Official Title: A Single-Center, Randomized, Adaptive, Investigator/Subject Blind, Single Ascending Dose, Placebo-Controlled Phase I Study to Investigate the Safety, Tolerability, Immunogenicity and Pharmacokinetics of Intravenously Administered RO7126209 in Healthy Participants

NCT Number: NCT04023994

Document Date: Protocol Version 4: 31-Jul-2020

PROTOCOL

TITLE:	**A SINGLE-CENTER, RANDOMIZED, ADAPTIVE, INVESTIGATOR/ SUBJECT BLIND, SINGLE ASCENDING DOSE, PLACEBO-CONTROLLED PHASE I STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY AND PHARMACOKINETICS OF INTRAVENOUSLY ADMINISTERED RO7126209 IN HEALTHY PARTICIPANTS**
PROTOCOL NUMBER:	BP41192
VERSION:	4
IND NUMBER:	140740
TEST PRODUCT:	RO7126209
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 15 May 2019
DATE AMENDED:	Version 2: 05 July 2019 Version 3: 19 December 2019 Version 4: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
31-Jul-2020 09:24:00	Company Signatory	[redacted]

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A SINGLE-CENTER, RANDOMIZED, ADAPTIVE, INVESTIGATOR/ SUBJECT BLIND, SINGLE ASCENDING DOSE, PLACEBO-CONTROLLED PHASE I STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY AND PHARMACOKINETICS OF INTRAVENOUSLY ADMINISTERED RO7126209 IN HEALTHY PARTICIPANTS**
PROTOCOL NUMBER:	BP41192
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TEST PRODUCT:	RO7126209
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files, and return a copy to your local Site Monitor.

PROTOCOL AMENDMENT, VERSION 4:

RATIONALE

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AD	Alzheimer's Disease
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ARIA	Amyloid-related imaging abnormalities
AST	Aspartate aminotransferase
AUC	Area under the curve
BBB	Blood-brain barrier
BE	Bioequivalence
BM	Bone marrow
BP	Blood pressure
BS	Brain shuttle
[redacted]	[redacted]
CL	Clearance
CL/F	Apparent clearance
CMC	Chemistry manufacturing and control
C_{max}	Maximum concentration
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTD	Common technical document
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLE	Dose-limiting event
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture

Abbreviation	Definition
EDTRS	Early Diabetic Treatment Retinopathy Study
EEA	European Economic Area
ESF	Eligibility screening form
EU	European Commission
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
HBsAg	Hepatitis B surface antigen
HBcAb	Total hepatitis B core antibody
HCV	Hepatitis C
HDL	High-density lipoproteins
[redacted]	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgE	Immunoglobulin E
[redacted]	[redacted]
[redacted]	[redacted]
IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRF	Independent review facility
IRR	Infusion-related reaction
IUD	Intrauterine device
IV	Intravenous
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
LH	Luteinizing hormone
LPLV	Last participant, last visit
LPLO	Last participant, last observation
MAD	Multiple-ascending doses

Abbreviation	Definition
MD	Multiple doses
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHP	Non-human primate
NOAEL	No-observed-adverse-effect level
NSAESI	Non-serious adverse event of special interest
OTC	Over-the-counter
PD	Pharmacodynamic
PET	Positron emission tomography
PK	Pharmacokinetic
PT	Prothrombin time
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBC	Red blood cell
RNA	Ribonucleic acid
RR	RR interval
SAD	Single ascending dose
SAE	Serious adverse event
SC	Subcutaneous
SD	Single dose
[redacted]	[redacted]
SoA	Schedule of activities
SOC	Scientific Oversight Committee
SOP	Standard operating procedure
SPA	Statistical Programmer
SUSAR	Suspected unexpected serious adverse reactions
[redacted]	[redacted]
[redacted]	[redacted]
t_{max}	Time of maximum concentration observed
TQT	Thorough QT
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States

Abbreviation	Definition
V	Volume
V/F	Apparent volume of distribution
WBC	White blood cell

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A SINGLE-CENTER, RANDOMIZED, ADAPTIVE, INVESTIGATOR/ SUBJECT BLIND, SINGLE ASCENDING DOSE, PLACEBO-CONTROLLED PHASE I STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY AND PHARMACOKINETICS OF INTRAVENOUSLY ADMINISTERED RO7126209 IN HEALTHY PARTICIPANTS**
PROTOCOL NUMBER:	BP41192
VERSION:	3
TEST PRODUCT:	RO7126209
PHASE:	I

RATIONALE

RO7126209 is a bispecific (2+1) monoclonal antibody (mAb) construct that combines, by recombinant fusion the anti-Aβ antibody gantenerumab with a Brain Shuttle module [redacted] RO7126209 is being developed for the treatment of Alzheimer's Disease. This is the first study in which RO7126209 will be administered to humans. A randomized, investigator and subject blind, adaptive, placebo-controlled, parallel design was chosen to assess the safety, tolerability, immunogenicity and pharmacokinetics (PK) following single ascending doses of RO7126209 administered intravenously to healthy participants.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of single ascending intravenous (IV) doses of RO7126209 in healthy participants	• Incidence, severity, and causal relationship of adverse events (AEs). • Incidence of abnormal laboratory findings. • Incidence of abnormal vital signs and electrocardiogram (ECG) parameters

Objectives	Endpoints
Secondary	
• To investigate the single IV dose PK of RO7126209 in plasma of healthy participants	• Plasma PK parameters of RO7126209
• To investigate the cerebrospinal fluid (CSF) penetration after a single dose of RO7126209 in healthy participants	• Cerebral spinal fluid (CSF) concentration of RO7126209
• To evaluate the immunogenicity of a single dose of RO7126209 in healthy participants	• Incidence of anti-RO7126209 antibodies (ADAs)

OVERALL DESIGN

Study Design

Study BP41192 is a randomized, adaptive, placebo-controlled parallel group study to investigate the safety, tolerability, immunogenicity and pharmacokinetics of single ascending intravenous doses of RO7126209 in healthy participants.

This study uses a parallel group design, with participants recruited in 5 planned sequential cohorts. [redacted]. Participants will receive a single IV dose of either RO7126209 or placebo. A minimum of 4 active treatment and 2 placebo participants will be included in the first two dose levels. Starting in dose level 3, and in all subsequent cohorts, a minimum of 6 active treatment and 2 placebo participants will be included. Based upon the review of emerging data there will be the option to adjust the number of participants on active treatment or placebo per dose level. If a dose level is repeated or if a lower dose is investigated, the added group will consist of at least 2 participants on active treatment and 1 on placebo.

RO7126209 doses will be administered in ascending order, starting with a dose of 0.1 mg/kg that is expected to be well tolerated. Subsequent doses will be selected in an adaptive manner during study conduct based on emerging safety, tolerability and PK data. A Bayesian adaptive design using the continual reassessment method (CRM) for predicting anticipated maximum dose-limiting events (DLE) rate to guide dose effect relationship will also be applied for dose escalation.

Intermediate dose escalation steps other than those anticipated may be used, doses may be repeated or adjusted based on safety, tolerability and pharmacokinetic data at each dose level, as well as on model-based prediction of the anticipated maximum DLE rate.

In each dose group, sentinel dosing will be employed to allow for an evaluation of safety data by the Investigator up to 48 hours following intravenous administration of RO7126209 or placebo before subsequent participants are dosed. Therefore, the participants will be divided into two groups: 2 participants will be dosed one day (sentinel group with 1 on active treatment and 1 on placebo) and the remaining participants of that dose group no earlier than 72 hours after the first dosing occasion.

There will be at least 2 weeks between each dose level in order to permit adequate time for collation and review of emerging data before the next dose is administered.

The participants, investigators, and site personnel (except site personnel responsible for study drug accountability, reconciliation, record maintenance and drug preparation) will be blinded to treatment assignments.

Participants in the sentinel group will receive a single IV infusion of study medication (RO7126209 or matching placebo) [redacted]. No food will be permitted from 2 hours prior to dosing until 4 hours after start of infusion on Day 1.

Treatment Groups

The following tentative dose levels are planned:

- Dose level 1: 0.1 mg/kg RO7126209 or matching placebo
- Dose level 2: 0.3 mg/kg RO7126209 or matching placebo
- Dose level 3: 0.9 mg/kg RO7126209 or matching placebo
- Dose level 4: 2.7 mg/kg RO7126209 or matching placebo
- Dose level 5: 5.4 mg/kg RO7126209 or matching placebo

The dose levels are tentative, and may be revised based on emerging data. Higher doses than planned may be administered provided that all the dose escalation increments and stopping rules are followed. [redacted] with a maximum of 60 participants enrolled in the study.

If the safety data (AEs, ECGs, vital signs, laboratory safety tests, [redacted] assessments) of the first 48 hours following intravenous administration of RO7126209 or placebo is acceptable based on the judgment of the Investigator, the remaining participants will be dosed no earlier than 72 hours after the first dosing occasion.

Dose Escalation Decision Criteria

The decision to escalate to the next dose level will be made jointly by the Sponsor study team, the Investigator and any other person the Investigator or Clinical Pharmacologist considers necessary to assist with the decision.

Dose decisions (to escalate, reduce, or repeat) between cohorts will be made following review of all available cumulative (i.e., including emergent data from all previous cohorts) safety data (including AEs, laboratory safety test results, safety biomarker, ECGs, vital signs, [redacted]

The starting dose will be 0.1 mg/kg. Study treatment will be adaptive in nature. Doses may be repeated, adjusted downwards, or intermediate doses may be investigated based on safety, tolerability and PK data at each dose level, as well as on model-based prediction of the anticipated maximum DLE rate.

[redacted]

Due to the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor. This will not constitute a premature termination of the study.

The IMPs for this study are RO7126209 and matching placebo.

Length of Study

The total duration of the study for each participant will be approximately 16 weeks divided as follows:

- Screening: Up to 8 weeks
- In clinic period: Days -2 to 10
- Final follow-up: Day 57 ± 4

End of Study

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur 57 ± 4 days after last dose administration.

PARTICIPANT POPULATION

The participants in this study will be healthy male volunteers, between 18 and 40 years of age, inclusive, who fulfill all of the given inclusion criteria.

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria

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

Informed Consent

1. [redacted]

Age

2. [redacted]

Type of Participants

3. Healthy status is defined by the absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, ophthalmologic examination, hematology, blood chemistry, coagulation, serology, and urinalysis.
4. [redacted]

Weight

5. Body mass index (BMI) of 18-30 kg/m^2 inclusive

Sex

6. Male participants

During the treatment period (from dosing on Day 1) and until the final follow-up visit (Day 57 ± 4 days), agreement to:

- Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year, with a partner who is a woman of childbearing potential.

- With pregnant female partner, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.
- Refrain from donating sperm from Day 1 of the study until 90 days after last dose.

[redacted]

Exclusion Criteria

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

Medical Conditions

1. Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study.
2. History of any clinically significant gastrointestinal, renal, hepatic, broncho-pulmonary, neurological, psychiatric, cardiovascular, endocrinological, ophthalmologic, hematological or allergic disease, metabolic disorder, cancer or cirrhosis.
3. Any suspicion or history of alcohol abuse and/or suspicion of regular consumption of drug of abuse within the last 5 years.
4. Positive result on hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV) 1 and 2.
5. [redacted]
6. [redacted]
7. History or presence of clinically significant ECG abnormalities [redacted].
8. Clinically significant abnormalities [redacted]
9. Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration.
10. Impaired hepatic function as indicated by screening aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq$ 1.5 $\times$ the upper limit of normal (ULN) or abnormal total bilirubin unless due to Gilbert's disease.

11. Any clinically relevant history of hypersensitivity or allergic reactions, either spontaneous or following drug administration, or exposure to foods or environmental agents.
12. History of hypersensitivity to biologic agents or any of the excipients in the formulation.
13. History of raised intra-cerebral pressure or vertebral joint pathology.

Prior/Concomitant Therapy

14. Use of prohibited medication or herbal remedies as described in the section of concomitant medications.
15. Prior administration of gantenerumab (RO4909832).
16. Any vaccination within two months prior to Day 1.

Prior/Concurrent Clinical Study Experience

17. Participation in an investigational drug medicinal product or medical device study within 30 days before screening or within seven times the elimination half-life if known, whichever is longer.

Other Exclusions

18. Participants who regularly smoke more than 5 cigarettes daily or equivalent and are unable or unwilling not to smoke during the in-house period.
19. Donation or loss of blood over 500 mL within three months prior to Day 1 and donation of blood for the duration of the study until follow-up.
20. [redacted]
21. Claustrophobia, presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan.
22. Inability or unwillingness to meet study requirements (see inclusion criteria).

NUMBER OF PARTICIPANTS

Thirty-six participants are expected to be enrolled in this study. [redacted] with the maximum number of participants not exceeding 60. A minimum of 4 active treatment and 2 placebo participants will be included in the first two dose levels. Starting at dose levels 3, a minimum of 6 active treatment and 2 placebo participants will be included. Based upon the review of emerging data there will be the option to adjust the number of participants on active treatment or placebo per dose level.

CONCOMITANT MEDICATIONS

As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 14 days or 5 half-lives (whichever is longer) prior to study drug administration until follow-up.

