatment. Alterations in activated microglia and astrocytes due to therapeutic intervention will be measured using a PET CCI radioligand, CCI . PET imaging in

this subset of participants and analysis of CSF and/or serum samples in all participants will provide measures of both central and peripheral inflammation following treatment with an investigational agent/matching placebo. Commercially Confidential Information

The study design is described in Figure 3-1.

Figure 3-1 Study design schematic



B = Baseline
R = Randomization
EOC = End of cohort

Randomization for any participant can occur after informed consent is obtained and eligibility is confirmed, ideally as close to Day 1 as possible. Participants will be randomized into any of the treatment arms open to enrolment for which the participant meets the eligibility criteria.
Treatment arm(s) will be defined for each cohort.
EOC2 visit only required for an extended half-life. For all other treatments, EOC1 will serve as End of Cohort visit.

4 Rationale

This study is designed to safely allow rapid and efficient screening of potentially efficacious agents in participants with early AD. The rationale for key aspects of the design is provided below.

4.1 Rationale for study design

Evidence continues to accumulate showing the critical role inflammation plays in the pathogenesis of AD. While several inflammatory mechanisms have been identified as potential therapeutic targets, it is currently unknown if one pathway is superior to another. Novartis has several anti-inflammatory agents in its portfolio that are well situated to be studied in AD. By applying a platform study protocol, Novartis can potentially assess multiple investigational agents, in a perpetual manner, in a single trial. This is considered an efficient way to screen for agents that suggest high efficacy (Woodcock and LaVange 2017).

Platform designs allow for the removal of investigational agents based on emerging data, and facilitates introduction of new agents by protocol amendment. Moreover, platform designs may allow for a reduced number of placebo participants as well as the potential to compare between cohorts and/or agents tested. Master protocol designs also offer potential advantages to participants in that they have the ability to use fewer participant resources, provide greater opportunity to be on active agent, and reach conclusions more quickly than traditional clinical trials. In the EXPLAIN-AD study, continuity of sites, including sites performing PET CCI , a central imaging reader, and central labs across all cohorts and

investigational agents will specifically contribute to this master protocol advantage. In oncology, where master protocols are more frequently utilized, a review article suggested that master protocols also decrease heterogeneity of the study population, allowing for a more targeted approach to disease subtypes (Bitterman et al 2020).

Commercially Confidential Information

All of these aspects of master protocol design, as well as an enriched ability to learn from parallel or prior cohorts within these trials, provide a strong rationale to apply this novel trial design to an area of high unmet need, such as AD.

Addition of new cohorts to the platform study occurs through protocol amendments. The core part of the EXPLAIN-AD platform protocol (Section 1 through Section 16) is not expected to significantly change over time. New agent-specific information is added to Section 17 using self-contained, cohort-specific modules in the form of amendments. This modular approach is expected to provide a consistent, reliable approach to adding new treatment cohorts.

The cohort-specific modules (Section 17) will contain the mechanism of action, non-clinical information, proposed dose and dosing regimen, and rationale for each investigational agent including anticipated safety, potential agent-agent interactions, unique inclusion or exclusion criteria, unique stopping rules or dose reduction criteria and other treatment specific information.

4.2 Rationale for Study Population

This platform trial will only include amyloid and tau confirmed early AD participants (MCI due to AD; stage 3 and mild AD; stage 4) with evidence of peripheral inflammation CCI . This is in order to target individuals with the greatest likelihood of showing symptomatic enhancements from an anti-inflammatory treatment intervention.

The rationale for intervening during the early stages of AD is partially based on CCI PET imaging studies demonstrating evidence of brain inflammation increasing as disease progresses. Neuroinflammation, as an early feature of AD, can already be detected in the MCI stage prior to the onset of dementia (Bradburn et al 2019; Nordengen et al 2019; Parbo et al 2017).

Moreover, researchers have proposed that previous anti-inflammatory trials may not have been intervening early enough in the disease and therefore may not have been able to demonstrate beneficial drug treatment effects (King et al 2019).

According to the FDA's guidance for industry "U.S. Food and Drug Administration Center for Drug Evaluation and 2018," drug development in participants who are early in the disease is advantageous for several reasons, including "the development of characteristic pathophysiological changes that greatly precede the development of clinically evident findings and the slowly progressive course of AD."

Participation in this platform trial requires that participants have AD. A clinical diagnosis of AD is not considered sufficient to reliably identify individuals with AD pathology. Confirmation of CSF amyloid and tau is considered crucial to establishing a robust diagnosis of AD. Clinically diagnosed MCI, without any biochemical verification, is an especially heterogeneous condition, which may result from various brain disorders such as AD, depression, traumatic brain injury, the prodromal phase of frontotemporal dementia and dementia with Lewy bodies. Commercially Confidential Information

Commercially Confidential Information

Clinical Staging

MCI/Stage 3

- Performance in the impaired/abnormal range on objective cognitive tests;
- Evidence of decline from baseline, documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral assessments;
- May be characterized by cognitive presentations that are not primarily amnestic;
- Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, that is, may take more time or be less efficient but still can complete, either self-reported or corroborated by a study partner.

Mild AD/Stage 4:

- Mild dementia;
- Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing;
- Clearly evident functional impact on daily life, affecting mainly instrumental activities. No longer fully independent/requires occasional assistance with daily life activities (Jack et al 2018).

4.3 Rationale for Objectives (Endpoints)

Primary Endpoint

The success of each individual agent tested in EXPLAIN-AD will be determined by a positive result on the NTB total score, the primary endpoint of this study. The NTB is a widely accepted and validated test battery that has been used in numerous industry-sponsored clinical drug trials in AD.

The NTB was selected as the primary endpoint of EXPLAIN-AD primarily for the three reasons detailed below:

Firstly, the NTB allows examination of pro-cognitive agent effects using a well-established neuropsychological assessment with psychometric properties suitable for the early stages of AD (Harrison et al 2007). In comparison, the psychometric limitations of the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog) in participants with early AD are well-recognized (Karin et al 2014).

Secondly, the NTB is a composite of multiple globally-established neuropsychological tests that provide a thorough assessment of the cognitive domains affected by early AD, in particular, memory, executive function, attention and verbal fluency.

Commercially Confidential Information

Thirdly, the NTB has shown good assay sensitivity to symptomatic treatment effects in AD drug intervention trials where other endpoints have failed (Karin et al 2014; Gilman et al 2005).

The NTB sub-tests selected for this trial include the Rey Auditory Verbal Learning Test – immediate and delayed recall (RAVLT-I and RAVLT-D), Wechsler Memory Scale – Digit Span (WMDS), Controlled Word Association Test (COWAT) and Category Fluency Test (CFT).

The NTB is administered directly to the participant by a trained test administrator. The total administration time is estimated to take 35 min on average. Scores of each of the individual sub-tests in the NTB are standardized into z-scores and then added up to provide an overall total score for the NTB.

Secondary Endpoints

Key secondary objectives of EXPLAIN-AD (listed in Table 2-1) are to determine the safety of each individual agent and to demonstrate how each individual agent affects imaging markers of inflammation in early AD.

Safety and tolerability of each agent will be evaluated via adverse events, laboratory measurements, vital signs, physical examination, ECG findings and suicidality assessment.

PET CCI will be examined in a subset of participants CCI . The PET CCI signal is considered a marker of central inflammation (a marker for activated microglia and astrocytes) and the signal strength has been shown to correlate with

worsening clinical severity in participants with MCI or AD, measures of cognition and various clinical scores (Zou et al 2020; Kreisl et al 2016; Kreisl et al 2013). Sample size calculations suggest that PET CCI imaging requires smaller sample sizes than other endpoints in this study, in order to be statistically powered to detect agent treatment effects (see Section 12.8.2).

Changes in microglia activation will be assessed in whole, regional and focal brain regions from baseline to completion of week 12. For each agent, a positive readout on PET CCI will be considered as proof of mechanism.

Additional Secondary Endpoints

EXPLAIN-AD will explore the symptomatic effect of each investigational agent on neuropsychiatric symptoms in early AD. Neuropsychiatric symptoms are hallmarks of AD with more than 90% of participants experiencing neuropsychiatric disturbance at some stage of the disease. Neuropsychiatric disturbances cause substantial distress for participants and caregivers and contribute to early institutionalization.

An anti-inflammatory cytokine, IL-10, has been negatively correlated with NPI-total, agitation and night-time behavior (Holmgren et al 2014), while pro-inflammatory cytokines, such as TNF-α,have been linked to increased anxiety, depression and agitation in AD (Holmes et al 2011). A phase 2 trial on a TNF-α inhibitor in mild to moderate AD showed trends towards positive treatment effects on neuropsychiatric symptoms in mild to moderate AD (Butchart et al 2015).

The Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D) is an instrument to screen for changes in behavior and psychiatric well-being. Twelve neuropsychiatric domains are assessed in the NPI-D: delusions, apathy, hallucinations, disinhibition, agitation, irritability, depression, aberrant motor behavior, anxiety, nighttime behaviors, euphoria and appetite and eating changes. The NPI-D is a study partner reported outcome measure and the total score (ranging from 0-144 with a higher score suggesting more behavioral disturbances) is based on frequency (1= rarely, 2=sometimes, 3=often, 4=very often) and severity (1=mild, 2=moderate, 3=severe) of each neuropsychiatric domain. The NPI-D also provides a separate caregiver distress score for each of the neuropsychiatric domains, ranging from 0=not at all, to 5=very severely or extremely.

Commercially Confidential Information

EXPLAIN-AD seeks to evaluate the effects on each investigational agent on function (i.e. activities of daily living) in early AD.

The ECog scale measures cognitively-relevant everyday abilities and is comprised of 39 items covering six cognitively-relevant domains: Everyday Memory, Everyday Language, Everyday Visuospatial Abilities, Everyday Planning, Everyday Organization, and Everyday Divided Attention (Farias et al 2008).

The questionnaire is a self-reported measure and can be completed by both the participant (ECog-participant) and/or study partner (ECog-informant). However, as “lack of insight” is a common feature in early AD (Vogel et al 2004) and in order to reduce participant burden, only

the ECog-informant version will be used in EXPLAIN-AD. Within each domain, ability to perform a specific task is rated on a six-point scale ranging from: 1) no difficulty, 2) mild difficulty, 3) moderate difficulty, 4) severe difficulty, or 5) unable to do. The total score for the 39 items ranges from 39 to 195, with greater scores indicating worse function.

Because inflammation has been strongly associated with executive function and memory, EXPLAIN-AD will examine the treatment effects of each individual agent on NTB total score (primary endpoint) as well as the Memory and Executive function sub-composites of the NTB (secondary endpoint). Scores of each of the individual sub-tests in the NTB are standardized into z-scores and then added up to provide an overall total score as well as total scores for the Memory and Executive function sub-composites.

EXPLAIN-AD will further explore any treatment effects of each investigational agent on a globally-recognized test of executive function; The Digit Symbol Substitution Test (DSST; Winblad et al 2008).

Moreover, at-home eCognitive assessments Commercially Confidential Information will be deployed in EXPLAIN-AD in order to allow more frequent monitoring of cognition in a more natural setting (see Table 8-1 and Section 8.3.6 for more details).

Commercially Confidential Information

Commercially Confidential Information

4.4 Rationale for Selection of Drugs

This study is designed to test a number of different investigational agents. Each of the candidate agents to be studied must have the following attributes:

- Prospect of lowering central inflammation in AD based on preclinical and/or clinical studies;
- Prospect of clinically meaningful benefit in AD based on mechanism of action and pathway biology;
- Healthy participant PK, safety and tolerability data available for each investigational agent at comparable or higher exposure;
- Sufficient toxicology coverage for the 6-month treatment period.

4.5 Rationale for Study Follow-up Period

All participants receiving treatment in this study should have safety evaluations and collection of concomitant treatments and/or adverse event data until the predefined end of cohort date for each investigational agent. Please refer to Section 9.1.1 for details pertaining to early study discontinuation and associated safety follow-up.

For monoclonal antibodies, and other biologic agents with a long half-life, the end of cohort completion visit (EOC2) will be extended to day 281. The rationale for extending this is based on the following: 1) the typical half-life of a monoclonal antibody is approximately four weeks, 2) assuming monthly dosing of the monoclonal antibody, the duration of time between last dose on week 20 and EOC2 is 20 weeks, and 3) 20 weeks would be approximately 5 half-lives after last dose, which is the longest duration of safety observation expected to be required of any agent to be included in the study.

4.6 Rationale for dose/regimen and duration of treatment

Please refer to Section 17 (cohort-specific information) for a detailed rationale of each investigational agent.

In general, the dose of the agent to be studied will be chosen based on an evaluation of all available preclinical and/or clinical data to ensure target or pathway modulation and acceptable safety and tolerability and will be detailed in the corresponding Section 17. Dosing will be optimized for CNS exposure to the agent.

Commercially Confidential Information

In this study canakinumab will initially be administered subcutaneously at a dose of 150mg at day 1 and day 29, and then at the highest approved dose (300mg) every 4 weeks from day 57.

Twenty-four weeks is considered the shortest study duration that will allow measurable changes in improvement of endpoints including cognitive performance in the study population (Cummings 2008). Thus, the entire study duration, which includes a twenty week treatment period, will be at minimum twenty-four weeks.

4.7 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Matching placebo will be used in a participant and investigator-blinded fashion within each cohort. The use of a placebo control is considered essential to ensure study validity and allow for appropriate assessments of safety and tolerability data as well as efficacy data (see Section 17.1 for agent-specific treatment vs placebo randomization allocation). No active comparator is used in this study.

4.8 Purpose and timing of interim analyses/design adaptations

Commercially Confidential Information

4.9 Risks and benefits

Detailed descriptions of the expected safety, tolerability and efficacy characteristics of each investigational agent can be found in Section 17.

