Official Title: A Double-Blind, Randomized, Parallel-Group, Phase 2 Study to Investigate the Effect of RO7049665 on the Time to Relapse Following Steroid Tapering in Patients With Autoimmune Hepatitis

NCT Number: NCT04790916

Document Date: Protocol Version 2: 05-Aug-2021

PROTOCOL

TITLE:	**A DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP, PHASE 2 STUDY TO INVESTIGATE THE EFFECT OF RO7049665 ON THE TIME TO RELAPSE FOLLOWING STEROID TAPERING IN PATIENTS WITH AUTOIMMUNE HEPATITIS**
PROTOCOL NUMBER:	BP42698
VERSION:	2
EUDRACT NUMBER:	2020-003990-23
IND NUMBER:	NA
TEST PRODUCT:	RO7049665
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 15 September 2020
DATE AMENDED:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
05-Aug-2021 14:33:23	Company Signatory	[redacted]

PROTOCOL ACCEPTANCE FORM

TITLE:	**A DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP, PHASE 2 STUDY TO INVESTIGATE THE EFFECT OF RO7049665 ON THE TIME TO RELAPSE FOLLOWING STEROID TAPERING IN PATIENTS WITH AUTOIMMUNE HEPATITIS**
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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 2
RATIONALE

European Association for the Study of the Liver (EASL) provides guidelines for the diagnosis and treatment of patients with Autoimmune Hepatitis. However, not all countries and sites adhere to the EASL guidelines and have instead developed their own local rules and practices. Therefore, protocol BP42698 has been amended to incorporate the following changes based on feedback from sites and investigators, in order to better adapt the eligibility criteria for the patients to the local practices. Changes to the protocol, along with a rationale for each change, are summarized below.

- Section 5.1 (inclusion criteria #4, #5 and #7):
  - Inclusion criterion 4: changes have been done to clarify the IgG measurements and local practice and to adapt the time in biochemical remission to local practice.
  - Inclusion criterion 5: stable use of corticosteroid (CCS) ± non-specific immunosuppressants has been updated to ≥ 3 months instead of 6 months, and without dose increase in the 6 months prior to the randomization.
  - Inclusion criterion 7: conditions around previous CCS tapering were adjusted.
- Section 8.2.2. (Vital signs): A new body area (forehead) has been introduced for body temperature measurements based on a request by a South Korean site.
- Section 8.3.7. (Management of specific adverse events): The text regarding the role of the Medical Monitor has been updated.

Additional minor changes have been made to improve clarity and consistency. Substantial new information appears in *Book Antiqua* italics. This amendment represents cumulative changes to the original protocol.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AIH	Autoimmune hepatitis
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
CCS	Corticosteroid
CL	Clearance
CLS	Capillary leakage syndrome
C_{max}	Maximum concentration
COA	Clinical outcome assessment
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report form
EASL	*European Association for the Study of the Liver*
EBV	Epstein-Barr virus
EDC	Electronic data capture
EIH	Entry-into-human
EQ-5D-5L	EuroQoL five dimensions questionnaire-five levels
EU	European union
FACIT	Functional assessment of chronic illness therapy
FDA	Food and drug administration
FFPE	Formalin-fixed paraffin embedded
FSH	Follicle-stimulating hormone
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBcAb	Total hepatitis B core antibody
HCV	Hepatitis C

HDL	High-density lipoproteins
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IB	Investigator's brochure
ICF	Informed consent form
ICH	International council on harmonisation
IEC	Independent ethics committee
IHC	Immunohistochemistry
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IMC	Internal monitoring committee
IMP	Investigational medicinal product
IND	Investigational new drug (application)
INR	International normalized ratio
IRB	Institutional review board
IUD	Intrauterine device
IV	Intravenous
IxRS	Interactive (voice/web) response system
LDL	Low-density lipoproteins
LPLV	Last participant, last visit
LPLO	Last participant, last observation
MAD	Multiple-ascending doses
MoA	Mode of action
NK	Natural killer
NOAEL	No-observed-adverse-effect level
NSAESI	Non-serious adverse event of special interest
NSI	Non-specific immunosuppressants
NYHA	New York Heart Association
OLE	Open-label extension
OTC	Over-the-counter
pSTAT5	Phosphorylated signal transducer and activator of transcription 5
PD	Pharmacodynamic
PK	Pharmacokinetic
PIIINP	Procollagen III amino-terminal peptide
PRO	Patient-reported outcome (also refers to participant)