Use of the following therapies is prohibited during the study:

- [redacted].
- Vaccination is prohibited within two months prior to Day 1.
- [redacted]
- Use of all other concomitant medications, herbal preparations (whether as teas or formulations), including prescription, and over-the-counter drugs is prohibited from 14 days, prior to Day 1, or five times the elimination half-life of the medications, whichever is longer, until follow-up.

1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1.

Figure 1 Overview of Study Design

Screening	In-House Period			Ambulatory Visits	Follow-up
	Admission to Clinic/Eligibility Confirmation	Randomization and Study Drug Administration	In-house Postdose Assessments		
Day -56 to -3	Day -2 and Day -1	Day 1 (IV administration of RO7126209/placebo)	Until Day 10	From Day 15 to Day 43	Day 57 ± 4

1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities is provided in Table 1 and Table 2.

Table 1 Overall Schedule of Activities

Assessment	Screening[a]																Follow-Up
	Day -56/-3	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10	Day 15±1	Day 22±1	Day 29±2	Day 43±3	Day 57±4
Time relative to dose (h)	NA	NA	NA	0	24	48	72	96	120	144	168	NA	NA	NA	NA	NA	NA
Written Informed Consent	✓																
Inclusion/Exclusion Criteria	✓	✓															
Brain MRI [l]	✓									✓							✓
Demographics	✓																
Medical History	✓																
Medication History	✓	✓															
Physical Examination [b]	✓	✓															✓
Vital Signs [c]	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Respiratory rate [j]		✓		✓	✓	✓					✓						
12-lead ECG [d]	✓	✓		✓	✓		✓		✓		✓	✓	✓		✓	✓	✓
Neurological Examination	✓	✓		✓	✓	✓	✓		✓		✓		✓		✓		✓
Full hematology	✓	✓			✓			✓			✓		✓		✓		✓
[redacted]																	
Full Blood	✓ [q]	✓			✓						✓		✓		✓		✓

Assessment	Screening[a]																Follow-Up
	Day -56/-3	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10	Day 15±1	Day 22±1	Day 29±2	Day 43±3	Day 57±4
Time relative to dose (h)	NA	NA	NA	0	24	48	72	96	120	144	168	NA	NA	NA	NA	NA	NA
Chemistry																	
[redacted]																	
Urinalysis[e]	✓	✓			✓		✓						✓		✓		✓
Serology[f]	✓																
Cerebral spinal fluid [redacted]			✓[n]			✓[o]		✓[o]									
[redacted]																	
Coagulation	✓	✓				✓[o]		✓[o]									✓
Alcohol Test	✓	✓															
Drugs of Abuse	✓	✓															
In-house Period		←----------										----------→					
Randomization				✓													
Standard Meal[g]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓					
Drug Administration				✓													
Pharmacokinetic				✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓

Assessment	Screening[a]																Follow-Up
	Day -56/-3	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 10**	**Day 15±1**	**Day 22±1**	**Day 29±2**	**Day 43±3**	**Day 57±4**
Time relative to dose (h)	NA	NA	NA	0	24	48	72	96	120	144	168	NA	NA	NA	NA	NA	NA
Sampling (Blood) [i]																	
Infusion-related reaction blood sample [redacted]				✓	←----------→												
[redacted]																	
Previous and concomitant Medications	←----------→																
Adverse Events [h]	←----------→																
Anti-RO7126209 Antibodies				✓							✓				✓		✓[p]

a) Safety tests can be repeated once during screening period at discretion of the Investigator.

b) A complete physical examination will be performed at screening (including height and weight), and abbreviated physical examinations at all other visits (including weight).

c) Includes single measurements of systolic and diastolic blood pressure, pulse rate and body temperature. All measurements to be taken after the participant has rested in a supine position for at least 5 minutes.

d) Triplicate 12-lead ECGs (within 5 minutes) will be measured after the participant has rested in a supine position for at least 10 minutes.

e) Dipstick analysis of protein, blood, glucose, pH and leukocytes.

f) Hepatitis B, C, HIV 1 and 2.

Table 1 Overall Schedule of Activities (cont.)

g) Participants will have to be fasted (water consumption is permitted) for at least 10 hours prior to full panel biochemistry laboratory safety tests (with the exception of screening and follow-up where a fasting period of 4 hours is sufficient). On Day 1, no food is permitted from 2 hours prior to dosing until 4 hours after start of the infusion. On all other days of the in-house period, standard breakfast, lunch, dinner and snack will be provided up to discharge, at the times deemed convenient by the clinical site.

h) Intensity of adverse events will be graded on a five-point scale (Grade 1, Grade 2, Grade 3, Grade 4 and Grade 5) based on the NCI CTCAE (v5), which can be found at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

i) The Sponsor may decide to terminate PK sampling earlier and/or timing of PK sampling may be modified based on emerging PK data (e.g., consecutive postdose PK samples with below the limit of quantification [BLQ] concentration).

j) Respiratory rate to be measured after the participant has rested in a supine position for at least 5 minutes.

[redacted]

o) Participants will be randomized to two subgroups per dose group. One subgroup will have the CSF sampling on Day 3, the other subgroup on Day 5. The safety biomarker (blood) and coagulation sample will be taken accordingly.

p) In case of ADA positive results at follow-up visit, the participant will be asked to come back to the unit monthly for additional ADA testing until *this is no longer clinically indicated (see Section 8.7)*. At each visit a corresponding PK sample must be also taken.

Table 1 Overall Schedule of Activities (cont.)

Table 2 Specific Schedule of Assessments

Procedure	Day -2	Day -1	Day 1 Nominal Time												Day 2
			- 2 h	Predose	0 h	0.25 h	0.5 h	1 h	2 h	3 h	4 h	6 h	8 h	12 h	24 h
Standard Meals [a]	✓	✓	✓								✓		✓		✓
Alcohol Test	✓														
Drugs of Abuse	✓														
Medication History	✓														
Physical Examination [h]	✓														
Inclusion/Exclusion Criteria	✓														
12-lead ECGs [b,e]	✓		✓[c]					✓	✓		✓		✓	✓	✓
Vital signs [d,e]	✓			✓			✓	✓	✓		✓		✓	✓	✓
Respiratory rate [e,g]	✓			✓			✓		✓		✓		✓		✓
Neurological Examination	✓			✓							✓			✓	✓
Cerebral spinal fluid (CSF) [redacted] [j]		✓													
[redacted]															
Coagulation	✓														
Pharmacokinetic Sampling (Blood) [e]				✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anti-RO7126209 Antibodies				✓											
Full hematology and full blood chemistry	✓														✓
[redacted]															
Urinalysis [f]	✓														✓

Procedure	Day -2	Day -1	Day 1 Nominal Time												Day 2
			- 2 h	Predose	0 h	0.25 h	0.5 h	1 h	2 h	3 h	4 h	6 h	8 h	12 h	24 h
[redacted]															
Drug Administration					✓										

a) Participants will have to be fasted (water consumption is permitted) for at least 10 hours prior to full panel biochemistry laboratory safety tests (with the exception of screening and follow-up where a fasting period of 4 hours is sufficient. No food is permitted from 2 hours prior to dosing until 4 hours after start of the infusion on Day 1. On all other days of the in-house period, standard breakfast, lunch, dinner and snack will be provided at the times deemed convenient by the site.

b) Triplicate 12-lead ECGs (within 5 minutes) will be measured after the participant has rested in a supine position for at least 10 minutes.

c) Three triplicate ECGs (9 in total) will be recorded within 1 hour prior to breakfast (at least 2 hours prior to dosing) and used as the baseline time point.

d) Includes single measurements of blood pressure (systolic and diastolic), pulse rate and body temperature. All measurements to be taken after the participant has rested in a supine position for at least 5 minutes.

e) Order of Assessments: (1) ECGs; (2) Vital signs; (3) Respiratory Rate; (4) PK blood sampling; (5) Laboratory safety tests and other blood sampling (anti-RO7126209 antibodies).

f) Dipstick analysis of protein, blood, glucose, pH and leukocytes.

g) Respiratory rate to be measured after the participant has rested in a supine position for at least 5 minutes.

h) Abbreviated physical examinations (including weight).

i) [redacted]

[redacted]

2. INTRODUCTION

2.1 STUDY RATIONALE

RO7126209 is a bispecific (2+1) monoclonal antibody (mAb) construct that combines, by recombinant fusion the anti-Aβ antibody gantenerumab with a Brain Shuttle module that [redacted] RO7126209 is being developed for the treatment of Alzheimer's Disease (AD). This is the first study in which RO7126209 will be administered to humans. A randomized, investigator and subject blind, adaptive, placebo-controlled, parallel design was chosen to assess the safety, tolerability, immunogenicity and pharmacokinetics (PK) following single ascending doses of RO7126209 administered intravenously to healthy participants.

The rationale for the study design is provided in Section 4.2.

2.2 BACKGROUND

2.2.1 Background on Disease

The World Health Organization estimates that around 50 million people worldwide are living with dementia and that 10 million new cases are diagnosed every year. The total number of people with dementia is estimated to reach 82 million in 2030 and will almost triple by 2050 to 152 million. AD is the most common form of dementia, accounting for 60%-70% of cases (World Health Organization 2017). The prevalence of AD increases with age, with a global prevalence of 5%-8% in people aged 60 years or over.

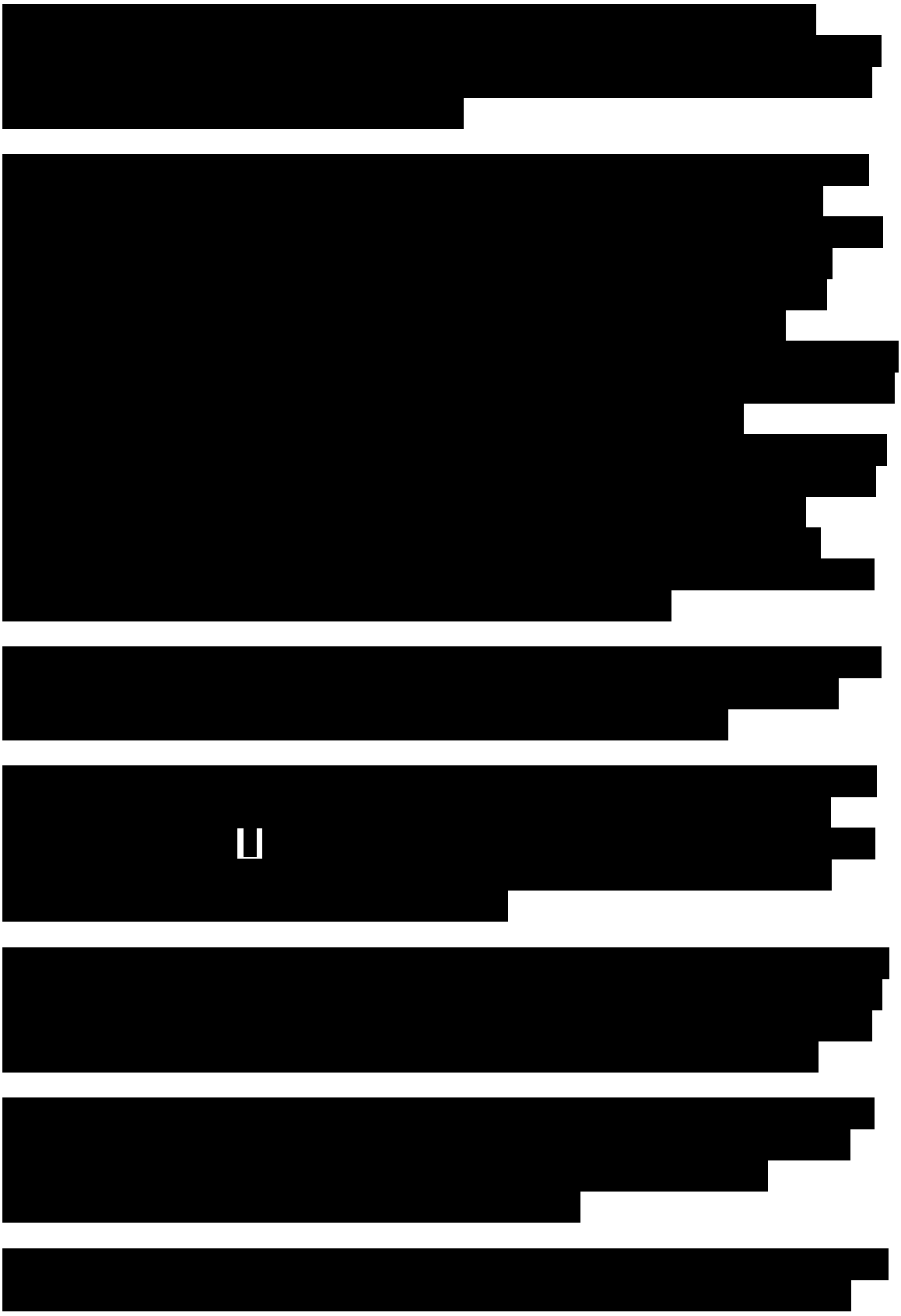
AD is clinically characterized by a progressive impairment in cognitive and executive abilities, which results in decreased function and gradual loss of independence (Mesterton et al. 2010). There is great inter-individual variability in AD progression with survival dependent on many factors, including age at onset. In general, the clinical picture evolves from “predementia” or “prodromal AD” to mild, moderate, and then severe AD. At the early stage of AD, a slight impairment of memory, language, and visuospatial function can be observed. As AD advances, patients become progressively impaired not only in terms of cognition but also in activities of daily living and the burden on caregivers significantly increases. The median survival time following a diagnosis of AD depends on the patient’s age at diagnosis and ranges from 8.3 years for persons diagnosed with AD at 65 years old to 3.4 years for those 90 years old (Brookmeyer et al. 2002). On average, individuals live 6 years after diagnosis (Helzner et al. 2008).