The key risks associated with participation in the EXPLAIN-AD study and their mitigation include:

1. Adverse events often related to lumbar puncture include local pain from the procedure, headaches, infection and meningitis. This will be monitored throughout the study. Each CSF sample collected in the study will be analyzed for safety labs.
2. For the subset of participants undergoing PET scanning, this clinical study will involve exposure to radiation. Published dosimetry for CCI (Brown et al 2007) shows a total maximal amount of radiation exposure per participant in the study from the PET scans will be approximately7.9 mSv (790 mrem) if the maximal injected radioactivity (600 MBq) is injected. This amount of radiation is equivalent to approximately 2.6 years

of exposure to background radiation (average yearly background dose is approximately 3 mSv in the US). If a low dose CT scan is acquired for attenuation correction, the maximal total radiation exposure will be approximately 9.3 mSv (930 mrem). This amount of radiation is equivalent to approximately 3.1 years of exposure to background radiation. For effective radiation doses between 3 mSv (300 mrem) and 50 mSv (5000 mrem), the risk is considered to be minimal. The local regulations apply and the effective dose will vary depending on the average and approved injected radioactivity at a given imaging site. Therefore, the radiation exposure in this study involves minimal risk and is necessary to obtain the desired research information.

3. This study allows enrolling women of childbearing potential and sexually active males, and the treatments may involve unknown risks to the fetus if pregnancy were to occur during the study. Women of child-bearing potential and sexually active males (if male contraception is required for the agent) must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study. Therefore, this risk is mitigated by requiring proof the participant is not pregnant prior to start of treatment and requiring either effective contraception during and, for an appropriate interval, after treatment, as appropriate for each investigational agent. See Section 17 for further details on contraception requirements for each agent and note that male contraception may not be required depending on the agent.

Based on the above risk considerations, additional safety measures employed in EXPLAIN-AD include, but are not limited to:

- The study employs safety management measures, which are considered relevant and appropriate for this participant population and protocol to facilitate safe conduct of the study.
- The study will only be conducted by investigators who have broad experience with participants who have dementia and multiple comorbidities and concomitant medications.
- Participants with advanced AD will not be enrolled.
- Specific exclusion criteria, prohibited medications and dietary restrictions will be put in place that are pertinent to each agent being tested.
- This protocol pre-specifies both liver and renal events requiring intervention (Section 16.2 and Section 16.3, respectively).
- The study will also be monitored by an external Data Monitoring Committee (DMC) Section 10.3, which will provide an additional layer of oversight for safety events. For further details, please refer to Section 10.2 and the standalone Safety Surveillance Plan.

There is no direct benefit expected for participants in the study; however:

1. Study participants will receive a potentially efficacious treatment; where currently, limited treatment options are available. Over the duration of the study, participants may have the clinical benefit of improvement in cognition and neuropsychiatric symptoms associated with AD.
2. Study participants will contribute to the potential identification of efficacious therapies for treatment of AD, which has a high unmet medical need and increasing prevalence.

4.9.1 Potential risk associated with the COVID-19 Pandemic

Novartis is committed to supporting the safety and well-being of our study participants, investigators, and site staff. All local regulations and site requirements are being applied in the countries that are affected by the COVID-19 pandemic, including COVID-19 testing of participants if applicable. The Novartis clinical trial team will review the situation in each participating country and work with investigators to continue to ensure the safety of participants during the conduct of the trial. A benefit/risk assessment has been made and has been determined to be positive for the participants to be enrolled. As the COVID-19 situation evolves, investigators must use their best judgment to minimize risk to participants during the conduct of the study.

4.9.2 Potential risks associated with arterial cannulation

Arterial line placement is considered a safe procedure, with a low rate of major complications. However, it is not entirely without risk. Arterial cannulation may cause mild-to-moderate pain, hematoma, inflammation, bleeding or bruising at the puncture site. It may also cause spasm or clotting of the artery with a temporary decrease in blood flow. In rare instances, blocking of the artery, tearing of the artery, arterial leakage, poor healing or infection at the site of the catheter insertion may occur.

Risks are minimized by having the procedure performed by an experienced health care professional. Pain is minimized by using a local anesthetic. Infection can be avoided by cleansing of the skin prior to catheter insertion.

4.9.3 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 231 days (33 weeks) for small molecules and 285 days (approximately 41 weeks) for large molecules from each participant as part of the study. Additional samples may be required for safety monitoring. The total volume of blood is not to exceed 430 mL per agent within a cohort. A participant will be randomized to one agent only.

Timings of blood sample collection are outlined in the assessment schedule (Table 8-1) and in Table 17-4 in Section 17 of the protocol describing agent-specific blood and CSF collection.

A summary blood log is provided in the SOM. Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and central laboratory manual. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

4.9.4 CSF sample volume

A volume of approximately 12 mL of CSF is planned to be collected from all participants at screening and again following completion of 12 weeks resulting in a total of approximately 24 mL of CSF

throughout the cohort. Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and central laboratory manual. Lumbar puncture procedures will be performed by qualified site staff using local site procedures.

5 Population

The study population will consist of cognitively impaired male and female participants having a diagnosis of MCI due to AD or mild AD based on NIA-AA criteria and confirmed amyloid and tau positivity via CSF sampling. In addition, the study population must show evidence of peripheral inflammation. Approximately 86 participants per investigational agent and matching placebo will be randomized (see Section 12.8).

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria within the screening period unless otherwise stipulated below, but prior to randomization:

1. Written informed consent must be obtained before any assessment is performed as a part of the study.
2. Male or female, age ≥ 45 years and ≤ 90 years at the time of signing the informed consent.
3. Fluency in local language and evidence of adequate pre-morbid intellectual functioning and adequate visual and auditory abilities to perform all aspects of the cognitive and functional assessments.
4. Participant has a reliable study partner or caregiver (e.g., spouse, sibling, close friend) who, in the investigator's judgement, has frequent, direct contact with the participant at least several days a week, can accompany the participant to all visits, is fluent in and able to read the local language in which study assessments are administered, and is also able to provide information to study investigator/staff. All effort should be made to keep the same study partner throughout the duration of the study.
5. A diagnosis of probable MCI due to AD or mild AD according to the National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria at screening and at least a 6 month decline in cognitive function prior to screening documented in the medical record.
6. Inclusion criterion #6 has been revised and is now replaced as #6(a).

6(a) Confirmed amyloid **and** tau positivity via CSF sampling performed at screening. Historical data cannot be used except for potential re-screened participants approved by Sponsor that had CSF sample previously analyzed by Central lab for EXPLAIN-AD study.

All participants must have confirmed positivity of CCI . In addition, all participants must have confirmed positivity in **one** of the following Tau markers:

Commercially Confidential Information as determined by the central laboratory, in order to further classify the participants using the AT(N) profile.

7. Inclusion criterion #7 has been revised and is now replaced as #7a.

7(a) Commercially Confidential Information

8. Inclusion criterion #8 has been deleted from inclusion criteria section, and moved to exclusion criteria section (i.e., exclusion criterion #30).
9. Inclusion criterion #9 has been revised and is now replaced as #9(a).

9(a) Mini-Mental State Examination (MMSE) total score of 20 to 24 (inclusive) at screening; OR, MMSE total score of 25-30 (inclusive) plus a DSST score at least 0.5 standard deviation (SD) below normative data at screening.

10. **For participants undergoing PET** CCI **:** Participants with a binding pattern of high affinity binding (HAB) or mixed affinity binding (MAB) CCI -binding profile phenotype can undergo PET CCI imaging in this study. Genotyping will be performed at screening by the Central Laboratory. Those who are low-binding affinity phenotype can continue participation in the cohort, but not undergo the PET CCI .

5.2 Exclusion criteria

IMPORTANT

The exclusion criteria for the core protocol are located in this section (Section 5.2). These exclusion criteria apply to all participants enrolled into this study. However, there may also be additional cohort specific exclusion criteria which are provided in Section 17 for each of the investigational agents.

Participants fulfilling any of the following criteria and any criteria detailed in the cohort-specific information (Section 17) are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible participants.

1. Exclusion criterion #1 has been revised and is now replaced as #1a.

1(a) Exclusion criterion #1(a) has been revised and is now replaced as #1(b).

1(b) Use of an investigational agent or an approved product with the intent to modulate inflammation or modulate the course of AD (e.g., Tau ASOs, gene therapy, amyloid or tau vaccine):

- Previous use of small molecules is allowed if discontinued for at least five half-lives, or at least 30 days from when the expected pharmacodynamic effect has returned to baseline prior to screening, whichever is longer
- Previous use of monoclonal or polyclonal antibodies or other biologics is allowed if discontinued for at least five half-lives prior to screening

2. Exclusion criterion #2 has been revised and is now replaced as exclusion #2a.

2(a) Current medical or neurological condition that in the judgement of the investigator, might impact cognition or performance on cognitive assessments, e.g., MCI not due to AD, non-Alzheimer dementia, Huntington's disease, Parkinson's disease, stroke, schizophrenia, bipolar disorder, active major depression, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), active seizure disorder, or history of traumatic brain injury associated with loss of consciousness and ongoing residual transient or permanent neurological signs/symptoms including cognitive deficits, and/or associated with skull fracture.

3. Exclusion criterion #3 has been deleted and this exclusion # will not be replaced.

4. Excluson criterion #4 has been revised and is now replaced as exclusion #4(a).

4(a) Diagnosis of vascular dementia prior to baseline (e.g., modified Hachinski Ischaemic Scale score > 6 or those who meet the NINDS-AIREN criteria for vascular dementia).

5. Exclusion criterion #5 has been revised and is now replaced as exclusion #5a.

5(a) Treatment with any immunosuppressive drugs and/or oral prednisolone greater than 10 mg/day (or equivalent) within the past 30 days of baseline.

- Previous or current use of less than or equal to 10 mg/day of prednisolone (or equivalent) is allowed if the dose has been stable (i.e. no change in dose) for at least 3 months prior to baseline.

6. Participants with suspected or proven immunocompromised state, including:
(a) those with evidence of Human Immunodeficiency Virus (HIV), Hepatitis B virus (HBV) or Hepatitis C virus (HCV), infections at screening (participants on anti-retroviral therapy are excluded); or
(b) those with any other medical condition at screening and/or baseline, which, in the opinion of the investigator, places the participant at unacceptable risk for participation in immunomodulatory therapy

7. Vaccination or immunization with any live vaccine or the pneumococcal vaccine within the past 3 months of baseline.

8. Exclusion criterion #8 has been revised and is now replaced as exclusion #8a.

8(a) Clinically significant, active infection at baseline that remains unresolved prior to Day 1, initial dose day visit.

9. Evidence of active or latent tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines), or a positive Quantiferon test. Participants with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the participant has no evidence of active tuberculosis.
If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated prior to enrollment.

10. Exclusion criterion #10 has been deleted and this exclusion # will not be replaced.

11. Current use of medications, other than cholinesterase inhibitors and/or memantine, that could alter cognition, as determined by the investigator.

12. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.

13. Unlikely to cooperate in the study; not able to attend scheduled examinations and visits; or not able to follow study instructions per the judgement of the investigator.

14. Current alcohol (>14 units per week) or current cannabis use; or history of alcohol or drug abuse or dependence (except nicotine dependence) within 2 years before the screening visit.

15. History of clinically significant carotid or vertebrobasilar stenosis or plaque.

16. Within 1 year before the screening or between screening and baseline, any of the following: myocardial infarction; moderate or severe congestive heart failure, New York Heart Association class III or IV; hospitalization for, or symptom of, unstable angina; syncope due to orthostatic hypotension or unexplained syncope; known significant structural heart disease (e.g., significant valvular disease, hypertrophic cardiomyopathy), or hospitalization for arrhythmia.

17. Current significant ECG findings as reported by site that are assessed as clinically significant by the investigator (e.g., sustained ventricular tachycardia; significant second or third degree atrioventricular block without a pacemaker; long QT syndrome or clinically meaningful prolonged QT interval) at screening.

    QTcF interval >450 ms for males and >460 ms for females, is exclusionary.
18. Contraindication to lumbar puncture as determined by review of the medical records or screening laboratory values, e.g. low platelet count, abnormal prothrombin time international normalized ratio (PT-INR), history of back surgery (with the exception of microdiscectomy or laminectomy over one level), signs or symptoms of intracranial pressure, spinal deformities or other spinal conditions that, in the judgment of the investigator, would preclude a lumbar puncture.
19. History of malignancy of any organ system, treated or untreated, within the past 60 months of screening and/or baseline, regardless of whether there is evidence of local recurrence or metastases. However, localized nonmalignant tumors not requiring systemic chemo- or radio-therapy, localized basal or squamous cell carcinoma of the skin, in-situ cervical cancer, localized vulvar carcinoma and localized prostate carcinoma with no progression over the past two years are permitted.
20. Exclusion #20 has been revised and is now replaced as exclusion #20a.

20(a) Any of the following laboratory abnormalities at the screening and/or baseline visit, deemed clinically significant, as determined by the investigator:

    (i) Vitamin B12 levels below the lower limit of normal;

    (ii) Folate levels below the lower limit of normal;

    (iii) Thyroid-stimulating hormone (TSH) levels above the upper limit of normal and a free thyroxine (FT4) level below the lower limit of normal

21. Surgical intervention planned during the study period starting from screening through end of cohort visit.
22. Exclusion #22 has been revised and is now replaced as exclusion #22a.

22(a) Abnormal laboratory values considered to be clinically significant at screening and or/baseline including (but not limited to): INR > 1.5x ULN (exempt of patients on therapeutic anticoagulation that will be paused for lumbar puncture), GGT > 3x ULN, Bilirubin > 1.5x ULN, Creatinine > 2x ULN, Hemoglobin < 8 or > 18 g/dL, hematocrit level < 33%; WBC > 20,000/mm^3 or < 3000/mm^3, platelets < 100,000/mm^3, GFR ≤ 35 mL/min/1.73m^2

23. Score "yes" on item four or five of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past six months prior to screening; OR scored "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior" (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years prior to Screening visit.
24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test at screening through end of cohort safety visit.
25. **At the time of screening for participants undergoing PET** CCI **:**

(a) Total dosimetry above the acceptable exposure in the country when combining the previous or planned Nuclear Medicine Radiology exposure and the scheduled study PET CCI scan(s) for all participants participating in the study (Section 4.9).