PROMIS	Patient-reported outcomes measurement information system
PT	Prothrombin time
Q2W	Every 2 weeks
QoL	Quality of life
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
RBR	Research biosample repository
RNA	Ribonucleic acid
RR	RR interval
SAD	Single-ascending dose
SAE	Serious adverse event
SC	Subcutaneous
SMA	Smooth muscle antibodies
SoA	Schedule of activities
SoC	Standard of care
t_{max}	Time of maximum concentration observed
T_{eff}	Effector T cell
T_{reg}	Regulatory T cell
TEAE	Treatment-emergent adverse event
TIMP-1	Tissue inhibitor of matrix metalloproteinase 1
TSH	Thyroid-stimulating hormone
UC	Ulcerative colitis
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
Vz/F	Apparent volume of distribution
WBC	White blood cell
WES	Whole exome sequencing
WGS	Whole genome sequencing
WHO	World Health Organization
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP, PHASE 2 STUDY TO INVESTIGATE THE EFFECT OF RO7049665 ON THE TIME TO RELAPSE FOLLOWING STEROID TAPERING IN PATIENTS WITH AUTOIMMUNE HEPATITIS**
SHORT TITLE	**Double-Blinded, Parallel-Group, Phase 2 Study for the Effect of RO7049665 in Patients with AIH**
PROTOCOL NUMBER:	BP42698
VERSION:	2
TEST PRODUCT:	RO7049665
PHASE:	2

RATIONALE

RO7049665 is a novel dimeric interleukin 2 (IL-2) mutein that is being developed as a therapy for chronic inflammatory and autoimmune conditions, including ulcerative colitis (UC) and autoimmune hepatitis (AIH). It is expected to treat the impaired regulatory T cell (T_{reg}) numbers or function associated with autoimmune diseases without the broad-based immunostimulatory effects of IL-2. Specifically, RO7049665 was engineered to address and overcome the pharmacologic, safety, and functional liabilities of aldesleukin, a recombinant human IL-2 therapy currently approved for the treatment of renal cell carcinoma and malignant melanoma.

Study BP42698 is the first study where RO7049665 is administered to patients with AIH. The primary objective of this study is to evaluate the effect of RO7049665 on time to relapse following forced corticosteroid (CCS) tapering in participants with CCS-controlled AIH. In addition, secondary objectives are to assess the changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and immunoglobulin G (IgG), to investigate the multiple-dose pharmacokinetics of RO7049665 in this patient population, and to evaluate the safety and tolerability of RO7049665 in participants with AIH. The study results will be used to support further clinical development of RO7049665.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of RO7049665 on time to relapse following forced CCS tapering as measured by the hazard ratio between 7.5 mg RO7049665 and placebo.	• Time to relapse from start of randomization.
Secondary	
• To assess changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and IgG over time and by dose.	• ALT, AST, and IgG (for both Δ, absolute and relative [ULN]) over time.
• To evaluate the effect of RO7049665 on time to relapse following forced CCS tapering as measured by the hazard ratio between 3.5 mg RO7049665 and placebo.	• Time to relapse from randomization.
• To evaluate the safety and tolerability of RO7049665 in participants with AIH.	• Incidence and severity of adverse events. • Changes in vital signs, physical examination, ECG parameters, and safety laboratory parameters. • ADA emergence and neutralizing potential.

OVERALL DESIGN

Study BP42698 is a 3-parallel arm (two dose levels of RO7049665 versus placebo), randomized, placebo-controlled, double-blind, event-driven phase 2 study to assess efficacy of RO7049665 over placebo in patients with AIH in stable biochemical remission. Two dose levels will be assessed: 3.5 mg RO7049665 (subcutaneously [SC], every second week [Q2W]) and 7.5 mg RO7049665 (SC, Q2W), with matching placebo.

Study Design

This is an event-driven study, which means that participants stay in the study and on treatment until the participant experiences an event (e.g., ALT rises > 2 $\times$ upper limit of normal [ULN] or IgG increases > 1.5 $\times$ ULN), the necessary number of events (a total of 45 events) is reached, the participant stops for other reasons or withdraws consent, or the study ends.

Patients eligible for the study must be in biochemical remission for at least 2 years *(or less if according to the local practice)*, be on stable treatment (CCSs $\pm$ non-specific immunosuppressants [NSIs]) for at least *3* months prior to *randomization (and who have not had a dose increase 6 months prior to randomization)*, and show no signs of inflammation (HAI $\leq$ 3) on a liver biopsy taken no more than 12 months prior to randomization. For eligible patients this will be the first attempt to taper out CCS completely *within the last 3 years*.

At study entry, the disease status of the participants should allow for a stepwise removal of all immunosuppressive treatment *according to local guidelines or practice. If no local guidelines exist, EASL guidelines should be applied*. Participants will start with study treatment on study Day 1 and start tapering CCS use from Day 8 onwards (see tapering schedule, Section 1.3, Table 3) to allow for complete CCS withdrawal within a maximum of 12 weeks, depending on the starting dose. Last dose of NSI therapy, if any, will be taken on study Day –1.