Pathologically, AD is characterized by the presence of cerebral Aβ plaques, neurofibrillary tangles, and a loss of neurons. Aβ is a peptide derived from proteolytic processing of the amyloid precursor protein, APP. This peptide exists in two major forms: $A\beta_{1-40}$ and $A\beta_{1-42}$ (Citron et al. 2004). Although the etiology of AD is not completely understood, current research suggests that Aβ processing and deposition play a critical role in the cascade of biological events involved in the pathogenesis of the disease. Consequently, therapies targeting this process have the potential to significantly alter the progression of the disease.

Because of its increasing prevalence, long duration, and high cost of care, AD is expected to continue to represent a major public health problem for decades to come.

2.2.2 Background on RO7126209

[redacted]



[redacted]

A detailed description of the chemistry, pharmacology, and safety of RO7126209 is provided in the RO7126209 Investigator Brochure (IB).

2.3 BENEFIT/RISK ASSESSMENT

No therapeutic benefit is anticipated for participants in this study as is common for Phase 1 studies involving healthy volunteers. There is no previous clinical experience with RO7126209 – this is a 'first-in-human' study.

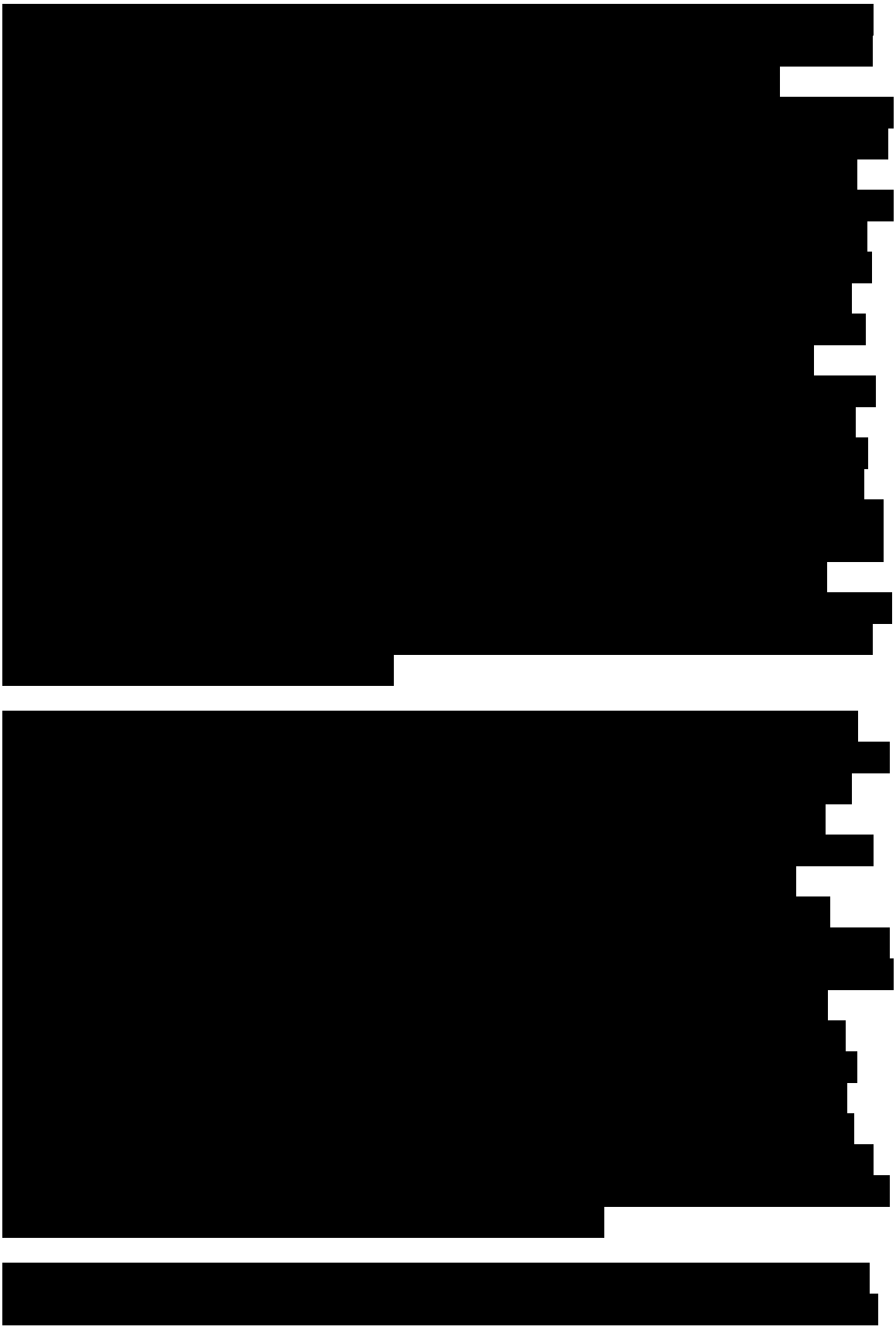
The eligibility criteria, the study design, and procedures adopted are considered to be appropriate for the safe conduct of the planned study. Participants will be closely monitored for safety consistent with standard practices for first-in-human studies, and under continuous medical observation during the study (until Day 10). The investigative site will be equipped with resuscitation equipment.

This study is adaptive in nature and planned doses may be adjusted (increased, decreased, or repeated) or intermediate doses explored based on emerging safety, tolerability, and PK data. The starting dose of 0.1 mg/kg (see Section 4.3.1) is expected to be well tolerated and associated with no or only minimal effect(s).

[redacted]

[redacted]

[redacted]



[redacted]

Overall, the level of risk for healthy participants is considered acceptable as it is mitigated by careful monitoring, sentinel cohorts at every new ascending dose level, careful dose escalation, and study stopping criteria.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of RO7126209 is provided in the RO7126209 IB.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 3.

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of single ascending intravenous doses of RO7126209 in healthy participants	• Incidence, severity, and causal relationship of AEs. • Incidence of abnormal laboratory findings. • Incidence of abnormal vital signs and electrocardiogram (ECG) parameters
Secondary	
• To investigate the single intravenous dose pharmacokinetics (PK) of RO7126209 in plasma of healthy participants	• Plasma PK parameters of RO7126209
• To investigate the CSF penetration after a single dose of RO7126209 in healthy participants	• CSF concentration of RO7126209
• To evaluate the immunogenicity of a single dose of RO7126209 in healthy participants	• Incidence of anti-RO7126209 antibodies (ADAs)
Exploratory	
• To explore PK/safety relationships of RO7126209 in healthy participants	• Relationship between plasma exposure of RO7126209 and safety measurements

4. STUDY DESIGN

4.1 OVERALL DESIGN

An overview of the study design is provided in Section 1.2.

Study BP41192 is a randomized, adaptive, placebo-controlled parallel group study to investigate the safety, tolerability, immunogenicity and pharmacokinetics of single ascending intravenous doses of RO7126209 in healthy participants.

This study uses a parallel group design, with participants recruited in 5 planned sequential cohorts. Participants will receive a single IV dose of either RO7126209 or placebo. Thirty-six participants are expected to be enrolled in this study. [redacted], with the maximum number of participants not exceeding 60. A minimum of 4 active treatment and 2 placebo participants will be included in the first two dose levels. Starting at dose level 3, and in all subsequent cohorts, a minimum of 6 active treatment and 2 placebo participants will be included. Based upon the review of emerging data there will be the option to adjust the number of participants on active treatment or placebo per dose level. If a dose level is repeated or if a lower dose is investigated, the added group will consist of at least 2 participants on active and 1 on placebo.

In accordance with standard practice for first-in-human studies, RO7126209 doses will be administered in ascending order, starting with a dose of 0.1 mg/kg that is anticipated to be well tolerated (Section 4.3.1). Subsequent doses will be selected in an adaptive manner during study conduct based on emerging safety, tolerability and PK data. A Bayesian adaptive design using the continual reassessment method (CRM) for predicting (see Section 9.3.4 and Appendix 6) the anticipated maximum dose-limiting event (DLE) rate to guide dose effect relationship will also be applied for dose escalation.

Intermediate dose escalation steps other than those anticipated (Section 1.2) may be used, doses may be repeated, or adjusted based on safety, tolerability and PK data at each dose level, as well as on model-based prediction of the anticipated maximum DLE rate.

In each dose group, sentinel dosing will be employed to allow for an evaluation of safety data by the Investigator up to 48 hours following intravenous administration of RO7126209 or placebo before subsequent participants are dosed. [redacted]

There will be at least 2 weeks between each dose level in order to permit adequate time for collation and review of emerging data before the next dose is administered.

The participants, investigators, and site personnel (except site personnel responsible for study drug accountability, reconciliation, record maintenance and drug preparation) will be blinded to treatment assignments.

Participants in the sentinel group will receive a single IV infusion of study medication (RO7126209 or matching placebo [redacted]

4.1.1 Length of the Study

The total duration of the study for each participant will be approximately 16 weeks divided as follows:

- Screening: Up to 8 weeks
- In clinic period: Days -2 to 10
- Final follow-up: Day 57 ± 4

4.1.2 Treatment Groups

The following tentative dose levels are planned:

- Dose level 1: 0.1 mg/kg RO7126209 or matching placebo
- Dose level 2: 0.3 mg/kg RO7126209 or matching placebo
- Dose level 3: 0.9 mg/kg RO7126209 or matching placebo
- Dose level 4: 2.7 mg/kg RO7126209 or matching placebo
- Dose level 5: 5.4 mg/kg RO7126209 or matching placebo

The dose levels are tentative, and may be revised based on emerging data. Higher doses than planned may be administered provided that all the dose escalation increments and stopping rules are followed. [redacted] with a maximum of 60 participants enrolled in the study.

If the safety data (AEs, ECGs, vital signs, laboratory safety tests, [redacted] assessments) of the first 48 hours following intravenous administration of RO7126209 or placebo is acceptable based on the judgment of the Investigator, the remaining participants will be dosed [redacted] after the first dosing occasion.

4.1.3 Dose Escalation Decision Criteria

The decision to escalate to the next dose level will be made jointly by the Sponsor study team, the Investigator and any other person the Investigator or Clinical Pharmacologist considers necessary to assist with the decision (Section 4.1.4 and Section 4.1.5).

Dose decisions (to escalate, reduce, or repeat) between cohorts will be made following review of all available cumulative (i.e., including emergent data from all previous cohorts) safety data (including AEs, laboratory safety test results, safety biomarkers, ECGs, vital signs, [redacted] assessments) collected [redacted]

[redacted]

[redacted]

The starting dose will be 0.1 mg/kg. Study treatment will be adaptive in nature. Doses may be repeated, adjusted downwards, or intermediate doses may be investigated based on safety, tolerability and PK data at each dose level, as well as on model-based prediction of the anticipated maximum DLE rate.

4.1.4 Stopping Rules Criteria

4.1.4.1 General Study Stopping Rules

[redacted]

- [redacted]
- [redacted]

4.1.4.2 Stopping Rules after Sentinel Cohort

[redacted]

- [redacted]
- [redacted]

[redacted]

4.1.4.3 Dose Escalation Stopping Rules

[redacted]

In case dose escalation is stopped, lower doses within the tolerated dose range could be investigated or a dose repeated in subsequent cohorts (or additional participants added), in order to increase the amount of data within the tolerated dose range.

On the basis of the safety and tolerability profile and observed PK, the number of participants at the next dose level may be revised or a dose level may be expanded.

Due to the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor. This will not constitute a premature termination of the study.

4.1.5 Communication Strategy

A safety review team will provide dose recommendations for all cohorts of the study. The representatives of the safety review team will be from Clinical Pharmacology, Biometrics, Safety Science, Clinical Science, and Operations together with the Investigator(s) and the Project lead of the CRO (and any other the Investigator or Clinical Pharmacologist considers necessary to assist with the decision).

There will be an ongoing review of available data (see Section 4.1.3) prior to dosing remaining participants of a dose group after evaluation of the sentinel cohort and initiation of the next dose. A Dose Escalation Meeting will be conducted between the Sponsor study team and Investigator prior to dosing of the next dose level.

[redacted]

In addition to these communications, the Sponsor and investigators will be in regular contact throughout the study by email/telephone/fax, as per normal interactions during the conduct of a clinical study, and the Sponsor will arrange regular teleconferences and meetings to discuss study status.

The Sponsor will be available 24 hours a day to discuss any medical or study-related issues that may arise during the conduct of this study.

Additional details for communication strategy and dose-escalation procedure can be found in the separate Medical Data Review Plan.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

4.2.1 Rationale for Study Population

The study will be conducted in healthy male participants aged 18 to 40 years (inclusive).