(b) Contraindication to PET scan investigations such as severe claustrophobia or inability to remain supine for extended periods.

26. **At the time of screening for participants undergoing PET CCI :**

Any contraindications to the arterial line sampling, including but not limited to the following:

- Thromboangiitis obliterans (Buerger disease)
- Full-thickness burns over the cannulation site
- Inadequate circulation to the extremity
- Raynaud syndrome
- Use of anticoagulation
- Clinically significant atherosclerosis of the upper extremity
- Coagulopathy
- Inadequate collateral flow
- Infection at the cannulation site
- Partial-thickness burn at the cannulation site
- Previous surgery in the area
- Synthetic vascular graft

27. **At the time of screening for participants undergoing PET CCI and only if a historical (within 2 years) MRI of the brain is not available:**

Unable to undergo MRI due to, for example, claustrophobia, or presents absolute contraindications to MRI (e.g. brain aneurysm clip, implanted cardiac pacemaker, pacemaker wires or defibrillator, prosthetic heart valves, cochlear implant, implanted insulin pump, metallic implants, metallic foreign bodies, tattoos (as determined by radiologist).

28. Sexually active males unwilling to use a condom during intercourse while taking investigational agent and for 5 times the terminal half-life of investigational agent after stopping investigational agent, **if male contraception is required for the agent**. When applicable to the investigational agent, a condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of the investigational agent via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified above. Refer to the agent-specific requirements for male contraception in the Cohort-specific exclusion criteria in Section 17.

29. Exclusion #29 has been revised and is now replaced as 29(a).

29(a) Current participation in an investigational trial or any previous use of experimental therapy unless discontinued for at least 180 days or 5 half-lives prior to screening, (whichever is greater), or if discontinued for at least 30 days prior to baselinefor non-interventional and observational trials.

30. Unstable dose of ChEIs and /or memantine within 3 months of baseline

- Previous or current use is not required but is allowed if dose level has been stable (i.e., no changes in dose) for at least 3 months prior to baseline.

31. Any other concurrent disease, condition, or laboratory abnormality that, in the view of either the Investigator or the Sponsor, may put the safety of the participant at risk, or places the participant at high risk of poor compliance with the study protocol, or of not completing the study, or could interfere with accurate collection or interpretation of study data.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatments, and instructions to be followed for participant numbering, prescribing/dispensing, and taking study treatments, are outlined in the SOM and/or Pharmacy Manual.

Refer to the 'dietary restrictions and smoking' in Section 6.2.4.1 for details of dosing and food intake, if relevant.

6.1.1 Investigational and control drugs

Refer to cohort-specific information in Section 17.

6.1.2 Additional study treatments

There are no additional study treatments. However, a PET CCI will be administered to a subset of participants underdoing the PET scan.

6.1.3 Treatment arms/group

Refer to cohort-specific information in Section 17.

6.2 Other treatment(s)

Refer to Section 17 for guidance for other treatments based on the specific investigational agent/cohort.

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Agent-specific permitted concomitant therapy is listed in Section 17 where applicable for each agent.

6.2.2 Prohibited medication

Treatment-specific prohibited medications are provided in Section 17 for the individual agents/cohorts. Any medications prohibited in the core protocol are as listed in the core exclusion (Section 5.2) criteria. Unless otherwise specified, these medications are also prohibited during study treatment.

Please refer to the respective cohort-specific information in Section 17 (Table 17-4) for additional restrictions, as applicable.

6.2.3 Rescue medication

Following randomization, the investigator must avoid initiating a symptomatic .7(such as ChEIs or memantine). Symptomatic treatments for AD (such as ChEIs or memantine) can be continued, in addition to the investigational treatment; however, dosage should not be adjusted in the 3 months preceding baseline and for the duration of the study.

Use of symptomatic treatment for AD must be recorded on the Concomitant medications/Significant non-drug therapies in the eCRF.

6.2.4 Restriction for study participants

For the duration of the study, participants should be informed and reminded of the restrictions outlined in the agent-specific Section 17 and also within Section 6.

6.2.4.1 Dietary restrictions and smoking

Participants should not consume alcohol for a period of 48 hours prior to dosing. Cannabis use is not permitted during the study. Section 17 also describes restrictions for cruciferous vegetable consumption and grapefruit consumption for each agent if these restrictions are applicable to the agent.

6.2.4.2 Other restrictions

No other restrictions apply.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

The participant number assigned to a participant at screening remains the unique identifier for the participant throughout the study. For information on participant numbering, please see ‘participant numbering’ section in the SOM.

6.3.2 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of participants.

6.4 Treatment blinding

This is a participant- and investigator-blinded study. Participants and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the study drugs will be concealed by the use of placebo substances that match the study drugs with regards to packaging, labeling, schedule of administration, appearance, and odor.

Site staff

All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place.

Sponsor staff

The following unblinded sponsor roles are required for this study:

- Unblinded clinical staff managing drug re-supply to site
- Unblinded sample bioanalyst(s) (e.g., PK, PD)

Sponsor clinical staff are required to assist in the management and re-supply of investigational drug product. These individuals are not provided with randomization lists directly, but may be unblinded through communication of drug re-supply needs.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The trial statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-1. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis CCI are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock for each investigational agent, all sponsor roles may be considered unblinded.

Table 6-1 Blinding levels

Role	Time or Event		
	Randomization list generated	Treatment allocation & dosing	Safety event (single participant unblinded)
Participants	B	B	B
Site staff	B	B	B
Unblinded site staff (see text for details)	NA	NA	NA
Drug Supply and Randomization Office	UI	UI	UI
Unblinded sponsor staff (see text for details)	UI	UI	UI
Statistician/statistical programmer/data analysts	UI	UI	UI
Independent committees used for assessing interim results	B	UI	UI
All other sponsor staff not identified above	B	B	UI

B Remains blinded
NA Not applicable
UI Allowed to be unblinded on individual patient level

6.5 Dose escalation and dose modification

Please refer to cohort-specific information in Section 17 for safety-related dose adjustments and interruptions of study treatment. Dose adjustment for any reason other than for safety will be subject to a protocol amendment.

Dose challenge following a dose-related or suspected dose-related AE will not be permitted.

6.6 Additional treatment guidance

Any additional treatment guidance will be detailed in Section 17 in an agent-specific manner.

6.6.1 Treatment compliance

Pharmacokinetic parameters (measures of treatment exposure) for study drug taken during each arm (see Section 17) will be determined as detailed in pharmacokinetics section (Section 8.5.1).

Pill counts (where agent-appropriate) will also be conducted at the site to verify compliance with treatment.

6.6.2 Recommended treatment of adverse events

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational agent treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- name
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

In case of emergency code breaking, the participant should be discontinued from the cohort.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under the agent-specific investigational and control drugs section (Table 17-2).

Section 17 of this protocol describes the route of administration for treatments used in each arm of the study.

Study drug administration will occur at the study site and at home between clinic visits, if applicable.

See the SOM and Pharmacy Manual for further details.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. Each investigational agent will have its own unique set of informed consent forms where appropriate (e.g., main ICF, study partner ICF).

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or the Core Data Sheet (CDS) for study drugs that are marketed by the regulatory body of the country where the study drugs are being used. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A subset of participants will undergo PET CCI . In addition, sleep assessments will be carried out in a subset of participants only at sites where this is technically feasible and available.

Commercially Confidential Information

The study partner who will assess the participant during the study will be required to sign a separate informed consent that details their involvement and the demographic information that will be collected from the study partner. In case of change of person in this role during the study, the new study partner will be asked to sign an informed consent. Demographics collected include relationship to the participant, age and gender, frequency that the study partner is in contact with the participant, if the study partner is familiar with the use of mobile and tablet technology, and if the study partner considers that the participant is familiar with the use of mobile and tablet technology.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Refer to the SOM for a complete list of ICFs included in this study.

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as described by the visit window. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who discontinue the study treatment are to return for the Early Termination Visit as indicated in the Assessment Schedule. Participants who discontinue from the study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit, if they agree, as soon as possible, at which time all of the assessments listed for the Early Termination Visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

Step-up visits are intended for use where an agent requires gradual increase to full therapeutic level. The step-up visits do not apply to all agents. See Section 17 for agent-specific use of step-up visit schedule.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Table 8-1 Assessment Schedule

Period	Screening		Treatment										End of Cohort		Safety Follow-Up
Visit Name	Screening	Baseline	Initial Dose Day	Step-Up Visit			Treatment	Step-Up Visit	Treatment				End of Cohort Visit (EOC1) for All Molecules	End of Cohort Visit (EOC2) for Large Molecules Only - Extended Safety Visit	Early Termination Visit (Only when discontinuation from treatment/study occurs. See Section 9.)
Days	-60 to -8	-7 to -1	1	8 ±1	15 ±1	22 ±1	29 ±2	36 ±1	57 ±2	85 ±3	113 ±2	141 ±2	171 -0 +2	281 ±2	30 days post last dose
Informed consent	X														
Informed Consent - Study Partner/Caregiver	X														
PET CCI & Genotyping CCI Consent	X														

Commercially Confidential Information

Inclusion / Exclusion criteria	X	X													
Physical Examination/Neurological Examination	S		S		S		S		S	S	S	S	S		S
Smoking and alcohol history	S														
Alcohol Test and Drug Screen	S														
Pregnancy and assessments of fertility	S	S			S		S		S	S	S	S	S	S	S
Hepatitis and HIV Screen	S														
Tuberculosis test	S													S	
Demography	X														
Medical history/current medical conditions	X	X	X				X		X	X	X	X	X	X	X

Period	Screening		Treatment										End of Cohort		Safety Follow-Up
Visit Name	Screening	Baseline	Initial Dose Day	Step-Up Visit			Treatment	Step-Up Visit	Treatment				End of Cohort Visit (EOC1) for All Molecules	End of Cohort Visit (EOC2) for Large Molecules Only - Extended Safety Visit	Early Termination Visit (Only when discontinuation from treatment/study occurs. See Section 9.)
Days	-60 to -8	-7 to -1	1	8 ±1	15 ±1	22 ±1	29 ±2	36 ±1	57 ±2	85 ±3	113 ±2	141 ±2	171 -0 +2	281 ±2	30 days post last dose
Body Height	X														
Vital signs and body measurements	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X		X		X					X			X	X	X
Blood collection CCI	X														
Hematology	X	X			X		X		X	X	X	X	X	X	X
Clinical Chemistry	X	X			X		X		X	X	X	X	X	X	X
Urinalysis	X	X			X		X		X	X	X	X	X	X	X
Commercially Confidential Information															
Randomization			X												
Drug dispensation			See Section 17 for study drug administration and step-up regimen												
CSF Collection	See Section 17 for specific time point for study drug arm														
PK/PD/Immunogenicity/ CCI	See Section 17 for specific time point for study drug arm														
eCSSRS	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Mini-Mental State Examination	X														

Period	Screening		Treatment										End of Cohort		Safety Follow-Up
Visit Name	Screening	Baseline	Initial Dose Day	Step-Up Visit			Treatment	Step-Up Visit	Treatment				End of Cohort Visit (EOC1) for All Molecules	End of Cohort Visit (EOC2) for Large Molecules Only - Extended Safety Visit	Early Termination Visit (Only when discontinuation from treatment/study occurs. See Section 9.)
Days	-60 to -8	-7 to -1	1	8 ±1	15 ±1	22 ±1	29 ±2	36 ±1	57 ±2	85 ±3	113 ±2	141 ±2	171 -0 +2	281 ±2	30 days post last dose
Everyday Cognition Scale - Study Partner		X							X	X			X	X	
Neuropsychiatric Inventory - Caregiver Distress Scale		X					X		X	X			X		
Neuropsychological Test Battery	X	X					X		X	X		X	X		
Digit Symbol Substitution CCI	X	X					X		X	X		X	X		
Commercially Confidential Information															
eCognitive At-Home Participant Assessment		2 times per week at baseline leading up to Day 1; 2 times per week in the week preceding Day 57; 2 times per week in the week preceding Day 85													
eNeuropsychiatric At-Home Caregiver Assessment		At least 2 times per week at baseline leading up to Day 1; At least 3 times during the week preceding Day 29; At least 3 times during the week preceding Day 57; At least 3 times during the week preceding Day 85													
Commercially Confidential Information															
Blood collection for CCI genotyping CCI , PET Sites Only)	X														

Period	Screening		Treatment										End of Cohort		Safety Follow-Up
Visit Name	**Screening**	**Baseline**	**Initial Dose Day**	**Step-Up Visit**			**Treatment**	**Step-Up Visit**	**Treatment**				**End of Cohort Visit (EOC1) for All Molecules**	**End of Cohort Visit (EOC2) for Large Molecules Only - Extended Safety Visit**	**Early Termination Visit (Only when discontinuation from treatment/study occurs. See Section 9.)**
Days	**-60 to -8**	**-7 to -1**	**1**	**8 ±1**	**15 ±1**	**22 ±1**	**29 ±2**	**36 ±1**	**57 ±2**	**85 ±3**	**113 ±2**	**141 ±2**	**171 -0 +2**	**281 ±2**	**30 days post last dose**
MRI (only if historical data within 2 years is not available, and for PET Sites Only)	X														
CCI PET Scan (PET Sites Only)		X								X					
Arterial Blood Collection (PET Sites Only)		X								X					
Participant & Study Partner Feedback Survey			One time after second administration of at-home participant and study partner assessments												
Study completion information													X		X

8.1 Screening

It is permissible to re-screen a participant if s/he fails the initial screening or was not randomized in the required timeframe; however, each case must be discussed and agreed upon with the Sponsor on a case-by-case basis. Participants need to be re-consented for re-screening and a new participant number must be assigned.

In the case where a safety laboratory assessment at screening or baseline is outside of the range specified in the laboratory manual, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges and it is deemed clinically significant by the investigator, then the participant must be excluded from the study.

A participant may not be enrolled in more than one cohort.

Certain limited data on screening failures will be collected. Further information on what data must be collected and further information on re-screening is outlined in the SOM.