The healthy volunteer population has been selected to minimize the risk of ARIA. ARIA-E (edema) and ARIA-H (microhemorrhages) are common side effects of monoclonal antibodies targeting fibrillar forms of amyloid beta. As the main objective of this study is the characterization of the general safety and tolerability profile, immunogenicity and pharmacokinetics of RO7126209, the absence of confounding diseases in healthy volunteers allows for a clearer and more consistent assessment of the main objectives. In addition, healthy volunteers are unlikely to require concomitant medications which could impact PK and safety parameters.

In line with the above paragraph the age range has been limited to 40 years to reduce the risk of amyloid plaque in the brain. According to a recent publication (Pletnikova 2018) the risk of occurrence of diffuse amyloid plaque in the study population is low.

[redacted]

4.2.2 Rationale for Control Group

This study is designed to be adequate and well-controlled. Participants will be randomized to RO7126209 or placebo treatment. The randomization scheme to active and placebo groups is considered necessary to generate an adequate within study comparator dataset to allow proper evaluation of the magnitude of any treatment effects. The study is Investigator/participant-blind to eliminate potential bias.

4.2.3 Rationale for Biomarker Assessments

[redacted]

4.2.4 Rationale for CSF Sampling

CSF samples will be taken to monitor safety and to measure RO7126209 concentrations.

[redacted]

4.3 DOSE JUSTIFICATION

4.3.1 Justification for Starting Dose

The starting dose of RO7126209 is proposed to be 0.1 mg/kg IV. The planned starting dose was selected based on the nonclinical findings, relevant regulatory guidelines (EMA 2015, FDA 2005) and clinical experience with gantenerumab, the Aβ targeting entity in RO7126209.

A starting dose of 6 mg/kg RO7126209 was initially calculated based on the NOAEL [redacted] and on the recommendations provided in the FDA guidance, using body weight conversion (following the recommendation for IV administered proteins for proteins of molecular weight >100 kDa), of a 10-fold safety factor between human equivalent dose (HED) and maximum recommended starting dose (MRSD). Given the estimated pharmacologically active systemic exposure described below, the MRSD level is predicted to show potential therapeutic activity. Thus the starting dose was lowered to 0.1 mg/kg, based on a comparison of projected brain concentrations (using the translational PKPD model) and clinical experience from gantenerumab. Details for the estimation of the therapeutic dose range for RO7126209 and considerations for the safety of the proposed starting dose are given below.

For the selection of a potential pharmacologically active dose range for RO7126209 a translational PKPD model was developed, incorporating preclinical information on brain penetration in NHPs from both RO7126209 and gantenerumab, and an internally developed PKPD model from gantenerumab (see RO7126209 IB). [redacted]

1.6 - 3 mg/kg.

[redacted]

[redacted]

Monoclonal antibodies targeting fibrillar forms of amyloid beta like gantenerumab may be associated with the occurrence of ARIAs. The gantenerumab target dose of 510 mg SC Q2W is administered only after an up-titration period of 9 months to mitigate incidence and severity of ARIAs. As this side effect is also expected to occur before reaching the target dose of RO7126209, the starting dose has been lowered to reach brain exposures similar to gantenerumab doses that have not been associated with ARIAs in patients with AD. [redacted] 0.1 mg/kg [redacted]

The population selected for BP41192, healthy young male volunteers, is not expected to experience ARIAs due to lack of fibrillar forms of amyloid beta in the brain. However, clinical experience with gantenerumab and the potential for ARIA findings have been taken into account in order to characterize the general safety and tolerability profile and PK of the dose range which is likely to be tested in future studies in Alzheimer's Disease patients.

Safety Margins

The safety margins associated with the starting dose based on the preclinical toxicokinetic data, and estimated NOAEL in the 2-week GLP toxicology study and projected human PK are provided in Table 4 below. Note that, taking a conservative approach, the high exposure scenario was used for the calculation of the safety margins.

If safety allows, the highest dose to be tested in the SAD will be selected so that the [redacted]

In conclusion the non- clinical data and the PKPD translational model that draws upon gantenerumab clinical data support a starting dose of 0.1 mg/kg IV for RO7126209.

4.3.2 Justification for Dose Escalation

With a starting dose of 0.1 mg/kg, the dose expected to reach similar brain concentration as 400 mg gantenerumab IV, which was well tolerated in the single ascending dose study in AD patients (BN18726), will be reached after the second dose escalation step (0.9 mg/kg). 1.6 to 3 mg/kg (2.7 mg/kg). 2.7 mg/kg 5.4 mg/kg). 5.4 mg/kg

[redacted]
5.4 mg/kg.

Table 5 Tentative Dose Escalation

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
0.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur 57 ± 4 days after last dose administration.

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants in this study will be healthy male volunteers, between 18 and 40 years of age, inclusive, who fulfill all of the given inclusion criteria.

Prospective approval of protocol deviations from recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

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

Informed Consent

1. [redacted]

Age

2. [redacted]

Type of Participants

3. Healthy status is defined by the absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, ophthalmologic examination, hematology, blood chemistry, coagulation, serology, and urinalysis.
4. [redacted]

Weight

5. BMI of 18-30 kg/m^2 inclusive

Sex

6. Male participants

During the treatment period (from dosing on Day 1) and until the final follow-up visit (Day 57 $\pm$ 4 days), agreement to:

- Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year, with a partner who is a woman of childbearing potential (WOCBP, as defined in Section 1 of Appendix 5).
- With pregnant female partner, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.
- Refrain from donating sperm from Day 1 of the study until 90 days after last dose.

[redacted]

5.2 EXCLUSION CRITERIA

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

Medical Conditions

1. Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study.
2. History of any clinically significant gastrointestinal, renal, hepatic, broncho-pulmonary, neurological, psychiatric, cardiovascular, endocrinological, ophthalmologic, hematological or allergic disease, metabolic disorder, cancer or cirrhosis.
3. Any suspicion or history of alcohol abuse and/or suspicion of regular consumption of drug of abuse within the last 5 years.
4. Positive result on hepatitis B (HBV), hepatitis C (HCV), or human immunodeficient virus (HIV) 1 and 2.
5. [redacted]
6. [redacted]
7. History or presence of clinically significant ECG abnormalities [redacted]
8. Clinically significant abnormalities (as judged by the Investigator) [redacted]
9. Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration.
10. Impaired hepatic function as indicated by screening aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 1.5 \times$ the upper limit of normal (ULN) or abnormal total bilirubin unless due to Gilbert's disease.
11. Any clinically relevant history of hypersensitivity or allergic reactions, either spontaneous or following drug administration, or exposure to foods or environmental agents.
12. History of hypersensitivity to biologic agents or any of the excipients in the formulation.
13. History of raised intra-cerebral pressure or vertebral joint pathology

Prior/Concomitant Therapy

14. Use of prohibited medication or herbal remedies as described in the section of concomitant medications
15. Prior administration of gantenerumab (RO4909832)
16. Any vaccination within two months prior to Day 1

Prior/Concurrent Clinical Study Experience

17. Participation in an investigational drug medicinal product or medical device study within 30 days before screening or within seven times the elimination half-life if known, whichever is longer.

23. **Other Exclusions**

18. Participants who regularly smoke more than 5 cigarettes daily or equivalent and are unable or unwilling not to smoke during the in-house period.
19. Donation or loss of blood over 500 mL within three months prior to Day 1 and donation of blood for the duration of the study until follow-up.
20. [redacted]
21. Claustrophobia, presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan.
22. Inability or unwillingness to meet study requirements (see inclusion criteria).

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

Participants will have to be fasted (water consumption is permitted) for at least 10 hours prior to laboratory safety tests for full panel biochemistry (with the exception of screening and follow-up where a fasting period of 4 hours is sufficient).

On dosing day (Day 1), no food is permitted from 2 hours prior to dosing until 4 hours after start of infusion. On all other days of the in-house period, standard breakfast, lunch, dinner and snack will be provided at the times deemed convenient by the clinical site.

5.3.2 Caffeine, Alcohol, and Tobacco

Use of caffeine, alcohol and tobacco will be restricted as follows:

- The consumption of foods and beverages containing caffeine (e.g., tea, coffee and caffeinated soft drinks) will not be permitted from 24 hours before dosing until the end of the residential period (Day 10). During the period when participants are not resident in the unit, caffeine containing beverages must be no more than three cups per day, and methylxanthine containing drinks (e.g. cola) must be less than 1 L per day.

- Consumption of alcohol will not be allowed from 48 hours before dosing until the end of the residential period (Day 10) and should be limited to a maximum of 2 drinks/day (1 drink = 14 g of pure alcohol, i.e., 12 fl oz of regular beer or 5 fl oz of wine or 1.5 fl oz of distilled spirits) during out-clinic period until follow-up.
- The use of tobacco will not be permitted from 48 hours before dosing until the end of the residential period (Day 10) and should be limited to a maximum of 5 cigarettes a day or equivalent amount of tobacco during the out-clinic time until follow-up.

5.3.3 Activity

Light ambulatory activities will be permitted, with the level of activities kept as similar as possible on all days in the clinical research unit during the study. Participants are required to refrain from intense physical activity 96 hours before the screening visit, laboratory safety tests and follow-up visit.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment/entered in the study.

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

Individuals who do not meet the criteria for participation in this study (screen failure) will not be re-screened unless agreed with the Sponsor. However, safety tests can be repeated once during screening period in the case of a borderline result, at the discretion of the Investigator. A repeat of a screening safety test is not considered a re-screening.

5.5 RECRUITMENT PROCEDURES

Participants will be identified for potential recruitment using clinical database and IEC/IRB approved newspaper/radio/social-media advertisements prior to consenting to take place in this study.

6. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

All investigational medicinal products (IMPs) required for completion of this study (RO7126209 and matching placebo) will be provided by the Sponsor.

Study drug (RO7126209 or matching placebo) will be administered to the participants at the study center by investigational staff on the morning of Day 1.

6.1 TREATMENTS ADMINISTERED

Table 6 summarizes the treatments administered.

Table 6 Summary of Treatments Administered

Study Treatment Name:	RO7126209	Placebo
IMP and NIMP	IMP	IMP
Dose Formulation:	liquid concentrate for infusion	liquid concentrate for infusion
Unit Dose Strength(s)/Dosage Level(s):	[redacted]	
Dose:	Dose level 1: 0.1 mg/kg See Section 4.1.1 for dose-escalation information and Pharmacy Manual for details.	N/A
Route of Administration:	IV infusion	IV infusion
Packaging and Labeling:	[redacted]	

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

Please see the RO7126209 IB and pharmacy manual for more details.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study medication will be in accordance with Roche standard and local regulations.

The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced. Upon arrival of the IMPs at the site, site personnel will complete the following:

- Check the IMPs for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.

- Report any deviations or product complaints to the Study Monitor upon discovery.

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the randomization schedule and Pharmacy Manual.

The Investigator or delegate must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, Institution, or the Head of the Medical Institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

On Day 1, participant will be randomized to receive placebo or active treatment. The randomization numbers will be generated by the Sponsor or its designee.

The randomized treatment assignment will be allocated from the list sequentially to participants in the order in which they are enrolled.

The Investigator or designee will enter the corresponding participant number for allocation to the dose group/cohort in the appropriate place on each participant's eCRF.

The randomization list will be made available to the pharmacist preparing the study treatment, to the individual responsible for PK sample bioanalysis, to the Clinical Pharmacologist and Clinical Pharmacology Scientist, to the Data Acquisition Specialist

and to statisticians or programmers at Roche. Likewise, the pharmacometrician will be unblinded. PK and safety data can be received and cleaned on an ongoing basis. The data will be handled and cleaned in a secure area which is not accessible by any blinded SMT member.

6.3.2 Blinding

This is a Participant and Observer-Blinded Study.

Participants will be randomized to placebo or active treatment in each dose cohort/level. The randomization numbers will be generated by the Sponsor or its designee. This study is observer-blinded. This means that the participant, the Investigator(s), and all individuals in direct contact with the participant at the investigative site will be blinded, except the Pharmacist handling the study treatment. Members of the Sponsor's project and study teams who do not have direct contact with the participant may be unblinded at the Clinical Pharmacologist's discretion.

To allow informed recommendations or decisions regarding the dose-selection in this study, an integrated assessment of the safety, tolerability and available pharmacokinetics will be made prior to each dose-decision. The Clinical Pharmacologist or Clinical Pharmacology Scientist may share mean reports (e.g., tabular summaries or mean graphs by treatment group) with other individuals (e.g., drug safety physician, principal Investigator), involved in the dose decision process, but should not disclose individual treatment assignment.

If required, unblinded data (individual as well as at group level) may also be presented to the Drug Safety Committee or other experts of the Sponsor.

Single-participant emergency unblinding

If unblinding is necessary for immediate participant management (e.g., in the case of a SAE for which participant management might be affected by knowledge of treatment assignment), the Investigator will be able to break the treatment code. The Investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

As per Health Authority reporting requirements, the Sponsor will break the treatment code for all unexpected SAEs that are considered by the Investigator to be related to study treatment. The Sponsor must be notified before the blind is broken unless identification of the study treatment is required for medical emergency in which the knowledge of the specific blinded treatment will affect the immediate management of the participant's conditions (e.g., antidote is available). In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded and the name of all the person(s) who had to be unblinded in the source documentation and eCRF, as applicable.

6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the randomization schedule. This individual will write the date dispensed and participant number on the study treatment vial label and on the Drug Accountability Record. This individual will also record the study treatment number received by each participant during the study.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant within 30 days of screening until the follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency).

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

[redacted]

All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

All therapy and/or medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

6.5.1 Permitted Therapy

All medications (prescription and OTC) taken within 30 days of study screening and for the duration of the study will be recorded on the appropriate eCRF.

Acetaminophen is allowed up to a maximum dose of 2 g/day up to 48 hours prior to dosing, not to exceed 4 g total during the week prior to dosing.

Additionally, local anesthetic is permitted during the lumbar puncture [redacted].

6.5.2 Prohibited Therapy

As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 14 days or 5 half-lives (whichever is longer) prior to study drug administration until follow-up, with the exception of

medications to treat adverse events unless the rationale for the exception is discussed and clearly documented between the investigator, the medical and safety monitor and the Sponsor.

Use of the following therapies is prohibited during the study:

- [redacted]
- Vaccination is prohibited within two months prior to Day 1.
- [redacted]
- Use of all other concomitant medications, herbal preparations (whether as teas or formulations), including prescription, and over-the-counter drugs is prohibited from 14 days, prior to Day 1 of the trial (dosing day), or five times the elimination half-life of the medications, whichever is longer, until follow-up.

6.6 DOSE MODIFICATION

The decision to escalate to the next dose level will be made jointly by the Sponsor study team, the Investigator and any other person the Investigator or Clinical Pharmacologist considers necessary to assist with the decision as described in Section 4.1.3.

Based on emergent safety (e.g. infusion-related reactions), the duration of the infusion may be modified.

6.7 TREATMENT AFTER THE END OF THE STUDY

The Sponsor does not intend to provide RO7126209 or other study interventions to participants after conclusion of the study or any earlier participant withdrawal.

7. DISCONTINUATION OF STUDY, STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of withdrawals (e.g., participants withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to motivate participants to comply with all the study-specific procedures as outlined in this protocol.

Details on study and site closures are provided in Appendix 1 Study Governance Considerations Study.

7.1 DISCONTINUATION OF STUDY TREATMENT

Not applicable as this is a single dose administration study.

In case of an IRR or for any other safety reason, infusion might be stopped or performed at a lower rate (see Section 8.3.7).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason.

In addition, the Investigator has the right to withdraw a participant from the study for medical conditions that the Investigator or Sponsor determines, may jeopardize the participant's safety if he/she continues in the study.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants will not be followed for any reason after consent has been withdrawn.

When a participant voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will be used as part of the overall research data.

Participants who withdraw from the study for safety reasons will not be replaced. Participants who withdraw from the study for other reasons may be replaced.

See Schedule of Activities (SoA: Section 1.3) and Section 8.10.4 for data to be collected at safety and follow-up visits, and for any further evaluations that need to be completed.

7.3 LOST TO FOLLOW-UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of sites or of study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time points are summarized in the SoA; Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the Informed Consent Form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time-frame defined in the SoA.

8.1 EFFICACY ASSESSMENTS

Efficacy parameters will not be evaluated in this study.

8.2 SAFETY ASSESSMENTS

Planned time-points for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; ECGs; [redacted], MRI; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal in addition to head, eyes, ears, nose, throat, neck and lymph nodes systems. Height and weight will also be measured and recorded. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in participant's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[redacted]

8.2.3 Vital Signs

Vital signs including temperature (oral), pulse rate, respiratory rate, and blood pressure will be assessed. They will be taken before blood collection and will be measured at the time point specified in the SoA tables (Section 1.3).

Single blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available. When possible, the non-infusion arm should be used for all blood pressure measurements.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting in a room at comfortable temperature and without distractions (e.g., television, cell phones), with the healthy participant's arm unconstrained by clothing or other material.

Where the clinical significance of abnormal vital signs measurement at screening is considered uncertain, screening vital signs assessment may be repeated once during the screening period at the discretion of the Investigator to confirm eligibility.

8.2.4 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

At each time-point at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 5 minutes. The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT and QTc).

To minimize variability, it is important that participants be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws. In some cases, it may be

appropriate to repeat abnormal ECGs to rule out improper lead placement potentially contributing to the ECG abnormality.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the participant's permanent study file at the site. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory.

ECG characteristics, including heart rate, QRS duration, and PR, and QT intervals, will be recorded on the eCRF or loaded electronically. QTcF (Fridericia's correction) and RR will be calculated automatically, and recorded on the eCRF or loaded electronically. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF or loaded electronically. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

Where the clinical significance of abnormal ECG recordings at screening is considered uncertain, screening ECG assessment may be repeated once during the screening period at the discretion of the Investigator to confirm eligibility.

8.2.5 Clinical Safety Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. A list of clinical laboratory tests to be performed is provided in Appendix 4 and these assessments must be conducted in accordance with the separate laboratory manual and the SoA (Section 1.3).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- If laboratory values from non-protocol-specified laboratory assessments performed at the local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose-modification) then, the results must be recorded in the eCRF.

Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory.

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor participant safety.

Where the clinical significance of abnormal lab results at screening is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility.

If there is an alternative explanation for a positive urine or blood test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example, codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.

Based on continuous analysis of the data in this study and other studies, any sample type not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

[redacted]

[redacted]

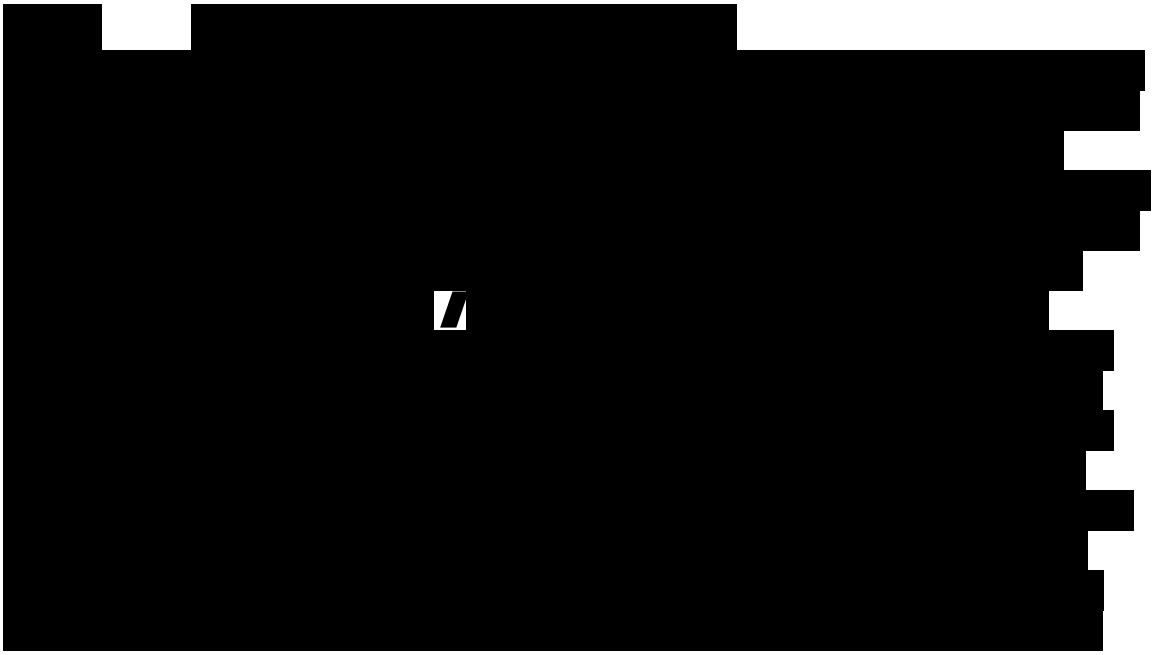
8.2.6 MRI

Brain MRI using at least a 1.5-Tesla machine will be performed for the eligible participants at screening to exclude microbleeds, lacunar infarcts, and space-occupying lesions (see Section 5.2, Exclusion criteria) and will include fluid-attenuated inversion recovery (FLAIR) sequence and T2*/gradient echo sequence (GRE). On Days 7 and 57 post dose brain MRI will be performed to confirm absence of brain side effects (e.g., inflammation). In case of clinical findings, CE-MRI may be performed.

Additional brain MRIs must be performed following the onset of a serious CNS adverse event or following a clinically significant worsening of a CNS adverse event. The results should be documented on the appropriate adverse event page and serious adverse event form (if applicable).

MRI data (e.g., images) may be shared with the Sponsor.

[redacted]



8.2.8 Medical History and Demographic Data

Medical history includes clinically significant diseases and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 30 days prior to the screening visit.

Demographic data will include age, sex, and self‑reported race/ethnicity.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 2. The non-serious adverse events of special interest and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Sections 8.3.6 and Section 8.3.7.

The Investigator and any qualified designees are responsible for ensuring that all adverse events (including assessment of seriousness, severity and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording adverse events are provided in Appendix 3.

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

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

Clinic staff will seek information on adverse events at each study day. All adverse events, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study treatment**, all adverse events caused by a protocol-mandated intervention should be reported (e.g., adverse events related to invasive procedures such as lumbar puncture). If the adverse event meets the criteria for serious adverse event (see Section 2 from Appendix 2), it should be reported immediately.

After initiation of study treatment, all adverse events, regardless of relationship to study treatment, will be reported until the last follow-up visit (57±4 days after dosing).

Post-study adverse events and serious adverse events: The Investigator is not required to actively monitor participants for adverse events after the end of the adverse event reporting period of 57 days ±4 days after dosing.

However, if the Investigator learns of any SAE (including a death) or other adverse events of concern that are believed to be related to prior treatment with study treatment, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

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

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant evaluation time−points.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

The Investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source

data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

8.3.3.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

For immediate and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, investigators, IRB and EC, see Appendix 2.

8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours a day 7 days a week. Medical Monitors' contact details will be available on a separate list generated by the study management team.

8.3.5 Pregnancy

Male participants will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 57 ± 4 days after dosing.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (Appendix 5).

8.3.6 Non-Serious Adverse Events of Special Interest

Non-serious adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2 for reporting instructions).

Non-serious adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Appendix 3.
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

8.3.7 Management of Specific Adverse Events

IRRs as defined by Kang and Saif (2007) are “any signs or symptoms experienced by patients during the infusion of pharmacologic or biologic agents or any event occurring on the first day of drug administration”. IRRs are common adverse drug reactions (ADRs) reported with the use of biologic therapies. IRRs are usually reported with the first or second infusion of a therapeutic monoclonal antibody and tend to be dose-related. Such reactions typically occur during or shortly after an infusion or within 24 hours after study drug infusion. IRRs is a basket term including other terms such as anaphylaxis, anaphylactoid reactions, complement activation-related pseudoallergy (CARPA) and cytokine release syndrome. Combinations of IRR types may occur in the same patient (Doesseger et al 2015).

IRR symptoms may be indistinguishable from an anaphylaxis Type 1 hypersensitivity reaction (i.e., flushing, rash, respiratory difficulty, hypotension, tachycardia); however,

hypersensitivity reactions (IgE-mediated) generally do not occur with the first exposure to a biologic therapy.

Anaphylactoid reactions may occur with the first exposure to an antigen and may be clinically indistinguishable from anaphylaxis. Unlike anaphylactic reactions, anaphylactoid reactions are milder upon repeated administration.

CARPA typically occurs within minutes after starting the infusion. However, it may be delayed, particularly in premedicated patients. The most frequent symptoms being flushing, rash, dyspnea, chest pain, back pain and subjective distress.

Cytokines release syndrome (CRS) can present as with a variety of symptoms ranging from mild, flu-like symptoms (fever, fatigue, headache, rash, arthralgia, and myalgia) to more severe cases characterized by hypotension as well as high fever and can progress to an uncontrolled systemic inflammatory response with vasopressor-requiring circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure. Laboratory abnormalities that are common in patients with CRS include cytopenias, elevated creatinine and liver enzymes, deranged coagulation parameters, and a high C-reactive protein (CRP) (Shimabukuro-Vornhagen et al 2018).

Figure 2 describes the process for the overall evaluation of AEs to determine whether an AE is an IRR.