8.1.1 Eligibility screening

All participants will be screened for HIV, HCV, and HBV and tuberculosis (active or latent, see further details in Section 8.1.1.1). A drug screen will also be done. Smoking and alcohol consumption is allowed during the study, but refer to restrictions in Section 6.2.4.1 and the agent-specific restrictions in Section 17.

The MMSE range of 20-24 was selected as a screening tool to identify participants with mild dementia. Participants can also be included into the trial if they score above 24 on the MMSE, however, in such cases participants are required to score at least 0.5 standard deviations or more below age and education matched normative values on the Wechsler Adult Intelligence Scale (WAIS)-IV DSST (also termed "Coding") as a means to exclude cognitively healthy individuals. Age-matched normative data, adjusted for years of education (adapted with permission from the Advanced Clinical Solutions (ACS) software, NCS Pearson, Inc.), will be used for screening eligibility for participants with MMSE score of 25-30 (inclusive). The DSST is a brief, well-established test that is relatively free of cultural bias, has good psychometric properties and has been shown to measure trajectory in MCI with higher sensitivity than many other conventional cognitive tests (Winblad et al 2008; Jutten et al 2018).

Additionally, participants will be screened for CCI for eligibility. For participants who consent to the PET CCI genotype status will also be included in the eligibility screen.

8.1.1.1 Tuberculosis screening

Either a central laboratory immunological test (QuantiFERON TB-Gold) **or** a locally performed skin test must be performed at the screening visit to screen the participant for latent tuberculosis infection.

The results must be known prior to randomization to determine the participant's eligibility for the study (refer to Section 5.2 for further details).

The tuberculosis test will be repeated at EOC2, when this visit is applicable.

Central laboratory test for Tuberculosis screening

The QuantiFERON TB-Gold test will be analyzed by the central laboratory. Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

Local skin test for Tuberculosis screening

A PPD skin test is to be performed at screening and read before randomization to determine the participant's eligibility for the study. The test dose is bioequivalent to 5 tuberculin units of standard PPD injected intradermally, usually into the volar surface of the forearm. The site is cleaned and the PPD extract is then injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48-72 hours to develop, the participant must return to the investigators' site within that time for a proper evaluation of the injection site. This will determine whether the participant has had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site (refer to Section 5.2).

8.1.2 Information to be collected on screening failures

Certain limited data on screening failures will be collected. Further information on what data must be collected and further information on re-screening is outlined in the SOM.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Participant demographic and baseline characteristic data are to be collected on all participants at screening, including: age, sex, race, predominant ethnicity (if permitted), family history of AD, years of education and CCI genotype (if available).

Relevant medical history/current medical condition present before signing the informed consent will be recorded. Investigators will have the discretion to record abnormal test and examination findings on the appropriate eCRF whenever, in their judgment, the test abnormality occurred prior to the informed consent signature. Details are outlined in the SOM.

Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, we need to assess the diversity of the study population as required by Health Authorities.

The study partner characteristics will be collected including the relationship to the participant, and frequency of contact with the participant, age and gender. Temporary unavailability or changes in study partner will also be collected. Study partners will be required to sign a separate informed consent.

8.3 Efficacy/Pharmacodynamics

Efficacy/pharmacodynamics of each drug regimen will be based on the following general classes of assessments:

- Cognitive assessment

- Assessments of neuropsychiatric symptoms and function (activities of daily living)
- Imaging of microglia activation in a subset of participants
- Total target for biotherapeutic agents

Pharmacodynamic (PD) samples will be collected, as defined in the Assessment Schedule (Table 8-1), with specific time points of each collection detailed in the Cohort-specific Section 17. Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing, and shipment.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected and total CSF volume collected will not exceed those stated in the protocol. PD samples will be obtained and evaluated in all participants and for all agents.

PD samples will be obtained and evaluated in all participants at all dose levels, including the placebo group.

Completed clinical efficacy assessments will be reviewed and examined by the investigator for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). The investigator should review not only the responses to the clinical assessments but also any unsolicited comments from the participant. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in the protocol.

8.3.1 Assessment of Cognition

The frequency of assessments is described in Table 8-1.

Various clinical Performance outcome (PerfO) measures will assess changes in cognition:

- The Neuropsychological Test Battery (NTB; total score, memory and executive functioning composite scores)
- The Digit Symbol Substitution Test (DSST; total score)
  Commercially Confidential Information
- At-home eCognitive testing Commercially Confidential Information

A tablet and/or an electronic pen may be applied to augment the administration, assessment frequency and scoring of the DSST, CCI and eCognitive testing (as detailed in the administration manual).

In clinic, cognitive testing must be administered in a quiet, relatively distraction-free environment, preferably prior to 1:00 pm local time and approximately the same time every visit for each participant (+/- 60 min). The total administration time for all cognitive assessments is approximately 45 min. In clinic, cognitive testing must be administered by a trained test administrator who completes the study-specific rater training. The same test administrator should administer a given test across all visits for a given participant. The initials of the test administrator will be collected for all clinical efficacy assessments. Instructions as to how to perform these assessments and their optimal sequence will be provided in the rating scales administration manual.

8.3.2 Assessment of Neuropsychiatric Symptoms and Function

The frequency of assessments is described in Table 8-1.

Observer and Clinician reported outcome (ObsRO and ClinRO) measures will assess changes in neuropsychiatric symptoms and function (activities of daily living):

- The Neuropsychiatric Inventory - Caregiver Distress Scale (NPI-D)
- Between clinic visit monitoring of changes in mood and neuropsychiatric symptoms
- The Everyday Cognition Scale (ECog - Study partner)

8.3.3 Assessment of microglial activation

For the PET CCI readout please refer to Section 8.5.6.

Commercially Confidential Information

8.3.5 Total target

For biotherapeutic agents, serum and CSF samples will be obtained and evaluated for total CCI concentrations Commercially Confidential Information as a pharmacodynamic (PD) marker for CCI . Agent-specific information, including a description of the analytical method, is detailed in Section 17, as applicable.

8.3.6 Appropriateness of efficacy assessments

Alzheimer's disease is characterized by a gradual decline in cognition several years preceding a clinical diagnosis of the illness. The period prior to a dementia diagnosis is often referred to as prodromal AD or MCI due to AD (Delrieu et al 2011).

Commercially Confidential Information

One of the earliest deficits to appear in the continuous cognitive decline of AD is distinctive episodic memory impairment characterized by problems with free and cued recall. This memory impairment is often accompanied by or followed by difficulties with executive function. Around this time, subtle, yet problematic, difficulties with activities of daily living (ADL) start to emerge. These early difficulties are typically seen in complex ADLs and are often missed with conventional assessments of basic function (Aisen et al 2017).

Neuropsychiatric symptoms cause substantial caregiver distress and are among the earliest signs of cognitive decline and AD. Nevertheless, the symptoms remain under-recognized and challenging to treat (Lanctôt et al 2017).

Demonstrating cognitive, neuropsychiatric and/or functional enhancement in the early symptomatic stages of AD represents important clinical outcomes with high face validity. The following criteria was applied for the selection of efficacy endpoints in this trial;

1. The endpoint covers key cognitive/functional/neuropsychiatric domains that are relevant to early stages of AD
2. The endpoint has acceptable psychometric properties for detecting symptomatic enhancements in early AD
3. The endpoint is globally accepted and established
4. The endpoint is relatively brief and non-burdensome for sites and participants

As detailed in Section 4.3, the NTB was selected as the primary endpoint for EXPLAIN-AD:

The NTB allows examination of pro-cognitive drug effects using a well-established neuropsychological assessment with psychometric properties suitable for the early stages of AD (Harrison et al 2007). In comparison, the psychometric limitations of the ADAS-Cog in participants with early AD is well-recognized (Karin et al 2014).

The NTB is a composite of multiple globally-established neuropsychological tests that provide a thorough assessment of the cognitive domains affected by early AD, in particular, memory, executive function attention and verbal fluency. In comparison the ADAS-Cog and RBANS lack comprehensive measures of executive function (Harrison et al 2007; Garcia et al 2008).

The NTB has shown good assay sensitivity to symptomatic treatment effects in AD drug intervention trials where other endpoints have failed (Karin et al 2014; Gilman et al 2005).

Because inflammation has been strongly associated with executive function and memory, EXPLAIN-AD will include two additional executive tests of function; the Digit Symbol Substitution Test (DSST) CCI .

The DSST CCI are often classified as measures of executive function although in reality they can be regarded as measuring a number of cognitive functions (Harrison 2018; CCI). The DSST has previously detected beneficial treatment effects in MCI when other endpoints have failed (Winblad et al 2008)

Commercially Confidential Information

Day-to-day variability in cognitive performance is an important yet under recognized feature of AD that may affect the accuracy of single-time point cognitive assessments (Zettergren et al 2011). EXPLAIN-AD will deploy at-home eCognitive testing in order to allow more frequent monitoring in more natural settings. These well-established and validated computerized tests CCI are brief and repeatable and provide a reliable assessment of cognitive processes that cannot easily be obtained through conventional paper-pencil tests. Moreover, studies suggest that increasing assessment frequency may improve detection of drug treatment effects on cognition (Jaeger et al 2011).

The ECog scale measures cognitively-relevant every day and complex abilities relevant to early AD (Farias et al 2008). Measuring changes in complex ADLs has important advantages as it may more closely reflect how individuals are functioning in the real world. An effect on measures of complex ADLs after an intervention has therefore ecological validity and is highly clinically relevant to participants and caregivers (Weintraub et al 2018).

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on prospective suicidality assessment and reporting, refer to Section 10.2.3.

For details on AE collection and reporting, refer to Section 10.1.1.

The methods, assessment, specification, and recording for each assessment will be detailed in the SOM.

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be performed at all visits starting from Initial Dose Day 1, except where a complete physical examination is required per investigator's judgement (see above). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event. Neurological examination will include cranial nerve function, motor function (tone, strength and reflexes), sensory function (small fiber, large fiber and cortical), coordination (cerebellar function) and balance/gait, in addition to the cognitive and neuropsychiatric evaluations being done as part of screening and endpoint assessment.

Assessment	Specification
Vital signs	Vital signs include BP and pulse measurements, and temperature. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated arm device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1 (under 'Vital signs and body measurements')

8.4.1 Pregnancy and assessments of fertility

See Section 17 for all specific pregnancy and fertility assessments for each investigational agent.

8.4.2 Laboratory evaluations

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Central and local laboratory evaluations will be collected. All blood, urine, and CSF collections will be analyzed centrally except for CSF red blood cell and white blood cell counts and differentials, and unless otherwise specified in the Cohort-specific details in Section 17. Each CSF sample will be divided into several aliquots for this purpose. Please refer to the central lab manual and SOM for further details on central and local lab collections.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

8.4.3 Electrocardiogram (ECG)

At a minimum the following will be performed:

Single 12-lead ECGs will be collected at the time points indicated in the Assessment Schedule (Table 8-1).

PR interval, QRS duration, heart rate, RR interval, QT interval, QTc will be assessed.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

As applicable, QTcF and QTcB may be calculated in-house. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening and Baseline visit(s) to assess eligibility. See the SOM for additional details.

Clinically significant abnormalities must be reported as adverse events.

For agents that require closer evaluation please see Section 17 (agent-specific safety information).

8.4.4 Appropriateness of safety measurements

Other than possible treatment-specific safety measures (Section 17), the safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

8.5.1 Pharmacokinetics

Agent concentrations will be assessed in serum (i.e. for biotherapeutic agents) or plasma (i.e. for low molecular weight agents) and CSF of all agent treated participants.

PK samples will be collected, as defined in the assessment schedule (Table 8-1), with specific time points of each collection detailed in the Cohort-specific Section 17. Instructions are outlined in the SOM regarding sample collection, numbering, processing, and shipment.

In order to better define the PK profile, the timing of the sample collection may be altered based on emergent data.

Agent-specific information, including a description of the analytical method is detailed in Section 17.

Commercially Confidential Information

8.5.4 Participant and Study Partner Feedback Survey

This study will utilize a survey in order to get feedback from participant and/or caregiver about their satisfaction with the at-home assessments of neuropsychiatric symptoms and cognition. The survey may be completed at any point after two administrations of the at-home assessments.

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

8.5.6 Imaging – for PET participating sites only

A subset of participants in EXPLAIN-AD will undergo PET imaging at baseline, and again following 12 weeks of treatment, to assess therapeutic effects of each investigational agent on microglia activation (see Table 8-1). Both PET imaging assessments must be conducted at approximately the same time of day for each participant (e.g., if baseline PET scan is performed in the AM or PM time-frame then follow-up PET scan must be performed in the same time-frame AM or PM).

Commercially Confidential Information

Triggering of inflammatory signaling pathways leads to the production and release of immune mediators, which compromises neuronal function and causes cell death. The two prominent immune mediators' astrocytes and microglial cells are the main types of cells in the inflammatory response which plays a significant role in neurodegeneration.

Radiolabeled entities selective for molecular processes of inflammation allow for identification of disease pathology and a more rapid assessment of inflammatory cell activity during therapeutic intervention. CCI is a mitochondrial protein that is co-localized with activated microglia and astrocytes of the brain. PET imaging of CCI have been performed as a marker for inflammation in brain and peripheral tissue(s) using the first generation PET radioligand CCI followed by second and third generation PET radioligands such as CCI and CCI , respectively. Alterations of binding of PET CCI radioligands have been found in participants with psychiatric disorders, Multiple Sclerosis, Parkinson's disease and Alzheimer's disease, as well as in participants with peripheral inflammation in participants with Rheumatoid Arthritis, respiratory disorders and cancer tumors. Several studies have detected significant retention of CCI in AD participants compared healthy controls. In addition, by studying the variability in the method using a test-retest study with CCI in participants with AD estimated a sample size of 3 to 12 participants needed to detect a 10% change depending on the image analysis and brain region assessed. Finally, a significant reduction in binding of CCI was found in participants with PD after 8 weeks of administration of an MPO inhibitor with changes ranging from -61% to 10% in 18 participants, demonstrating the validity of the methodology and technology to show a proof of mechanism of action in target tissue of interest.