Figure 2 Evaluation and Reporting of Infusion Related Reaction (IRR)

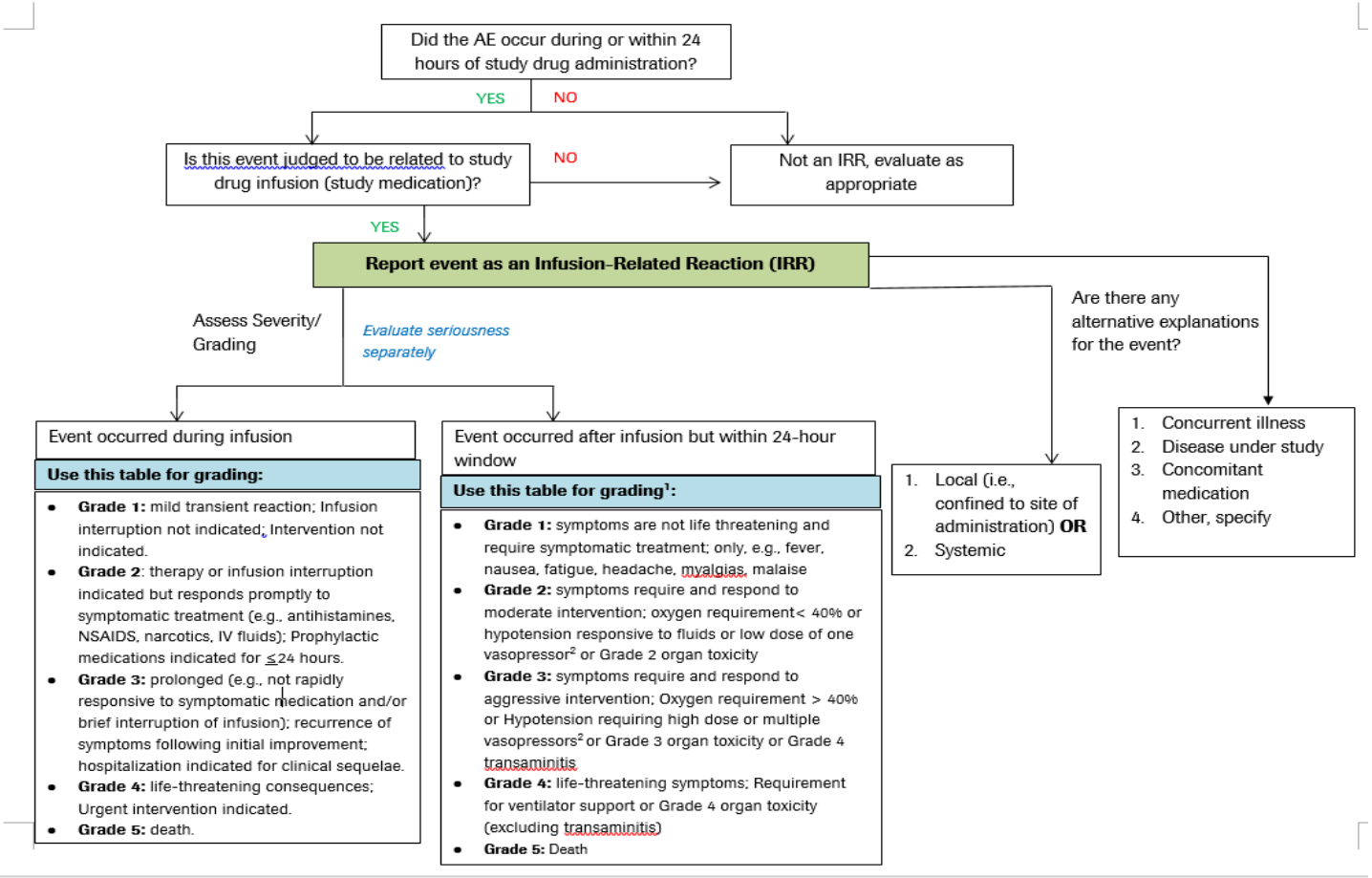


Figure 2 Evaluation and Reporting of Infusion Related Reaction (IRR) (cont.)

1. Source: Lee et al 2014.

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v5), which can be found at:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

2. Note: High-Dose Vasopressor (duration ≥3 hours) in table below

Pressor	Dose
Norepinephrine monotherapy	≥20 mcg/min
Dopamine monotherapy	≥10 mcg/kg/min
Phenylephrine monotherapy	≥200 mcg/min
Epinephrine monotherapy	≥10 mcg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥10 mcg/min [a]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 mcg/min [a]

Source: Russell et al 2008.

mcg =microgram; min =minute; VASST =Vasopressin and Septic Shock Trial.

[a] VASST vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min)] + [phenylephrine (mcg/min) ÷10].

Specific management steps for IRRs and hypersensitivity reactions of different severity are provided in Table 7. The participant should be monitored until complete resolution of the symptoms and treated as clinically indicated.

A blood sample will be taken in all participants at baseline (predose Day 1) and 6 hours post dose (the timing might be adjusted based on emerging data) [redacted] In case a Grade ≥ 3 IRR occurs, blood samples for the assessment [redacted] will be collected and analysed along with the paired baseline sample. The baseline and 6-hour (timing might be adjusted based on emerging data) post dose samples of all participants will be analysed to assess the relationship between dose, cytokine release and occurrence of IRRs as appropriate. Guidelines for managing infusion-related reactions with onset after infusion but within 24-hour window in presented in Table 8

Table 7 Guidelines for Managing Infusion-Related Reactions with onset during infusion

Event	Action to Be Taken
Grade 1	Stop or slow down study drug infusion to 50% of the initial rate. Assess vital signs. Clinical observation for improvement/resolution of symptoms. No treatment is needed.
Grade 2	Stop study drug infusion. Perform serial vital signs assessment every 15 minutes, supportive therapy (fluids [Normal Saline or Lactated Ringers], supplemental oxygen, diphenhydramine 25 – 50mg PO or IV Q6h for rash, acetaminophen 650 mg PO [or minimum recommended adult dose of paracetamol]) Q6h. ADA and PK levels should be drawn. If symptoms resolve completely during the visit, infusion may resume at 50% of the previous infusion rate.
Grade 3	Stop study drug infusion. Perform serial vital signs assessment as dictated by the patient's clinical symptoms, supportive therapy (fluids [Normal Saline or Lactated Ringers], supplemental oxygen, diphenhydramine 25 – 50mg PO or IV for rash, acetaminophen 650 mg PO [or minimum recommended adult dose of paracetamol], methylprednisolone 125 mg IV). Labs: [redacted] within 3 hours of the event and to be repeated in 48 – 72 hours post event. ADA and PK levels should be drawn.
Grade 4	Stop study drug infusion. Perform serial vital signs assessment every 5 minutes, supportive therapy (fluids [Normal Saline or Lactated Ringers], supplemental oxygen/ intubation and ventilatory support, diphenhydramine 25 – 50 mg PO or IV for rash, acetaminophen 650 mg PO [or minimum recommended adult dose of paracetamol], methylprednisolone 125 mg IV). Labs: [redacted] within 3 hours of the event and to be repeated in 48 – 72 hours post event. ADA and PK levels should be drawn.
Anaphylaxis	Stop study drug infusion. Assess vital signs every 5 minutes. Administer IV fluids (Normal saline or Lactated Ringers), supplemental oxygen/ventilatory support, for systemic symptoms (angioedema, bronchospasm) epinephrine 1:1000, 0.3 mL subcutaneous (may be repeated in 20 minutes; in patients on beta blockers, glucagon administration may be needed), diphenhydramine 25 – 50 mg IV, methylprednisolone 125 mg IV). Labs: [redacted] within 3 hours of the event and to be repeated in 48 – 72 hours post-event. Discontinue participants from the study. ADA and PK levels should be drawn (See Lieberman et al 2015 for anaphylaxis guidance).

Table 8 Guidelines for Managing Infusion-Related Reactions with onset after infusion but within 24-hour window

Event	Action to Be Taken
Grade 1	• Treat symptomatically as indicated, including antihistamines, antipyretics, and/or analgesics as needed. • Treat fever and neutropenia if present. • Monitor fluid balance; administer IV fluids as clinically indicated.
Grade 2	• Follow all Grade 1 recommendations. • Monitor cardiac and other organ function closely. • Hemodynamic support as indicated. • Oxygen for hypoxia. • Admit to ICU as appropriate. • If no improvement within 24 hours: – Notify Medical Monitor. – Consider administering tocilizumab 8 mg/kg e IV as a single dose. • ADA and PK levels should be drawn.
Grade 3	• Notify Medical Monitor. • Cardiopulmonary and organ function monitoring in Intensive Care Unit. • Hemodynamic support as indicated. • Oxygen for hypoxia. • Other supportive care as clinically indicated (e.g., fever and neutropenia, infection). • Administer tocilizumab 8 mg/kg IV. – If no clinical improvement within 24 hours: Administer repeat dose of tocilizumab 8 mg/kg. Consider initiating IV corticosteroids (e.g., methylprednisolone [2 mg/kg/day] or dexamethasone 10 mg for neurologic symptoms). • Labs: [redacted] within 3 hours of the event and to be repeated in 48 - 72 hours post event. ADA and PK levels should be drawn.
Grade 4	• Follow all Grade 3 management guidelines Labs: [redacted] within 3 hours of the event and to be repeated in 48 – 72 hours post event. ADA and PK levels should be drawn.

In case of signs/symptoms of IRR in the sentinel cohort, IRR risk mitigation steps may be implemented in the remaining participants of the dose level and the higher dose levels. The same approach will applied in case of signs/symptoms of IRRs in the

participants enrolled in the main cohort at a certain dose level for the higher dose levels. In order to reduce the occurrence and potential impact of IRRs, slower infusion time may be applied to all participants of the cohort (and the cohorts at higher dose level), after discussion and approval by the medical monitor.

8.4 TREATMENT OF OVERDOSE

Study treatment overdose is the accidental administration of a drug in a quantity that is higher than the assigned dose. An overdose or incorrect administration of study treatment is not an adverse event unless it results in untoward medical effects (see Sections 5 and 5.2 of Appendix 2 for further details).

In the event of an overdose, the Investigator should:

1. Contact the Sponsor's Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
3. Obtain blood samples for PK analysis according to the schedule of assessments if not medically contraindicated.
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the CRF.

8.5 LUMBAR PUNCTURES

[redacted] lumbar punctures per participant will be performed at the times indicated in the SoA (see Section 1.3) to collect CSF, performed by a qualified physician. Atraumatic needles will be used, the liquid will be sampled in a free flowing manner, which will take about 5 minutes. For details please see the Laboratory Manual

CSF Samples will be aliquoted per time point for the measurement of RO7126209 (Section 8.6.1), [redacted]

Details on processes for collection and shipment of these samples can be found in Sample Handling Manual.

8.6 PHARMACOKINETICS

As a general note, any volume of blood or CSF samples remaining after the specified analyses may be used for assay development/validation of exploratory assays and experiments. In addition, blood samples may be used to measure levels of total binding competent gantenerumab, characterize drug molecule integrity and potential soluble target interference. If performed, the results will be reported in a separate report to the CSR.

Any changes in the timing or addition of time-points for any planned study assessments must be documented and approved by the relevant study team member and then, archived in the Sponsor and site study files, but this will not constitute a protocol amendment.

Placebo-treated participants may not be analysed in the first instance, but retained for subsequent analysis if appropriate.

The PK blood and CSF samples will be destroyed 6 months after the release of final bioanalytical report at the CRO performing the analysis or shipped to Roche. In the latter case the samples may be stored up to 2 years after the date of final CSR. Details on sampling procedures, sample storage and shipment are given in the sample documentation.

8.6.1 Plasma

Mandatory blood samples to evaluate concentrations of RO7126209 in plasma will be collected as outlined in the SoA (see Section 1.3).

Blood samples must not be taken from the same arm as IV drug administration on Day 1. The date and time of each sample collection will be recorded in the eCRF.

Plasma concentrations of RO7126209 will be measured by a specific and validated [redacted] method. PK parameters will be estimated using standard non-compartmental methods.

During the course of the study, number of samples and PK sampling time-points may be modified on the basis of emerging data to ensure the pharmacokinetics of RO7126209 can be adequately characterized.

8.6.2 Cerebrospinal Fluid

CSF samples will be collected at the timepoints outlined in the SoA (Section 1.3) and as described in Section 8.5.

RO7126209 CSF concentrations will be measured by a specific and validated [redacted] method. CSF pharmacokinetic data will not be required for dose escalation decision.

8.7 IMMUNOGENICITY ASSESSMENTS

As RO7126209 is a bispecific monoclonal antibody there is a risk that ADA against RO7126209 could develop, potentially reducing its efficacy and/or potentially resulting in symptomatic hypersensitivity reaction, including immune-complex reactions. Antibodies to RO7126209 will be evaluated in blood samples collected from all participants according to the SoA (Section 1.3). ADA data will not be required for dose escalation decisions.

[redacted]

[redacted]

[redacted].The date and time of each sample will be recorded in the eCRF.

[redacted]

The blood samples will be destroyed 6 months after the release of final bioanalytical report at the CRO performing the analysis or shipped to Roche. In the latter case the samples may be stored up to 2 years after the date of final CSR. Details on sampling procedures, sample storage and shipment are given in the sample documentation.
Details on sampling procedures, sample storage and shipment are described in the sample documentation.

8.8 PHARMACODYNAMICS AND BIOMARKER ANALYSES

8.8.1 Biomarker Research Sample

CSF samples will be collected and aliquoted before and after study drug administration as described in the SoA (Section 1.3) and Section 8.5. [redacted]

The samples may also be used for research purposes to identify biomarkers useful for predicting and monitoring response to study treatment, identifying biomarkers useful for predicting and monitoring study treatment safety, assessing pharmacodynamic effects of study treatment, and investigating mechanism of therapy resistance. Additional markers may be measured in the case that a strong scientific rationale develops.

Unless otherwise specified below, samples will be destroyed no later than 5 years after the date of final CSR.

8.8.2 Clinical Genotyping

[redacted]

[redacted]

APOE ε4:

In case of occurrence of ARIA, a whole blood sample will be obtained for DNA extraction. These participants will be evaluated for APOE ε4 genotype in order to identify their status with respect to their known risk factors for ARIA.

Data arising from these analyses will be subject to the same confidentiality as the rest of the study.

The residual blood will be destroyed within 5 years after the date of final closure of the final CSR.

Details on processes for collection and shipment of these samples can be found in the Sample Handling Manual.

8.9 HEALTH ECONOMICS

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

8.10 TIMING OF STUDY ASSESSMENTS

8.10.1 Order of Assessments

At timepoints where more than one assessment is required, the following sequence should be followed as applicable, and priority will be given to the PK blood sample being taken at the scheduled time: (1) ECGs; (2) Vital signs; (3) Respiratory rate; (4) PK blood sampling; (5) Laboratory safety tests and other blood sampling (anti-RO7126209 antibodies); (6) CSF sampling; (7) others.

8.10.2 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) for enrolled participant and for participants who are not subsequently enrolled will be maintained at the study site.

All screening, and all pre-treatment assessments (related to entry criteria), must be completed and reviewed to confirm that participants meet all eligibility criteria.

[redacted] The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

Screening and pre-treatment assessments will be performed at the time points indicated in the SoA Section 1.3), unless otherwise specified.

8.10.3 Assessments during Treatment

Under no circumstances will participants who enroll in this study and have completed treatment as specified, be permitted to be allocated a new randomization number and re-enroll in the study.

All assessments must be performed as per SoA (see Section 1.3).

8.10.4 Assessments at Study Completion/Early Termination Visit

Participants who complete the study or discontinue from the study early (as described in Section 4.1.4 and Section 7) will be asked to return to the clinic 57± 4 days after the dose of study drug for a follow-up visit (see Section 1.3 and Section 8.10.5).

8.10.5 Follow-Up Assessments

Assessments at the follow-up/early termination visit will be performed as indicated in the SoA (see Section 1.3). After the study completion/early termination visit, adverse events should be followed as outlined in Sections 8.3.1 and 8.3.3.

9. STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

The maximum number of participants to be randomized was chosen based on practical clinical judgment. Thirty-six participants are expected to be enrolled in this study. Additional participants will be enrolled in [redacted] with the maximum number of participants not exceeding 60. A minimum of 4 active treatment and 2 placebo participants will be included in the first two dose levels. Starting at dose level 3 a minimum of 6 active treatment and 2 placebo participants will be included.

The number of participants may be adapted during the study to characterize precisely the safety and PK profile of RO7126209.

The current planned study design and sample size complies with standard safety review rules applied in single ascending dose studies.

9.2 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 9.

Table 9 Analysis Populations

Population	Description
Safety	All participants randomized to study treatment and who received at least one dose of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis.
Pharmacokinetic	All participants who have received active (RO7126209) treatment will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.
Immunogenicity	Participants who had at least one predose or at least one post dose ADA assessment will be included and analyzed according to the treatment they actually received. The relationship between ADA status and safety, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

9.3 STATISTICAL ANALYSES

9.3.1 Demographics and Baseline Characteristics

Demographic and other baseline characteristics of the safety analysis population will be listed and summarized with descriptive statistics.

9.3.2 Safety Analyses

All safety analyses will be based on the safety analysis population.

Table 10 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for adverse events will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level.
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units; Système International d'Unités) by individual listings with flagging of abnormal results. See Appendix 4 for details on standard reference ranges and data transformation and the definition of laboratory abnormalities.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate.
ECG data analysis	ECG data will be presented by individual listings. In addition, tabular summaries will be used, as appropriate.
[redacted]	
Concomitant medications	The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by utilizing a mapped term and appropriate drug dictionary level. Concomitant medications will be presented in summary tables and listings.

9.3.3 Pharmacokinetic Analyses

All PK Analyses will be carried out on the PK analysis population.

9.3.3.1 Plasma Pharmacokinetic Parameters

Plasma PK parameters of RO7126209 will be read directly from the plasma concentration versus time profiles or calculated by using standard non-compartmental methods.

Pharmacokinetic parameters of RO7126209 will include (if appropriate):

- C_{end}: observed plasma concentration at the end of the infusion
- $AUC_{0\text{-}24h}$: Area under the plasma concentration versus time curve from zero to 24 h postdose
- $AUC_{0\text{-}168h}$: Area under the plasma concentration versus time curve from zero to 168h postdose
- $AUC_{0\text{-}last}$: Area under the plasma concentration versus time curve from zero to the last measurable concentration
- $AUC_{0\text{-}inf}$: Area under the plasma concentration versus time curve extrapolated to infinity

- λ_z: Terminal rate constant calculated by linear regression of the log-transformed terminal part of the concentration time curve
- $T_{1/2}$: Apparent terminal half-life, computed as ln(2)/λz
- CL : the total body clearance calculated as Dose/AUC
- V: Volume of distribution at steady-state, estimated based on iv data using the following formula V = MRT *CL, where MRT is the mean residence time and CL total body clearance. Mean residence time is calculated as follows :
  MRT = ($AUMC_{0\text{-}inf}$ / $AUC_{0\text{-}inf}$) - $t_{infusion}$/2, where $t_{infusion}$ is the infusion duration

9.3.3.2 CSF Pharmacokinetic Parameters

Population pharmacokinetic analyses using non-linear mixed effects modeling will be performed to analyze the plasma and the CSF concentration data of RO7126209 following IV administration.

The results of this analysis will be reported in a document separate from the clinical study report.

9.3.3.3 Statistical Analyses

The following statistical analysis on the PK parameters ($AUC_{0\text{-}\infty,}$ [or if it cannot properly be determined $AUC_{0\text{-}t}$ or $AUC0_{last}$] and C_{max}) will be performed after completion of the study to explore dose-proportionality. The following linear model will be applied to the log-transformed, dose-normalized pharmacokinetic study variables:

$$y_{ij} \sim \mu + \lambda_j + \varepsilon_{ij} \quad (i=1,2,\ldots,N;\ j=1,2,\ldots,M)$$

where is the number of different doses, N is the total number of participants, μ denotes the general mean of the transformed variables, λ_j is the effect of dose j and ε_j is the residual error for participant i in the dose level j. The residual errors are assumed to be independent and identically distributed following a normal distribution with zero mean and variance σ^2.

Least square means with corresponding 90% confidence intervals (CI) will be derived for each dose level and plotted to evaluate if there are obvious trends for normalized PK parameters of decreasing/increasing with dose.

The following hypothesis will be tested (in an exploratory sense) for the primary pharmacokinetic parameters:

H_0: There is no deviation from dose-proportionality (i.e., $\lambda_1 = \lambda_2 = \ldots = \lambda_M$)

versus

H_1 : There is a deviation from dose-proportionality ($\lambda_1 \neq \lambda_2$ for some i, j).

All p values will be interpreted in an exploratory sense only.

9.3.4 Bayesian Analysis to Support Dose-Escalation Recommendations

A Bayesian CRM model will be used to inform decisions about the dose of RO7126209 to be given to the next cohort, based on the accumulating data for safety (measured by the occurrence of dose-limiting events [DLEs]) and PK. A DLE will be defined as any treatment-related adverse reaction (e.g., AE, laboratory abnormality, change in vital signs, ECG) occurring within 8 days after dosing, that would prevent another drug administration at the same dose level in a given participant.

Following the accumulation of safety and PK data for each cohort of participants, a CRM model will recommend doses which:

1. Limit to ≤ 20% the probability of a DLE rate ≥ 30% (Estimation of the highest dose D_1, such that: Prob(DLE rate at $D_1 \geq 30\%$) $\geq$ 20%).
2. Limit the probability of exceeding a predicted mean maximum exposure level (MEL) to 20%. (Estimation of D_2, such that Prob{$C_{max}(D_2) \geq C_{MEL}$ } $\leq$ 20%).

24.

If D_1 or D_2 is less than the default increment, min(D_1, D_2) will be selected, otherwise the default increment.

The CRM method uses the data of the last and all previous cohorts. All calculations will be performed using a Bayesian framework with the priors properly predefined.

However, clinical judgment will always override model estimates in the dose selection process.

Simulations were performed to examine the operating characteristics of the CRM model across some dose-response profiles for safety (DLEs) (Appendix 6).

9.3.5 Immunogenicity Analyses

The immunogenicity analyses will include all participants with at least one ADA assessment, irrespective of whether or not the participant receives any treatment (Shankar et al 2014).

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after study drug administration (post-baseline incidence during both the treatment and follow-up periods) will be summarized.

- Participants are considered to be ADA positive if they are ADA negative at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment-enhanced ADA response).

- Participants are considered to be ADA negative if they are ADA negative at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

9.3.6 Pharmacokinetic / Safety Relationships

Exploratory investigation of the relationship between plasma exposure of RO7126209 and safety measurements may be performed.

9.4 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed. Data for study drug administration and concomitant medication will be listed. The number of participants who were randomized, discontinued, and completed the study will be summarized and listed.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the participant (e.g., advertisements, diaries etc), and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (Section 2.3.1 of this Appendix).

The Investigator should follow the requirements for reporting all adverse events to the Sponsor. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

1.3. INFORMED CONSENT

The Sponsor's Master Informed Consent Form (and ancillary sample ICFs such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable,

and the IRB/IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant’s legally authorized representative.

The Consent Forms must be signed and dated by the participant or the participant’s legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

Participants must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the participant or the participant’s legally authorized representative. All signed and dated Consent Forms must remain in each participant’s study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include participant authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for participant authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

1.4. CONFIDENTIALITY

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant

names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

1.5. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., LPLV)

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

2.1.2. Source Data Records

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, COAs (paper or eCOA), evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable Health Authorities.

2.1.3. Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study.

2.3.1. Protocol Amendments

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or any non-substantial changes, as defined by regulatory requirements.

2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

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

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

2.3.3. Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

3. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

Appendix 2
Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting

1. DEFINITION OF ADVERSE EVENTS

According to the E2A ICH guideline for Good Clinical Practice, an **adverse event** is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events Meeting the AE Definition:

- Deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, X−ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

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

A serious adverse event is defined as any untoward medical occurrence that at any dose:

- **Results in death.**
- **Is life-threatening.**

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**

  Disability means substantial disruption of the participant's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**.
- **Other significant events**:

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

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

3.1. ASSESSMENT OF SEVERITY

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the categories provided in Table 1 (as a guidance for assessing adverse event severity).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as grade 1, grade 2, grade 3, grade 4, grade 5, according National Cancer Institute Common Terminology Criteria for Adverse Events NCI CTCAE (v5)); the event itself may be of relatively minor medical significance (such as grade 3 headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event.

Table 1 Adverse Event Severity Grading Scale

Severity	Description
Grade 1	mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
Grade 2	moderate; minimal, local, or non-invasive intervention indicated; or limiting age appropriate instrumental activities of daily living[a]
Grade 3	severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
Grade 4	life-threatening consequences or urgent intervention indicated.
Grade 5	death related to adverse event[d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the NCI CTCAE (v5), which can be found at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
a Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.
c If an event is assessed as a "significant medical event," it must be reported as a serious adverse event.
d Grade 4 and 5 events must be reported as serious adverse events.

3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment.
- Known association of the event with the study treatment or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

For participant receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

4. FOLLOW-UP OF AES AND SAES

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events
- Non-serious adverse events of special interest (NSAESI)
- Pregnancies (see Section 8.3.5)

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting serious adverse events to the local Health Authority and IRB/EC.

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS AND NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

Events that Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, adverse events and serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Events that Occur after Study Treatment Initiation

For reports of serious adverse events and non-serious adverse events of special interest (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/ Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Reporting of Post-Study Adverse Events and Serious Adverse Events

If the Investigator becomes aware of any other serious adverse event occurring after the end of the AE reporting period, if the event is believed to be related to prior study treatment the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to investigators.

5.2 REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). For RO7126209 or matching placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with RO7126209 or matching placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as Special Situations. Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

6. EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and NSAESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document{s}:

- RO7126209 IB

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Appendix 3
Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. INFUSION-RELATED REACTIONS

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., infusion-related reaction *or* anaphylactic reaction) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as “systemic reaction”. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a participant experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

1.2. OTHER ADVERSE EVENTS

For adverse events other than infusion-related reactions (see Section 1.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.

- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between participant evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

4. ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a

descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia”.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5. ABNORMAL VITAL SIGN VALUES

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator’s judgment.

It is the Investigator’s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

6. ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN.

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest.

7. DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

8. PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

9. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Appendix 2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The participant has not suffered an adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the central or local laboratory. The results will be entered into the eCRF or loaded electronically.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Full Hematology	• [redacted]
[redacted]	• [redacted]
Full Clinical Blood Chemistry	• ALT, AST, ALP, GGT, total, direct and unconjugated bilirubin, total protein, haptoglobin, albumin, sodium, chloride, potassium, phosphate, calcium, creatinine, urea, fasting glucose, total cholesterol, triglycerides, CPK, LDH, [redacted]
[redacted]	• [redacted]
Coagulation	• Prothrombin time (INR) and activated thromboplastin time (APTT).
Viral Serology	• HIV (specific tests HIV1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody.
Safety Biomarkers	• [redacted]

Laboratory Assessments	Parameters
Infusion-related reaction blood sample	• [redacted]
Thyroid Hormones	• Thyroid stimulating hormone (TSH) at screening only
Anti-Drug Antibodies	• Anti-RO7126209 antibodies in plasma will be determined using a validated ELISA method
Urinalysis	• Dipstick: pH, glucose, blood and protein. If there is a clinically significant positive result (may be confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results, it should be recorded and there is no need to perform microscopy and culture. • Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal.
Alcohol	• Urine
Drugs of abuse	• Urine tests for (at minimum): amphetamines incl. MDMA, cocaine, opiates, cannabinoids, methadone and benzodiazepines.