8.5.6.1 CCI PET imaging – for PET participating sites only

Only participants with a binding pattern of high affinity binding (HAB) or mixed affinity binding (MAB) CCI -binding profile phenotype, as evaluated by genotyping for the CCI polymorphism performed at screening, can undergo PET CCI imaging in this study (see Section 5.2).

For participants undergoing PET imaging **who do not have** a historical (within 2 years of the screening visit) magnetic resonance image (MRI) available, a 3-D structural MRI of the brain will be collected at screening or baseline (see Table 8-1 and Section 5.2). The MRI will be used for co-registration to the PET images to provide an anatomical image that will help for delineation of the brain regions of interest (ROIs). If a combined PET/MRI scanner is used, which allows simultaneous acquisition of the MRI and PET data, the anatomical MRI scan will be acquired at the beginning of the PET examination.

The MRI acquisition will be performed by a trained MRI professional at the site or nearby facility as per local procedures. MRI images will be sent to the central imaging vendor for image analysis of the PET data.

Specifics regarding the PET imaging methodology will be provided in more detail in the PET operations manual.

Briefly, a sub-set of participants will undergo a brain CCI /CT imaging on state-of-the-art, 3D PET/CT scanners. For consistency, the same PET/CT scanner should be used at screening and during the follow-up scan.

On each day of PET scanning, a cannula will be inserted into the left or right antecubital vein for radioligand administration and another cannula into the radial artery of the contralateral arm for blood sampling.

If High Resolution Research Tomograph (HRRT) PET or PET/CT systems are used, a transmission scan will be acquired to generate the attenuation correction for the emission PET sinograms using an appropriate method (^{137}Cs point source or a low dose CT scan respectively). If a PET/MRI scanner is used, an MRI scan will be acquired and used for anatomical localization and generation of the attenuation correction maps.

After the transmission scan, CCI (a range from a minimum of 350 MBq to a maximum of 600 MBq) will be injected as a bolus for about 30-60 (depending on the volume) sec via the venous cannula. The dynamic emission scan will be started simultaneously to the radioligand administration of CCI . The PET examination will have a total duration of approx. 90 minutes. Arterial blood samples will also be collected during the course of the PET scan to determine the metabolite corrected arterial plasma input function that will be used in the quantification of the PET data. Further details on the arterial blood collection will be available in the PET operations manual provided by the central imaging vendor.

The coded medical images will be used primarily for analysis as described in this protocol; however; the images may also be used for the development and evaluation of new analysis methods directly related to the area of the research that this study covers.

Incidental findings are beyond the scope of central imaging vendor. If an investigator/radiologist recognizes any incidental finding in the images during the course of

conducting the clinical trial, the investigator should follow up as part of his/her duty of care to ensure the safety and wellbeing of the participant.

8.5.7 Immunogenicity

Immunogenicity (IG) will be assessed in serum of all participants treated with biotherapeutic drug.

Immunogenicity samples will be collected at the time points defined in Table 17-4 and referenced in the assessment schedule (Table 8-1). Instructions are outlined in the SOM regarding sample collection, numbering, processing, and shipment.

In order to better define immunogenicity, the timing of the sample collection may be altered based on emergent data.

In case of suspected allergic hypersensitivity, the participant should return to the site and a sample to assess immunogenicity will be collected.

In case of positive immunogenicity, backup of previous pre-dose PK samples could be used to better characterize the onset of immunogenicity response.

In the case of an anaphylactic reaction occurring after injection, a sample will be taken at the time of the event and 8 weeks later. An immunogenicity positive participant at the end of the study will be followed up for three months.

Agent-specific information, including a description of the analytical method, is detailed in Section 17 as applicable.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- participant/guardian decision
- participant no longer has an available study partner
- Pregnancy
- Use of prohibited treatment as per recommendations in the cohort-specific prohibited treatment section within Section 17 and medications prohibited in the core protocol as stated in prohibited medication section within Section 6.2.2. Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding

- The investigator believes that continuation would negatively impact the safety of the participant or the risk/benefit ratio of trial participation
- Emergence of the following adverse events, that in the judgement of the investigator, taking into consideration the participant's overall status, prevent the participant from continuing participation in the study:
  - Severe lumbar puncture related complications such as meningitis
  - Severe neurological findings such as neuropathy
- Severe hypersensitivity reaction to study treatment occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension
- Any SAE, regardless of whether the event is suspected to be related to study drug
- Any severe adverse event that is suspected to be related to study drug (apart from liver and renal events - see below
  - If a liver or renal event occurs, follow guidelines outlined in Section 16.2 and Section 16.3, respectively, regarding discontinuation of study treatment
- Presence of any malignancy, other than those allowed in study exclusion criteria
- Any clinically significant infection
- Any additional circumstance listed in the Cohort-specific Section 17 as applicable to the participant's Cohort/study treatment assignment

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

Participants who discontinue from study treatment will be considered discontinued from the study and will be asked to return for the Early Termination Visit indicated in the Assessment Schedule (Table 8-1).

If the participant cannot or is unwilling to attend the Early Termination Visit, the site staff should contact the participant, or participant's caregiver by phone.. This telephone contact should preferably be done according to the study visit schedule for Early Termination Visit.

At a minimum, the following data should be collected during the telephone contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of assigned treatment code Section 6.6.3.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, or refuses further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation, or according to the study visit schedule for Early Termination Visit should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent

Withdrawal of consent/opposition to use data/biological samples occurs only when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (Table 8.1).

Further details on withdrawal of consent or the exercise of participants' rights related to data are included in the corresponding informed consent form.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.3 Study stopping rules

Overall study stopping rules:

If any of the following occur within a cohort, enrollment in the study within that cohort will be placed on hold, and no new participants may be dosed, however enrollment and dosing in any other concurrently running cohorts without safety concerns may continue.

- One or more study-treatment related SAEs
- Two or more similar SAEs, regardless of suspected drug-relatedness
- Two or more participants experience hypersensitivity reactions or injection reactions of moderate to severe intensity
- Two or more participants experience a similar AE, which was assessed as severe in intensity, and are considered as potentially related to the study treatment
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold

The study may resume following the safety review, if the Investigators and Sponsor agree it is safe to proceed.

9.4 Study completion and post-study treatment

Cohort completion is defined as when the last participant finishes their End of Cohort (EOC1 and/or EOC2) visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early cohort termination decision, the date of that decision.

Study completion is defined as when the last participant of the final cohort of the study finishes their End of Cohort (EOC1 and/or EOC2) visit and any repeat assessments associated with the visit has been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

For participants who discontinue the study early and do not return for the Early Termination Visit (see Section 8), a safety follow-up call will be conducted 30 days after last administration of study treatment.

The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 and the SOM. Documentation of attempts to contact the participant should be recorded in the source documentation.

9.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be

necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant or clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade will be used to characterize the severity of the Adverse Events based on the this general guideline:

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. Its relationship to the study treatment and investigational PET CCI radioligand. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met

5. Action taken regarding with study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Drug interrupted/permanently discontinued

6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days (or 5 half-lives or end of study visit, whichever is longer) following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- They induce clinical signs or symptoms
- They are considered clinically significant
- They require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease.

Instructions are outlined in the SOM for data capture methodology regarding AE collection for participants that fail screening.

10.1.2 Serious adverse events

An SAE is defined as any adverse event (appearance of [or worsening of any pre-existing]) undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- Fatal
- Life-threatening
    - Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human 2003).

- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the participant's general condition
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human 2003).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred. Please see Section 10.1.5 for more details.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of cohort treatment must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE with paper backup Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last cohort agent administration should only be reported to Novartis Safety if the investigator suspects a causal relationship to cohort treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The trial participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Depending on the investigational agent being tested, if a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

Please see Section 17 for further guidance on each agent, if applicable, including whether male contraception is required for the agent.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections (Section 10.1.1 and Section 10.1.2, respectively).

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-1 in Section 16 for complete definitions of liver laboratory triggers and liver events.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently

reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (see Discontinuation of Study Treatment Section 9.1.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
  - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and GGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin or transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the participant is asymptomatic. Retesting should be continued up to resolution.
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
  - Exclusion of underlying liver disease, as specified in Table 16-4
  - Imaging such as abdominal US, CT or MRI, as appropriate.
  - Obtaining a history of exposure to environmental chemical agents.
  - Considering gastroenterology or hepatology consultations

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

Additional details can be found in the 'Liver Event Guide and Checklist' guidance document in the Appendix of the SOM, which details how the various assessments and results should be recorded, and other details that should be ascertained from the participant.

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Any one of the following:
  - Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR
  - New onset dipstick proteinuria ≥ 3+, OR
  - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed within 24-48 hours after the first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff as summarized in Section 16.3.

Every renal laboratory trigger or renal event should be followed up by the investigator or designated personnel at the trial site as summarized in Section 16.3.

Additional details can be found in the 'Renal Event Guide and Checklist' guidance document in the Appendix of the SOM, which details how the various assessments and results should be recorded, and other details that should be ascertained from the participant.

10.2.3 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The C-SSRS must be administered at each visit, including unplanned visits.

The C-SSRS will be administered by an individual who has received training and certification in its administration. At the first study visit, the "baseline/screening" version of the C-SSRS will be administered. This version assesses suicidal ideation and suicidal behavior during the participant's lifetime and during a predefined period. At subsequent visits, the "since last visit" version will be administered.

A validated version of the C-SSRS will be used to capture self-reported C-SSRS data utilizing an electronic tablet format (eC-SSRS). The eC-SSRS uses a detailed branched logic algorithm to perform the C-SSRS participant interview, evaluating each participant's suicidality ideation and behavior in a consistent manner. If the alert system assesses the participant as having positive suicidal signs, the investigator will be immediately notified by either email, and/or via telephone.

If, at any time after screening and/or baseline, the score is "yes" on item 4 or item 5 of the suicidal ideation section of the C-SSRS or "yes" on any item of the suicidal behavior section, the participant must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the participant is referred.

In addition, all life-threatening events must be reported as SAEs. For example, if a participant answers "yes" to one of the questions in the suicidal behavior section, an SAE must be reported if the event was life-threatening. All events of "Non-Suicidal Self-Injurious Behavior" (question also included in the suicidal behavior section) should be reported as AEs and assigned the appropriate severity grade.

10.3 Committees

10.3.1 Data Monitoring Committee

As described in the FDA Draft Guidance for Industry: Safety Assessment for IND Safety Reporting (CDER 2015), this study will include an external Data Monitoring Committee (DMC). The DMC will function independently of site investigators participating in the study. The DMC will assess the progress of the EXPLAIN-AD treatment cohorts and the safety

data. The Sponsor will continue, modify or terminate investigational agents based on these reviews.

Specific details regarding composition, responsibilities, data monitoring, meeting frequency, and documentation of DMC reports, minutes, and recommendations are described in the Safety Surveillance Plan for each agent and the DMC Charter.

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

For each completed cohort, the data analysis will be performed upon final database lock for the cohort, and the results will be reported while the study may be ongoing for subsequent cohorts. For all analysis sets, participants will be analyzed according to the study treatment(s) received.

The full analysis set (FAS) will include all participants who received any study drug. This set will be used for the primary endpoint analysis.

The safety analysis set is defined similarly as the FAS.

The PK analysis set will include all participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact PK data.

The PD (total target) analysis set for biotherapeutic agents will include all participants with available (total target) PD data and no protocol deviations with relevant impact on (total target) PD data.

The IG analysis set for biotherapeutic agents will include all participants with at least one available valid (i.e., not flagged for exclusion) IG concentration measurement, who received any biotherapeutic study drug and with no protocol deviations that impact IG data.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for all participants in the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be listed by treatment, participant, system organ class and preferred term.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in months to each treatment arm as well as dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical classification system, by treatment group and for all participants.

12.4 Analysis of the primary endpoint(s)

The primary aim of the study is to demonstrate the effect on cognition of each anti-inflammatory agent vs. placebo, as measured by the NTB response after the 24 week treatment period.

12.4.1 Definition of primary endpoint(s)

The primary endpoint, NTB total score, includes nine validated components: 1-2) Wechsler Memory Scale Visual-Paired Associates immediate and delayed scores; 3-4); Wechsler Memory Scale Verbal-Paired Associates immediate and delayed scores; 5-6) Rey Auditory Verbal Learning Test (RAVLT) immediate and delayed scores; 7) Wechsler Memory Scale

Digit Span; 8) Controlled Word Association Test (COWAT); and 9) Category Fluency Test (CFT). In order to reduce burden on sites and participants, components 1-4 will not be administered in EXPLAIN-AD (Harrison 2018; Harrison and Caveney 2012).

For each of the remaining five components, a raw score is first converted to a standardized z-score using baseline mean and SD (calculated from all randomized participants with baseline scores), and a total z-score is derived by averaging all resulting z-scores. A change from baseline is calculated as post-baseline z-score minus pre-treatment z-score, whereby a positive change indicates an improvement from baseline.

12.4.2 Statistical model, hypothesis, and method of analysis

The study research hypothesis is that each investigated anti-inflammatory agent provides an improvement over placebo in NTB response at 24 weeks.

The change from baseline in NTB total z-score will be analyzed using a restricted maximum likelihood (REML)-based mixed model with repeated measurements (MMRM), using FAS dataset. The model will include fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline and baseline-by-visit interaction. The model will also adjust for several important baseline prognostic factors, such as age and MMSE score. Unstructured covariance will be used to model within-patient errors, with Kenward-Roger approximation to estimate denominator degrees of freedom. If the unstructured covariance causes model convergence issues, then other simpler covariance structures will be considered. Least squares mean, the associated 2-sided 90% confidence interval and the p-value will be obtained for each treatment at each visit. The primary comparison will be the contrast between active treatment and placebo at 24 weeks. Both cohort-wise and combined cohort analysis (i.e., pooling placebo data across different cohorts) will be performed.

12.4.3 Handling of missing values/censoring/discontinuations

For an NTB outcome at any visit, if more than three out of five NTB items are missing, the total z-score will not be derived and will be set to missing. Completely missing visits will be handled through the MMRM model, which implicitly imputes missing data under missing at random (MAR) assumption.