The results of each test will be provided electronically or captured into the CRF. Investigators must document their review of each laboratory safety report.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Potential analysis considerations for analysing Laboratory data includes the use of Standard Reference Ranges and potential transformation of data for specific lab tests.

In this scenario, Roche standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

- Definition of Laboratory Abnormalities

For all laboratory parameters included in this analysis, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled “H” for high or “L” for low in participant listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for these laboratory parameters. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant’s baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as “HH” for very high or “LL” for very low.

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

- **Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

- **Women in the following categories are considered to be Woman of Non-Childbearing Potential (WONCBP)**

a) Pre-menarchal

b) Pre-menopausal female with one of the following:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c) Post-menopausal female

- A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

2 COLLECTION OF PREGNANCY INFORMATION

- **Male participants with partners who become pregnant**

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study (see Section 8.3.5 Pregnancy). This applies only to male participants who receive study treatment.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The

Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

3 ABORTIONS

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Any induced abortion due to maternal toxicity and/or embryofetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Elective or therapeutic abortion not associated with an underlying maternal or embryofetal toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

4 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Appendix 6
Statistical Details and Simulation of the Operating Characteristics of the Planned Design for Supporting the Dose-Escalation Recommendations

Statistical Models

Details on the statistical models, methods and algorithms as well as scenarios for evaluating the operating characteristics of the CRM designs are given below.

Model for safety analysis

The relationship between the dose and the probability of observing a DLE will be described by the following two-parameter logistic regression model:

$$\text{logit}(p) = \log\left(\frac{p}{1-p}\right) = \alpha + \beta \log\left(\frac{Dose}{D_{ref}}\right)$$

where p is the probability of observing a DLE at a given dose, α is the log of the odds for p at the reference dose ($Dref,$ here equals to 0.3 mg) and β is the slope of the curve. (detailed discussion about this model parameterization can be found in [Neuenschwander B.,Branson M., Gsponer T. Critical Aspects of the Bayesian Approach to Phase I Cancer Trials. Stat Med, 2008; 27:2420-2439.])

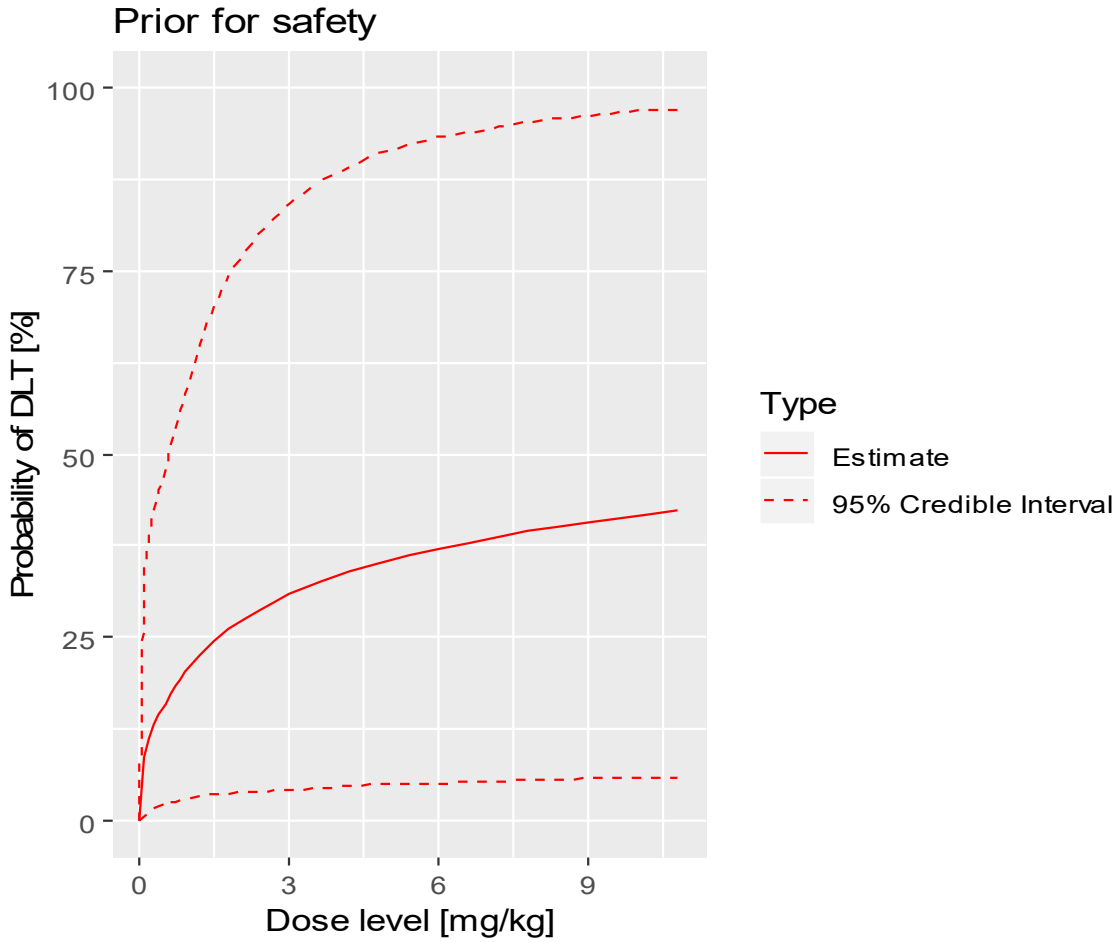
Since the model will be estimated using a Bayesian framework, priors need to be specified for α and β. Neuenschwander's 'minimally informative prior' will be used (Neuenschwander, 2008). This prior was built on the assumption that the starting dose (0.1 mg/kg) is safe (probability that DLE rate > 0.2 is less than 0.05) and with 10.8 mg/kg, the probability of DLE rate > 0.35 is 0.6.

The resulting bivariate distribution that will be used is:

$$\begin{pmatrix} \alpha \\ \log(\beta) \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} -2.078 \\ -0.948 \end{pmatrix}, \begin{pmatrix} 1.018 & -0.105 \\ -0.105 & 0.499 \end{pmatrix}\right)$$

Figure 1 shows the graph of the chosen prior with 95%-credible interval.

Figure 1. Prior for safety analysis.



Simulations for the operating characteristics

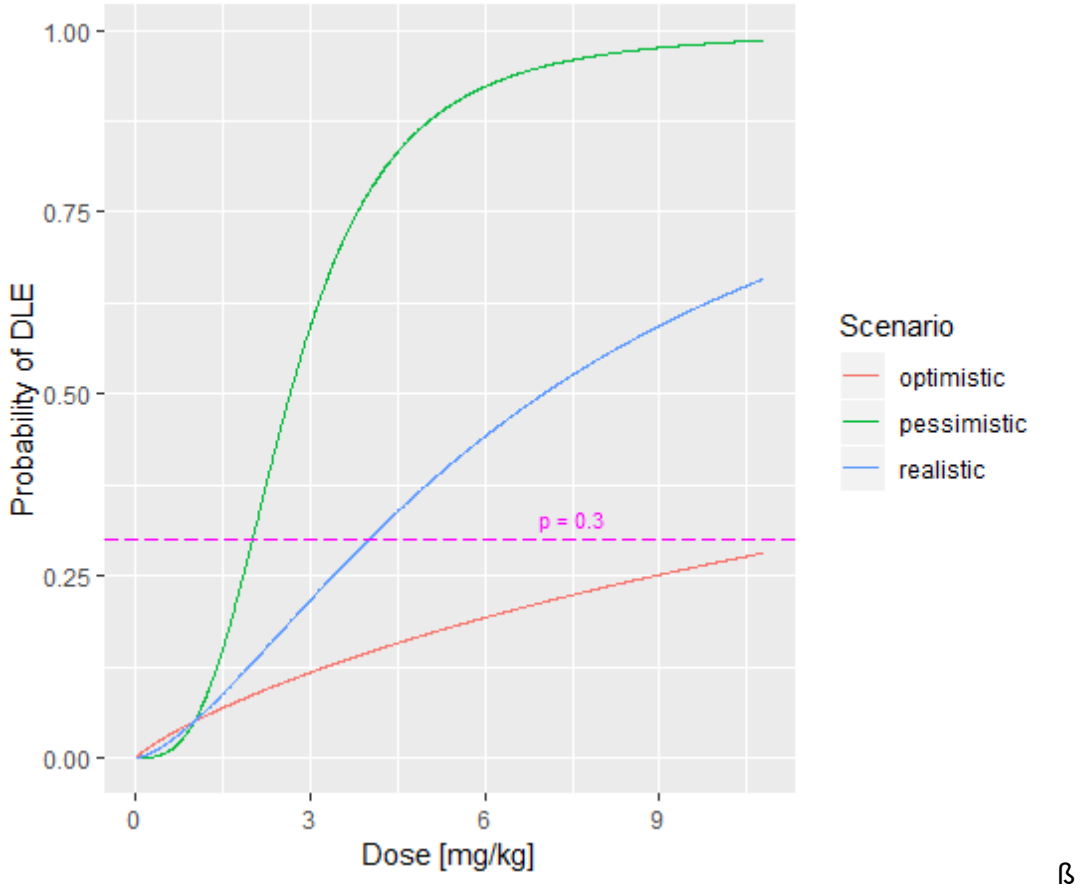
Simulations were performed to examine the operating characteristics of the CRM model across some dose-response profiles for safety (DLEs).

For the simulation, the following settings were made:

- Maximum number of cohorts: 6
- Cohort size: For the first 3 dose levels, 4+2 and the last 3 dose levels 6+2
- Decision criterion for safety: $prob(DLE\ rate \geq 30\%) < 0.2$
- The dose grid is (in mg/kg) 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.2 1.5 1.8 2.1 2.4 2.7 3.0 3.6 4.2 4.8 5.4 6.0 6.6 7.2 7.8 8.4 9.0 9.6 10.2 10.8

The simulations were based on a hypothetical ‘simulation truth’. Three scenarios based on a logistic regression models, an ‘optimistic’, a ‘realistic’ and a ‘pessimistic’ one, were chosen. The doses, where a DLE probability of 0.3 is achieved under these scenarios are 12 mg/kg, 4 mg/kg, and 2 mg/kg, respectively. Figure 2 below shows a graphical display of these parameters.

Figure 2. Simulation truths for evaluating operating characteristics for safety.



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Results from the simulations

The first table (Table 1) shows what the next recommended dose is for all possible number of DLEs observed, ***assuming no DLEs are observed until the current dose level***.

Table 1: Examination of the chosen safety decision algorithm.

dose	DLTs	next Dose
0.1	0	0.300
0.1	1	0.200
0.1	2	0.001
0.1	3	0.001
0.3	0	0.900
0.3	1	0.700
0.3	2	0.300
0.3	3	0.100
0.9	0	2.700
0.9	1	1.200
0.9	2	0.600
0.9	3	0.400
2.7	0	5.400
2.7	1	4.800
2.7	2	2.100
2.7	3	1.200
5.4	0	10.800
5.4	1	9.600
5.4	2	6.600
5.4	3	3.600

The next table (Table 2) displays operating characteristics based on 1000 simulations for the three scenarios described in the previous section. D_{max}, denotes the highest dose such that: Prob(DLE rate at D_{max} > 30%) < 20%).

Table 2: Operating characteristics; means and Intervals corresponding to 10 and 90 % quantiles.

Scenario	Proportions of DLEs on active [%]	Dose most often chosen as D_{max}	Observed DLE rate at . D_{max} [%]
optimistic	7.3(2.8,12.3ß)	4.4 mg/kg	11.7
realistic	9.2(4.8,11.9)	1.6 mg/kg	8.3
pessimistic	13.3(9.5,16.7)	0.8 mg/kg	13.1

Remarks and Conclusions

The proposed CRM design shows a good protection against overdosing and gives reasonable estimates for the mean of the doses as selected as $D_{max.}$ The results in Table 1have to be interpreted with caution for the lowest doses.

Appendix 7 Equivalent Visual Acuity Measurements

Snellen Visual Acuity				
4 meters	**6 meters**	**20 feet**	**Decimal fraction**	**LogMAR**
4/40	6/60	20/200	0.10	+1.0
4/32	6/48	20/160	0.125	+0.9
4/25	6/38	20/125	0.16	+0.8
4/20	6/30	20/100	0.20	+0.7
4/16	6/24	20/80	0.25	+0.6
4/12.5	6/20	20/63	0.32	+0.5
4/10	6/15	20/50	0.40	+0.4
4/8	6/12	20/40	0.50	+0.3
4/6.3	6/10	20/32	0.63	+0.2
4/5	6/7.5	20/25	0.80	+0.1
4/4	6/6	20/20	1.00	+0.0
4/3.2	6/5	20/16	1.25	-0.1
4/2.5	6/3.75	20/12.5	1.60	-0.2
4/2	6/3	20/10	2.00	-0.3