Commercially Confidential Information

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

To assess the robustness of the primary analysis results, several sensitivity analyses will be explored. The details will be described in the statistical analysis plan.

Supportive analyses

A supportive analysis will involve estimation of treatment effects and contrasts (anti-inflammatory agent vs. placebo) within subgroups (e.g., MCI or mild AD). The details will be described in the statistical analysis plan.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Memory, cognition, executive function, and neuropsychiatric outcomes

The "memory function" composite score is obtained by averaging the following z-scores from the NTB: RAVLT immediate and delayed scores.

The "executive function" composite score is obtained by averaging the following three z-scores from the NTB: Wechsler Memory Scale Digit Span, COWAT, and CFT.

The DSST is an attention-demanding component of the Wechsler Adult Intelligence Scale-IV. The DSST score is the number of digits coded correctly in a fixed amount of time, whereby higher scores denote better performance.

Commercially Confidential Information

The Everyday Cognition (ECog) scale is a validated informant-based measure comprised of 39 items covering six cognitively relevant domains (Farias et al 2008). Each item is scored on a 4-point scale (1=better or no change compared to 10 years earlier, 2=questionable/occasionally worse, 3=consistently a little worse, 4=consistently much worse). An "I don't know" response is also included. The total ECog score is calculated as the sum of all 39 items, and the average score is derived from the mean average of all responses. If the response is "I don't know", then the item is not included in the calculation. The lower total ECog and average ECog scores indicate better performance.

The NPI-D and the eNeuropsychiatric At-Home assessment are study partner reported outcome measures of 12 neuropsychiatric symptoms and the distress associated with these disturbances. The NPI-D total score is in the range from 0 to 144, with higher values indicating greater disturbance. The eNeuropsychiatric at-home assessment contains a subset of questions from the NPI-D and is scored similarly.

The memory function composite score, the executive function composite score, the DSST score, the overall eCognitive test scores, the total ECog score CCI , and the total NPI-D score will be analyzed using the same methodology as for the primary endpoint (Section 12.4).

PET CCI

The PET CCI will be examined at baseline and upon completion of week 12. An analysis of covariance (ANCOVA) will be performed on the log-transformed ratio to baseline of the relevant PET CCI outcome measure (details of the derivation of the outcome will be delineated in the statistical analysis plan). The model will include treatment group as a classification factor, log-transformed PET CCI , as well as other important baseline prognostic factors such as age and MMSE score, as covariates. The least squares estimates of mean treatment effects and treatment contrast, with corresponding 90% confidence intervals will be back transformed to the original scale. This analysis will be performed for each cohort separately. If deemed appropriate, data from the placebo group across different cohorts may be pooled.

Total CCI

For biotherapeutic agents, measurement of total CCI concentrations CCI is used as a PD marker to evaluate CCI . Total CCI concentration data will be listed by treatment, participant, and visit/sampling time point. Agent-specific information is detailed in Section 17, as applicable.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

The number (and proportion) of participants with adverse events of interest will be summarized by treatment.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

Standard 12-lead ECG

All ECG data will be listed by treatment group, participant and visit/time; abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment group and visit/time.

Other safety evaluations

C-SSRS data will be listed by treatment, participant, and visit/time; abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time, if deemed relevant.

Immunogenicity

For biotherapeutic agents, all immunogenicity results will be listed by treatment group, participant, and visit/time. Agent-specific information is detailed in Section 17, as applicable.

12.5.3 Pharmacokinetics

Agent serum concentration data (i.e. for biotherapeutic agents) or plasma concentration data (i.e. for low molecular weight agents) will be listed by treatment, participant, and visit/sampling time point. Commercially Confidential Information

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum.

Commercially Confidential Information

Pharmacokinetic parameters will be listed by treatment and participant. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is *Tmax* where median, minimum, and maximum will be presented, as applicable.

CSF to serum ratio will be calculated by the ratio of agent exposure in CSF to that in serum (for biotherapeutic agents) or plasma (for low molecular weight compounds).

Additional agent-specific information and pharmacokinetic parameters are detailed in Section 17.

12.5.4 PK/PD relationships

The relationships between individual PK profiles or derived PK parameters and efficacy/PD measurements may be explored using graphical approaches (e.g., scatter plots) and regression analysis as appropriate. Agent-specific information is detailed in Section 17, as applicable.

Commercially Confidential Information

Commercially Confidential Information

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

For the primary endpoint, change in NTB total z-score at week 24, data from 36 evaluable participants per arm (investigational agent and placebo) provides ~80% power to detect a statistically significant difference between the two groups at a 1-sided α=0.10 when the true standardized mean difference is 0.5. The effect size of 0.5 corresponds a moderate treatment effect which is thought to represent a clinically meaningful improvement at 24 weeks. To account for 15% dropout rate, approximately n=86 participants randomized in a 1:1 ratio would be needed to address the primary objective. These calculations take into account results of the published study by Frölich et al. (2019), where the standard deviation of the change in NTB total z-score was estimated to be ~0.38 for both active and placebo groups.

For smaller true effect sizes, the power is lower (Table 12-1 below).

Table 12-1 Sensitivity of power to changes in assumptions

SD (common to 2 arms)	True mean difference (Δ)	True effect size (Δ/SD)	alpha (1-sided)	Power
0.38	0.19	0.5	10%	80%
0.38	0.152	0.4	10%	66%
0.38	0.114	0.3	10%	50%
0.38	0.095	0.25	10%	41%

It is assumed that n=86 participants are randomized in a 1:1 ratio and the dropout rate is 15% (thus we have 72 evaluable participants, 36 per arm)

12.8.2 Secondary endpoint(s)

For the secondary endpoint, PET CCI , a comparison between an investigational agent and placebo will be based on data from approximately 10 participants per arm. Assuming inter-participant variability of 20%-25%, the power to detect statistically significant treatment difference (using 1-sided α=-0.05) is shown in Table 12-2 below. For the 25% true mean reduction in microglial activation due to an anti-inflammatory agent vs. placebo, there is at least 87% power (assuming coefficient of variation is 25% or less).

Table 12-2 Power for treatment comparison using log-transformed PET CCI at week 12

Coefficient of variation (CV)	True mean reduction (active vs. placebo)	α (1-sided)	Power
0.2	30%	5%	99%
0.2	25%	5%	93%
0.2	20%	5%	78%
0.25	30%	5%	93%
0.25	25%	5%	81%
0.25	20%	5%	62%

The assumed sample size is n=20 (10 per arm)

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

Commercially Confidential Information

Aisen PS, Cummings J, Jack CR, et al (2017) On the path to 2025: understanding the Alzheimer's disease continuum. Alzheimers Res Ther; 9:60.

Commercially Confidential Information

Basu A, Krady JK, Levison SW (2004) Interleukin-1: a master regulator of neuroinflammation. J. Neurosci. Res; 78:151-6.

Bitterman DS, Cagney DN, Singer LL, et al (2020) Master Protocol Trial Design for Efficient and Rational Evaluation of Novel Therapeutic Oncology Devices. J. Natl. Cancer Inst; 112:229-237.

Commercially Confidential Information

Bradburn S, Murgatroyd C, Ray N (2019) Neuroinflammation in mild cognitive impairment and Alzheimer's disease: A meta-analysis. Ageing Res. Rev; 50:1-8.

Commercially Confidential Information

Brown AK, Fujita M, Fujimura Y, et al (2007) Radiation dosimetry and biodistribution in monkey and man of 11C-PBR28: a PET radioligand to image inflammation. J. Nucl. Med; 48:2072-9.

Commercially Confidential Information

Butchart J, Brook L, Hopkins V, et al (2015) Etanercept in Alzheimer disease: A randomized, placebo-controlled, double-blind, phase 2 trial. Neurology; 84:2161-8.

Cacabelos R, Alvarez XA, Fernández-Novoa L, et al (1994) Brain interleukin-1 beta in Alzheimer's disease and vascular dementia. Methods Find Exp Clin Pharmacol; 16:141-51.

Chou RC, Kane M, Ghimire S, et al (2016) Treatment for Rheumatoid Arthritis and Risk of Alzheimer's Disease: A Nested Case-Control Analysis. CNS Drugs; 30:1111-1120.

Commercially Confidential Information

Cummings JL (2008) Controversies in Alzheimer's disease drug development. Int Rev Psychiatry; 20:389-95.

Delrieu J, Piau A, Caillaud C, et al (2011) Managing cognitive dysfunction through the continuum of Alzheimer's disease: role of pharmacotherapy. CNS Drugs; 25:213-26.

Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')' (2011) Official Journal C 172, 1-13. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52011XC0611(01)

Di Bona D, Plaia A, Vasto S, et al (2008) Association between the interleukin-1beta polymorphisms and Alzheimer's disease: a systematic review and meta-analysis. Brain Res Rev; 59:155-63.

Commercially Confidential Information

FDA Draft Guidance for Industry: Safety Assessment for IND Safety Reporting (CDER 2015).

Farias ST, Mungas D, Reed BR, et al (2008) The measurement of everyday cognition (ECog): scale development and psychometric properties. Neuropsychology; 22:531-44.

Forlenza OV, Diniz BS, Talib LL, et al (2009) Increased serum IL-1beta level in Alzheimer's disease and mild cognitive impairment. Dement Geriatr Cogn Disord; 28:507-12.

Garcia C, Leahy B, Corradi K, et al (2008) Component structure of the Repeatable Battery for the Assessment of Neuropsychological Status in dementia. Arch Clin Neuropsychol; 23:63-72.

Gilman S, Koller M, Black RS, et al (2005) Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology; 64:1553-62.

Harrison J, Minassian SL, Jenkins L, et al (2007) A neuropsychological test battery for use in Alzheimer disease clinical trials. Arch. Neurol; 64:1323-9.

Harrison JE & Caveney A (2012) 10 Years of the Neuropsychological Test Battery. PRO Newsletter 46; Fall Issue:1-5.

Harrison JE (2018) Cognition comes of age: comments on the new FDA draft guidance for early Alzheimer's disease. Alzheimers Res Ther; 10:61.

Heneka MT, Carson MJ, El Khoury J, et al (2015) Neuroinflammation in Alzheimer's disease. Lancet Neurol; 14:388-405.

Heringa SM, van den Berg E, Reijmer YD, et al (2014) Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population - the Hoorn Study. Psychoneuroendocrinology; 40:108-18.

Holmes C, Cunningham C, Zotova E, et al (2011) Proinflammatory cytokines, sickness behavior, and Alzheimer disease. Neurology; 77:212-8.

Holmgren S, Hjorth E, Schultzberg M, et al (2014) Neuropsychiatric symptoms in dementia-a role for neuroinflammation? Brain Res. Bull; 108:88-93.

Hori Y, Takeda S, Cho H, et al (2015) A Food and Drug Administration-approved asthma therapeutic agent impacts amyloid β in the brain in a transgenic model of Alzheimer disease. J. Biol. Chem; 290:1966-78.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (2003) ICH Harmonised Tripartite Guideline on the Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting E2D.

Jack CR, Bennett DA, Blennow K, et al (2018) NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement; 14:535-562.

Jaeger J, Hardemark H-G, Zettergren A, et al (2011) Does repeated daily testing improve measurement sensitivity to the cognitive effects of Donepezil in mild to moderate Alzheimer's Disease. Alzheimer's and Dementia; 74:P4-421.

Jutten RJ, Harrison J, Lee Meeuw Kjoe PR, et al (2018) A novel cognitive-functional composite measure to detect changes in early Alzheimer's disease: Test-retest reliability and feasibility. Alzheimers Dement (Amst); 10:153-160.

Karin A, Hannesdottir K, Jaeger J, et al (2014) Psychometric evaluation of ADAS-Cog and NTB for measuring drug response. Acta Neurol. Scand; 129:114-22.

King E, O'Brien J, Donaghy P, et al (2019) Inflammation in mild cognitive impairment due to Parkinson's disease, Lewy body disease, and Alzheimer's disease. Int J Geriatr Psychiatry; 34:1244-1250.

Kinney JW, Bemiller SM, Murtishaw AS, et al (2018) Inflammation as a central mechanism in Alzheimer's disease. Alzheimers Dement (N Y); 4:575-590.

Commercially Confidential Information

Kreisl WC, Lyoo CH, Liow JS, et al (2016) (11)C-PBR28 binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol. Aging; 44:53-61.

Kreisl WC, Lyoo CH, McGwier M, et al (2013) In vivo radioligand binding to translocator protein correlates with severity of Alzheimer's disease. Brain; 136:2228-38.

Commercially Confidential Information

Lanctôt KL, Amatniek J, Ancoli-Israel S, et al (2017) Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms. Alzheimers Dement (N Y); 3:440-449.

Commercially Confidential Information

Nordengen K, Kirsebom BE, Henjum K, et al (2019) Glial activation and inflammation along the Alzheimer's disease continuum. J Neuroinflammation; 16:46.

Commercially Confidential Information

Parbo P, Ismail R, Hansen KV, et al (2017) Brain inflammation accompanies amyloid in the majority of mild cognitive impairment cases due to Alzheimer's disease. Brain; 140:2002-2011.

Perez-Nievas BG, Stein TD, Tai HC, et al (2013) Dissecting phenotypic traits linked to human resilience to Alzheimer's pathology. Brain; 136:2510-26.

Polsek D, Gildeh N, Cash D, et al (2018) Obstructive sleep apnoea and Alzheimer's disease: In search of shared pathomechanisms. Neurosci Biobehav Rev; 86:142-149.

Prince M, Wimo A, Guerchet M, et al (2015) World Alzheimer's Report 2015: The Global Impact of Dementia. An Analysis of Prevalence, Incidence, Cost and Trends. In Alzheimer's Disease International (ADI), London, August 2015.

Quintanilla RA, Orellana DI, González-Billault C, et al (2004) Interleukin-6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway. Exp. Cell Res. 295:245-57.

Commercially Confidential Information

Commercially Confidential Information

Stella F, Forlenza OV, Laks J, et al (2015) Caregiver report versus clinician impression: disagreements in rating neuropsychiatric symptoms in Alzheimer's disease patients. Int J Geriatr Psychiatry; 30:1230-7.

Swardfager W, Lanctôt K, Rothenburg L, et al (2010) A meta-analysis of cytokines in Alzheimer's disease. Biol. Psychiatry; 68:930-41.

Tao Q, Ang TFA, DeCarli C, et al (2018) Association of Chronic Low-grade Inflammation With Risk of Alzheimer Disease in ApoE4 Carriers. JAMA Netw Open; 1:e183597.

Commercially Confidential Information

Teixeira FB, Saito MT, Matheus FC, et al (2017) Periodontitis and Alzheimer's Disease: A Possible Comorbidity between Oral Chronic Inflammatory Condition and Neuroinflammation. Front Aging Neurosci; 10:327.

U.S. Food and Drug Administration Center for Drug Evaluation and Research (2018) Early Alzheimer's Disease: Developing Drugs for Treatment. Guidance for Industry. Draft Guidance..

Commercially Confidential Information

Vogel A, Stokholm J, Gade A, et al (2004) Awareness of deficits in mild cognitive impairment and Alzheimer's disease: do MCI patients have impaired insight? Dement Geriatr Cogn Disord 17:181-7.

Commercially Confidential Information

Wang H, Mei Zl, Zhong KL, et al (2014) Pretreatment with antiasthmatic drug ibudilast ameliorates Aβ 1-42-induced memory impairment and neurotoxicity in mice. Pharmacol. Biochem. Behav; 124:373-9.

Weintraub S, Carrillo MC, Farias ST, et al (2018) Measuring cognition and function in the preclinical stage of Alzheimer's disease. Alzheimers Dement (N Y); 13:64-75.

Winblad B, Gauthier S, Scinto L, et al (2008) Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology; 70:2024-35.

Wisdom NM, Mignogna J, Collins RL (2012) Variability in Wechsler Adult Intelligence Scale-IV subtest performance across age. Arch Clin Neuropsychol; 27:389-97.

Woodcock J, LaVange LM (2017) Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N. Engl. J. Med; 377:62-70.

Commercially Confidential Information

Yu YJ, Watts RJ (2013) Developing therapeutic antibodies for neurodegenerative disease. Neurotherapeutics; 10:459-72.

Zettergren A, Jaeger J, Hardemark H-G, et al (2011) Repeated baseline cognitive measurements in mild to moderate AD patients reveal significant day-to-day variation. Alzheimers and Dementia; 7:P4-437.

Zhang C, Griciuc A, Hudry E, et al (2018) Cromolyn Reduces Levels of the Alzheimer's Disease-Associated Amyloid β-Protein by Promoting Microglial Phagocytosis. Sci Rep; 8:1144.

Commercially Confidential Information

Zou J, Tao S, Johnson A, et al (2020) Microglial activation, but not tau pathology, is independently associated with amyloid positivity and memory impairment. Neurobiol. Aging; 85:11-21.

16 Appendices

16.1 Appendix 1: Neurological Symptoms or Signs

New neurological findings are defined as clinical signs or symptoms that raise concern in respect to neurological conditions. They include but are not limited to:

- Significant new or worsening neurological symptoms or signs, as reported spontaneously by the participants/study partners at any time, or detected during the scheduled physical/neurological examinations, including but not limited to new or worsening peripheral neuropathies, visual disturbances or seizures
- Worsening of cognition not consistent with the previous clinical course, as reported spontaneously by the participants/study partners at any time or observed at the clinical assessments (e.g. NTB, NPI)

Investigators will be asked to review the finding and initiate any additional tests as needed. Summary of the findings will be provided to the Safety Monitor, regardless of the suspected relationship to investigational drug.

16.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline	• ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Table 16-2 Follow up requirements for liver laboratory triggers – ALT, AST, TBL

	ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
	If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:**	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

	ALT	TBL	Liver Symptoms	Action
	ALT > 2 x baseline or > 300 U/L (whichever occurs first)			

Table 16-3 Follow up requirements for liver laboratory triggers – Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 x ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 x ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

Table 16-4 Exclusion of Underlying Liver Disease

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, gGT, MCV, CD-transferrin
Nonalcoholic hepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion Ultrasound or MRI
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate
Wilson disease	Caeruloplasmin
Hematochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin defiency	Alpha-1-antitrypsin

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-5 Specific Renal Alert Criteria and Actions and Event Follow-up

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ³ 50 % **+** **OR if <18 years old, eGFR 35 mL/min/1.73 m²**	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider participant hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	• Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[+] Corresponds to KDIGO criteria for Acute Kidney Injury

Additional specialized assessments are available to assess renal function or renal pathology.

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

Table 16-6 Follow-up of Renal Events

FOLLOW-UP OF RENAL EVENTS
Assess, document and record in CRF • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
Monitor participant regularly (frequency at investigator's discretion) until - • Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. • Analysis of urine markers in samples collected over the course of the DIN event

17 Cohort Specific Information

This section contains details that pertain to specific cohorts and should be considered as supplementary to information presented in the preceding core protocol sections and respective Investigator Brochures or country-specific product labels for marketed agents. If there are no cohort- or treatment-specific details presented for a given topic (e.g., cohort- or treatment-specific eligibility criteria, study restrictions, food effects, etc.), then the information in the corresponding section in the core protocol for that topic should be implemented without further adjustment.

17.1 Cohort 1 ACZ885

Cohort 1 will evaluate the use of canakinumab (ACZ885 or Ilaris) as an anti-inflammatory agent for the symptomatic treatment of cognition in participants with MCI due to AD or mild AD who have evidence of peripheral inflammation.

Approximately 86 participants will be randomized in a 1:1 ratio to one of the following treatment arms:

- Arm 1: canakinumab 150 mg (1 x 150 mg solution) plus matching placebo (1 x 150 mg solution) SC q 4 weeks for the first 2 doses followed by 300 mg (2 x 150 mg solution) SC q 4 weeks for the subsequent 4 doses
- Arm 2: Matching placebo

17.1.1 Introduction

This treatment arm will evaluate canakinumab alone. As this treatment has an extended half-life, the EOC2 visit will serve as the end-of-study visit for participants randomized to this cohort.

The step-up visit schedule for day 8, 15, 22, and 36, does not apply to this agent/cohort.

17.1.2 Background

Key information on canakinumab is shown in Table 17-1. Please refer to sections following this table or the canakinumab and country-specific product label for additional details.

Table 17-1 Key Information on canakinumab

	canakinumab
Reference	IB
Drug type	Human monoclonal antibody
Half-life	26 days
Five half-lives	130 days
Generic name	Canakinumab
Formulation	Subcutaneous
Maximal planned clinical dose	300 mg q4 weeks
Target	Anti-human interleukin-1ß (IL-1ß) antibody
Pharmacology	Blocks the interaction of IL-1ß with the IL-1 receptor (IL-1R), leading to inhibition of its downstream targets, thereby preventing IL-1 β-induced gene activation and the production of inflammatory mediators.

	canakinumab
Metabolism	Elimination pathways for the IgG-type mAbs such as canakinumab are distinct from metabolic pathways of small molecules. The IgG-based molecules are cleared from the body by a combination of processes such as proteolysis by the liver, elimination by the reticuloendothelial system (RES) and nonspecific endocytosis.
Potential to interact with other drugs based on in vitro studies	No study was conducted with canakinumab or its mouse surrogate, 1BSUR, to investigate drug-drug interaction in non-clinical species.
Reference safety information (RSI)*	System organ classes (SOCs) in the reference safety information tables as of the latest IB include infections and infestations across all indications below, in addition to the following: *CAPS:* • Nervous system disorders *Periodic fever syndromes* • Investigations (platelet count decreased) *SJIA:* • Gastrointestinal disorders • Immune system disorders • Investigations (transaminsases increased, platelet count decreased, neutrophil count decreased, white blood cell count decreased) *Oncology:* • Investigations (blood creatine phosphokinase increased) • Blood and lymphatic system disorders *Gouty arthritis and Cardiovascular risk reduction:* • No additional SOCs Based on similarities of the patient population with Alzheimer's disease (including elderly, hypertensive, diabetes, cardiovascular disease, chronic obstructive pulmonary disease), the RSI Table 6-5 from the Cardiovascular risk reduction program (CANTOS) will be used as the RSI table for this study.
Selected safety risks†	For inflammatory indications, canakinumab is associated with an **increased incidence of infections**, including isolated cases of unusual or opportunistic infections (aspergillosis, atypical mycobaterial infections and herpes zoster). The majority of the events were mild to moderate, although serious infections with fatal outcome have been reported. The most frequent infections were predominantly of the upper respiratory tract. There is no significant difference in the safety profile observed in patients' ≥ 65 years of age.

	canakinumab
	In patients with cardiovascular risk (CANTOS), there was a slight increased risk of serious infections, as well as fatal sepsis, fatal pneumonia and fatal respiratory tract infection, in patients treated with canakinumab compared with placebo. However, the overall incidence remains low. In the large CANTOS study (>10,000 patients with cardiovascular risk), no tuberculosis reactivation was seen, and the overall frequency of reporting of opportunistic infections was low (0.1 - 0.2%) and balanced between patients on canakinumab and on placebo. **Malignancy events** have been reported in patients treated with canakinumab during clinical development. However, in patients with cardiovascular risk (CANTOS), the overall incidence of malignancy AEs was numerically lower in the canakinumab groups compared with placebo and this was largely due to a lower incidence of lung cancer. In inflammatory indications, the following **blood abnormalities** were observed: decreased white blood cell count and absolute neutrophil counts were reported. In patients with cardiovascular risk (CANTOS), small decreases in mean neutrophil counts were seen in patients taking canakinumab, but most patients remained within the normal range. Neutropenia was not associated with a greater risk of infections. In inflammatory indications, mild and transient decreases in platelet counts were observed at a higher incidence with canakinumab. In patients with cardiovascular risk (CANTOS), a dose-dependent increase in thrombocytopenia AEs and CTC Grade 1 platelet count abnormalities was observed for canakinumab relative to placebo. Grade 2 abnormalities occurred at low and comparable rates between canakinumab 150 mg group, while Grade 3 or 4 abnormalities were rare and rates were comparable across the treatment groups (0.4% of patients on 150 mg canakinumab and 0.4% of patients on placebo). The cumulative post-marketing patient exposure since the first launch of the product was estimated to be 44475 patient-treatment years (cut-off 30-Jun-2020). A review of safety data at the cut-off date of this document did not reveal any new or changing safety-related information beyond the known safety profile of canakinumab. All the safety data remains in accord with the previous cumulative experience.

*Reference safety information in Section 6 of the IB contains those serious adverse reactions that are considered causally related to the drug and therefore meet the health authority definition of "expected."

†Based on the current medical review of the preclinical and clinical data, these risks are or may reasonably be expected to be causally related to the drug and have potential clinical relevance. Please see Section 7 of the IB for additional information on other potential and hypothetical risks.

17.1.2.1 Interleukin I

IL-1ß is mainly produced by mononuclear phagocytes in response to injury and infection, and plays a clinically significant role in the pathobiology of autoinflammatory syndromes (e.g., CAPS, TRAPS, HIDS/MKD, FMF; Still's disease including both SJIA and AOSD, and gout). It may also play a key role in other chronic inflammatory conditions such as type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease.

A meta-analysis of the literature revealed that IL-1ß is one of the key peripheral cytokines that is raised in AD (Swardfager et al 2010). Increased levels of IL-1β have additionally been detected in the brain tissue of AD patients (Cacabelos et al 1994), and IL-1β polymorphisms appear to increase the risk of AD (Di Bona et al 2008). IL-1β levels are already elevated early on in the MCI stage of AD and appear to remain elevated as the disease progresses (Forlenza et al 2009).

IL-1ß is a major proinflammatory cytokine in the brain, playing an integral role in the orchestration of other proinflammatory cytokines, such as TNF-a and CCI Elevated levels of IL-1 have been implicated with increased APP production, beta amyloid plaque deposition and the steps leading up to hyperphosphorylation of tau (Kinney et al 2018; Quintanilla et al 2004). It has also been suggested that the increase of APP and amyloid burden results in a vicious circle of IL-1ß production and microglia activation (Kinney et al 2018). Disrupting IL-1β may delay the onset of neurodegeneration (Basu et al 2004).

Canakinumab is expected to treat the signs and symptoms of inflammation and potentially the underlying structural damage of the disease. Several genes involved in glial clearance of misfolded proteins and inflammatory reactions have been associated with increased risk of AD (Heneka et al 2015).

17.1.2.2 ACZ885

Canakinumab is a high-affinity human monoclonal antihuman interleukin-1ß antibody of the IgG1/k isotype, which is marketed and under ongoing development for the treatment of IL-1ß driven inflammatory and oncologic diseases. By binding specifically to human IL-1β, canakinumab blocks the interaction of IL-1β with the IL-1R, leading to inhibition of its downstream targets, thereby preventing IL-1 β-induced gene activation and the production of inflammatory mediators.

Commercially Confidential Information

17.1.2.2.2 ACZ885 Clinical data

Human safety and tolerability data

Canakinumab (Ilaris®) is approved for the treatment of periodic fever syndromes (CAPS, TRAPS, HIDS/MKD, FMF) and Still's disease (includes AOSD and SJIA) in pediatric and adult patients. Canakinumab (Ilaris®) is also approved for the symptomatic treatment of GA attacks. The post-marketing cumulative patient exposure since the first launch of the product is estimated to be approximately 44,475 patient-treatment years (cut-off 30-Jun-2020). A review of safety data at the cut-off date did not reveal any new or changing safety-related information beyond the known safety profile of canakinumab.

As of 30 June 2020, an estimated 14,062 patients have received canakinumab treatment in 82 Novartis-sponsored investigational clinical trials and 17 investigator-initiated trials in a wide spectrum of IL-1ß driven diseases such as CAPS, mild asthma, psoriasis, gouty arthritis (GA), rheumatoid arthritis (RA), system juvenile idiopathic arthritis (sJIA), and the majority of

participants (6717) being enrolled in the CANTOS study investigating the prevention of recurrent cardiovascular events in patients with a prior myocardial infarction and an elevated hs-CRP.

The doses administered i.v. ranged from 0.03 mg/kg to 10 mg/kg or a fixed dose of 600 mg, the doses administered s.c. ranged from 0.5 mg/kg to 9 mg/kg s.c. or fixed doses of 5 mg to 600 mg s.c., and the dose for intra articular administration was 150 mg to 600 mg. The frequency of dosing ranged from a single dose to quarterly repeated administration or treatment upon flare in GA. Every four weeks s.c. dosing of 4 mg/kg up to 300 mg is approved by the FDA in SJIA.

Canakinumab has a half-life varied between 3 and 4 weeks, and has been well-tolerated by patients at all dose levels investigated. So far, the duration of exposure to canakinumab is more than 8 years for the first 4 MWS patients enrolled in the CACZ885A2102 trial. Final and preliminary data from completed clinical trials demonstrate efficacy as well as good safety in patients with CAPS, SJIA, RA and gouty arthritis. The details of SAEs and AEs of the completed studies and relevant details of the SAEs of the ongoing studies are summarized in the latest version of the IB. Adverse events in unblinded studies ranged from mild to moderate in severity and included upper respiratory tract infections, nasopharyngitis and otitis, headache, nausea, diarrhea, and asthenic conditions.

Immunogenicity has not proved to be a significant concern for canakinumab. Canakinumab studies across multiple indications and dosing regiments have demonstrated that the incidence of treatment-emergent ADA development remains very low, in the range of 0.5% to 2.9%. No clinical consequences to these detected antibodies are evident.

Human pharmacokinetic data

Canakinumab has the expected pharmacokinetics of an IgG1-type antibody with a low volume of distribution (VSS=6.0 L) and low clearance that is dependent on body weight (e.g., CL=0.174 L/day in a CAPS patient of body weight 70 kg, 0.11 L/day in a SJIA patient of body weight 33 kg and 0.23 L/day in a gout patient of body weight 93 kg). Half-lifes vary between 21 and 30 days. Within the dose range studies, the pharmacokinetics of canakinumab were linear. The systemic exposure parameters, AUC and Cmax, increase in proportion to dose over the dose range of 0.30 to 10.0 mg/kg given as i.v. infusion and from 150 mg to 300 mg when administered as an s.c. injection. The absolute bioavailability of s.c. canakinumab is 70%. A mathematical model to characterize the binding kinetics of canakinumab to IL-1ß has been created. The model successfully fits the patient data and allows estimation of canakinumab clearance volumes of distribution, together with IL-1ß rate of release and half-lives.

Human pharmacodynamic data

Canakinumab binds to and inactivates IL-1ß and blocks downstream events of IL-1ß signaling, including IL-1ß production, IL-1ß pathway-related gene activation, elevation of acute phase proteins, such as serum amyloid A (SAA) and C-reactive protein (CRP), and mobilization of neutrophils and platelets from bone marrow.

Normally undetectable, serum IL-1ß becomes detectable in humans when complexed with canakinumab. These IL-1ß/canakinumab complexes are biologically inactive and have been utilized in all clinical studies as a surrogate PD marker because their increase reflects the reduction of free IL-1ß levels caused by binding to canakinumab.

17.1.2.3 ACZ885 Dose Rationale

Typically, a very small portion of systemically administered biotherapeutic antibodies crosses the blood brain barrier to enter the CNS with an estimated 0.1 – 0.2% of circulating antibodies found in the brain at steady-state concentrations (Yu and Watts 2013). To maximize the CNS exposure and expected pharmacological effect in the central nervous system, EXPLAIN-AD will escalate the dose regimen up to 300 mg s.c. every 4 weeks as this represents the currently highest approved dosing of canakinumab. US and European Health Authorities approvals for this dose regimen include different indications like TRAPS, HIDS/MKD and FMF and Still`s disease (AOSD and SJIA).

For additional information please review the following:

- For EMA Summary of Product Characteristics, 2020: https://www.ema.europa.eu/en/medicines/human/EPAR/ilaris#product-information-section;
- For FDA Highlights of Prescribing Information, 2016: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125319s088lbl.pdf

In Novartis study CACZ885D2201, NOMID and CINCA patients with a history of severe CNS inflammation were treated with canakinumab at 150 mg s.c. (or 2 mg/kg in patients ≤ 40kg) or 300 mg (or 4 mg/kg) with escalation up to 600 mg (or 8 mg/kg) up to every 4 weeks as necessary. In this 24-month open label study, approximately 0.3% of canakinumab was detected in the CSF of the patients as well as increased levels of IL-1beta, which indicates that canakinumab binds and stabilizes its target in the central nervous system. Overall, Canakinumab was well tolerated by the 11-34 years old patient population in this study (Investigator Brochure).

For the current study, AD patients with an age of greater than or equal to 45 years and less than or equal to 90 years will be enrolled. An elderly population was well represented in previous Novartis study CACZ885M2301 (CANTOS). In this double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab, 10061 stable post-myocardial infarction patients with elevated hsCRP were randomized for the prevention of recurrent cardiovascular events. 37.5% of these patients, who were at cardiovascular risk were ≥ 65 years old, as were very elderly patients (9.2% were ≥ 75 years old). The safety profile in elderly patients in CANTOS, treated with 300 mg canakinumab s.c. every 12 weeks was consistent with that in the overall population. In general, elderly patients have a higher rate of AEs, but that was the same for patients on canakinumab and on placebo (Investigator Brochure).

Hence, for the EXPLAIN-AD study, we will start at 150 mg every 4 weeks for the first two doses, and provided that the safety and tolerability of this initial dose is acceptable via investigator judgement, will then increase to 300 mg every 4 weeks for the remainder of the study period. Any deviations from this dosing scheme are not allowed. Any participant who, in the opinion of the investigator, does not tolerate the 150mg starting dose should be discontinued from study treatment. Additionally, in the opinion of the investigator, if any participant does not tolerate the 300mg dose, the dose cannot be modified or lowered and the participant should be discontinued from study treatment. See Section 9.1.1 and Section 17.1.4.1 for further details.

17.1.3 Specific Exclusion Criteria

IMPORTANT

The treatment specific exclusion criteria for this treatment arm are located below. However, there are also core exclusion criteria (Section 5.2) that apply to all participants enrolled into this study.

Participants fulfilling any of the following criteria are not eligible for this cohort:

1. History of septic arthritis in the past 12 months prior to the screening visit
2. History of sepsis of prosthesis in the past 12 months prior to the screening visit
3. History of leg ulcers
4. In-dwelling urinary catheter
5. History of ongoing, chronic or recurrent infectious disease
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using effective methods of contraception during dosing of investigational drug and until three months after last dose of study treatment. Effective contraception methods include:
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
   - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository.
   - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

   In case of use of oral contraception, women should be stable on the same pill for a minimum of 3 months before taking study treatment.

   Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

   If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).**Male contraception is not required for the study of canakinumab (Cohort 1).**

7. Participants with neutropenia, as defined by absolute neutrophil count (ANC) < 1.5 x 10^9 /l, or leukopenia, as defined by leukocytes less than 3,500 cells per microliter (3.5 × 10^9/L) at screening and/or baseline

17.1.4 Study Treatment

Table 17-2 Investigational Drug

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
1 mL canakinumab (ACZ885) solution at 150 mg/1 mL	Clear to opalescent, colorless to slightly brownish-yellowish solution for injection	Subcutaneous	Double-blind kits	Global
1 mL Placebo	Clear to opalescent colorless to slightly brownish-yellowish solution for injection	Subcutaneous	Double-blind kits	Global

Study medication at 1 x 150 mg canakinumab (ACZ885) solution plus 1 x 1 mL placebo solution will be administered subcutaneously in clinic once every 4 weeks for the first 2 doses, followed by 2 x 150 mg canakinumab (ACZ885) solution administered subcutaneously in clinic once every 4 weeks for the remainder of the study. Refer to the canakinumab (ACZ885) Pharmacy Manual for further information.

Table 17-3 Cohort 1 Agent Administration Schedule

Visit Name	Screening	Baseline	Treatment						EOC1	EOC2
Days	**-60 to -8**	**-7 to -1**	**1**	**29 (+/-2)**	**57 (+/-2)**	**85 (+/-3)**	**113 (+/-2)**	**141 (+/-2)**	**171 (+2)**	**281 (+/-2)**
Study agent administration			X	X	X	X	X	X		

17.1.4.1 Discontinuation from study treatment – Cohort 1

IMPORTANT

The Cohort-specific reasons for discontinuation from study treatment are located below. However, there are also core reasons for discontinuation from study treatment (Section 9.1.1) that also apply to all participants enrolled into this study. Please also refer to Section 9.1.1 for complete details on the discontinuation from study treatment.

In addition to those circumstances listed in Section 9.1.1, for participants enrolled in Cohort 1, discontinuation from study treatment is also required under the following circumstances:

- In the opinion of the investigator, participant does not tolerate the starting dose of 150mg administered at Day 1 or Day 29 **or** does not tolerate the increased dose of 300mg administered starting at Day 57
- Participant misses more than two doses

17.1.5 Drug-drug Interactions

Interactions between canakinumab (Ilaris) and other medicinal products have not been investigated in formal studies.

Immunization

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving canakinumab. Therefore, live vaccines should not be given concurrently with canakinumab.

Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as canakinumab, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin). Upon initiation of canakinumab, in participants being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

17.1.6 Food Effects

Not applicable for this investigational agent.

17.1.7 Specific Restrictions for Study Participants

17.1.7.1 Prohibited Medications

Use of the treatments displayed in Table 17-4 is not allowed for this treatment arm for the duration of the prohibited period defined below.

Table 17-4 Prohibited Medications Cohort 1

Medication	Prohibited Period
Live vaccinations	Must not be given before 90 days of the baseline visit. Must not be given until 130 days after end of study treatment dosing.
TNF inhibitors	Must be stopped before 90 days of the baseline visit. Must not be started until 130 days after end of study treatment dosing.

17.1.7.2 Dietary Restrictions

There are no specific dietary restrictions for this cohort including dietary supplements and nutraceuticals.

17.1.8 PK/PD/IG CCI Assessment Schedule

Commercially Confidential Information

Commercially Confidential Information

17.1.9 Pharmacokinetics

Canakinumab concentrations will be assessed in serum and in CSF of all agent-treated participants.

Serum and CSF PK samples will be collected at the timepoints defined in the PK/PD/IG Assessment Schedule (Table 17-5) according to the instructions outlined in the SOM regarding tube handling, sample collection, numbering, processing and shipment. Any CSF samples having more than 500 red blood cells/µL must be documented, as such high cell counts may impact PK analysis. In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples for blood and CSF draws and total blood and CFS volume collected will not exceed those stated in the protocol.

Commercially Confidential Information

17.1.9.1 Pharmacokinetic analytical method(s)

An ELISA method will be used for bioanalytical analysis of canakinumab in serum and CSF. The anticipated Lower Limit of Quantification (LLOQ) and method specifics will be listed in the central laboratory manual. The detailed method description to assess canakinumab concentration will be described in the bioanalytical raw data of the study and in the respective BDR.

Commercially Confidential Information

17.1.9.2 Pharmacokinetic parameters

Commercially Confidential Information

CSF to serum antibody concentration ratio [%] will be calculated as follows: (Canakinumab concentration in CSF / Canakinumab concentration in serum) * 100.

Commercially Confidential Information

A previously utilized and validated mixed effects modeling approach may be used to characterize the exposure-related PK parameters (i.e., AUC and CL) of canakinumab. These results may be reported in a separate report

17.1.10 Total CCI

Serum and CSF pharmacodynamic samples will be collected at the timepoints defined in the PK/PD/IG Assessment Schedule (Table 17-5). Instructions are outlined in the SOM regarding tube handling, sample collection, numbering, processing, and shipment.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Pharmacodynamic (PD) samples will be obtained and evaluated in all participants, including the placebo group.

Commercially Confidential Information

17.1.10.1 Total CCI assessment

Measurement of total Commercially Confidential Information in serum and CSF is used as a PD marker to evaluate CCI .

17.1.10.2 Total CCI analytical method

Total CCI will be analyzed in serum and CSF by means of a sandwich enzyme-linked immunosorbant (ELISA) assay; the anticipated Lower Limit of Quantification (LLOQ) and method specifics will be listed in the central laboratory manual. Details of the analytical method to assess total CCI in serum and CSF will be described in the Bioanalytical Data Report (BDR).

Concentrations of serum and CSF total Commercially Confidential Information will be given in mass per volume units. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

17.1.11 Immunogenicity (Anti-ACZ885 Antibodies)

IG samples will be obtained and evaluated in serum of all agent treated participants.

To assess potential immunogenicity, serum samples for determination of anti-canakinumab antibodies will be collected at the timepoints defined in the PK/PD/IG Assessment Schedule (Table 17-5). Instructions are outlined in the SOM regarding tube handling, sample collection, numbering, processing, and shipment. In order to better define immunogenicity, the timing of the IG sample collection may be altered based on emergent data. The number of samples for blood draws and total blood volume collected will not exceed those stated in the protocol.

IG serum samples remaining after completion of IG analysis may be used for exploratory assessment or other bioanalytical purposes (e.g., cross check between different sites).

17.1.11.1 Immunogenicity analytical method

An ELISA based method will be used for the detection of potential anti-canakinumab antibody formation. Method specifics will be listed in the central laboratory manual. The detailed method description to assess immunogenicity will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR).

Missing data will be labeled as such in the Bioanalytical Data Report.

17.1.12 Specific Safety Rules

17.1.12.1 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing assessed at the time points per the Assessment Schedule (Table 8-1). Additional pregnancy testing might be performed if requested by local requirements.

Serum HCG should be performed at screening and EOC1 visits and urine HCG at all other visits. A positive or equivocal urine HCG should be confirmed by serum HCG.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

17.1.12.2 Pregnancy reporting

Refer to Section 10.1.4 for guidance and actions to take if a female trial participant becomes pregnant.

17.1.13 Specific Study Design Considerations

As this treatment does have an extended half-life, the EOC2 visit will serve as the end-of-study visit for participants randomized to this cohort.