Randomization in a 1:1:1 fashion will occur after patient eligibility is confirmed and before the first dose of study treatment is administered. Randomization will be stratified by equivalent prednisolone dose ($\leq$ 7.5 mg daily versus $>$ 7.5 mg daily or dual therapy [CCS any dose, plus NSI]). Two interim analyses are planned. The first is planned for futility once 25% of events (i.e.,12 events) are observed. The second interim analysis for efficacy and futility is planned once 50% of events (i.e., 23 events) are observed.

Treatment Groups and Duration

The investigational medicinal products (IMPs) for this study are RO7049665 or matching placebo. The first three doses of study treatment will be administered by the investigational staff (i.e., Investigator or study nurse) at the study center under supervision of the Investigator. Administration of study treatment should be done in the abdomen. Once the safe administration of study treatment is confirmed, it is at the discretion of the Investigator whether to allow administration of study treatment at the participant's home via a home nurse.

Corticosteroids are considered non-investigational medicinal products (NIMPs).

No dosage modification of RO7049665 is permitted. Participants who have had study treatment temporarily interrupted should be considered to restart as soon as medically justified in the opinion of the Investigator after discussion with the Sponsor.

Length of Study

The study is anticipated to run for approximately 25 months (i.e., 19 months' recruitment and 6 months follow-up), until the necessary number of events is observed. It is not possible to estimate the duration of the study for an individual patient as this is an event-driven study; the occurrence of an event cannot be reliably estimated for an individual patient.

Study periods are divided as follows:

- Screening: Up to 28 days.
- Treatment period: Day 1 to relapse or final number of events is observed.
- Safety follow-up: 4 weeks after last administration of study treatment.
- End of study visit: Follow-up visit 28 days after last dose of study treatment. In the event that a participant is enrolled into an OLE study the follow-up visit will not apply and the last visit within the treatment period will be considered as the end of study visit.

End of Study

The goal of the study is achieved when any of the interim analyses results in a decision to stop the study or when the required number of events is reached, or if any of the stopping rules apply. At this point the study will be unblinded.

An individual participant has completed the study if he/she has completed all scheduled procedures as shown in the Schedule of Activities (SoA; see Section 1.3).

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur approximately 4 weeks after study closure when the final FU visit will be conducted. Study closure can occur either after:

- The first interim analysis for futility, or
- The second interim analysis for futility or efficacy, or
- 45 events are observed, or
- Early study termination.

The Sponsor may set up an open-label extension (OLE) study if RO7049665 development will be continued for participants not having had a relapse at the closure of BP42698.

Internal Monitoring Committee

In order to keep the study personnel blinded during interim analyses, an Internal Monitoring Committee (IMC) will be established.

The unblinded IMC will review the results of each interim analysis and will recommend to the study team whether the study should stop, continue, or be modified.

The IMC is a dedicated group of selected Sponsor representatives, who will be independent from the project and review the safety and efficacy data of the study, as well as the interim analyses. The roles, responsibilities, membership, scope of activities, time of meetings, and communication plan for the IMC will be documented in an appropriate charter.

PARTICIPANT POPULATION

The participants of this study are patients between 18 and 75 years of age, inclusive, with a diagnosis of AIH, with no evidence of cirrhosis with significant impairment of liver function stage (e.g., Child Pugh B or C). All participants in the study will have responded well to treatment with CCSs ± NSIs.

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. Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonisation (ICH) and local regulations.

Age

2. Between 18 to 75 years of age, inclusive, at the time of signing the informed consent.

Type of Participants and Disease Characteristics

3. Patients with a definite diagnosis of AIH (type 1, 2 and 3) as per simplified or revised original diagnostic criteria (including response to CCSs) (Hennes et al 2008).
4. Patients who have been in biochemical remission (complete normalization of serum transaminases and IgG levels *[if IgG is measured, as according to local practice])* for ≥ 2 years *(or less if according to the local practice)* prior to randomization. *At least two measurements of IgG levels within normal range at least two weeks apart need to be available before randomization.*
5. Patients who have been on stable treatment (CCSs ± NSIs) for at least *3* months prior to randomization *and who have not had a dose increase in the previous 6 months prior to randomization.*
6. No signs of liver inflammation (HAI ≤ 3) on a liver biopsy taken no more than 12 months prior to randomization.
7. Patients with AIH who have previously not attempted *(or not attempted in the last 3 years, if this is the local practice)* to taper CCS to 0 mg/day.

Weight

8. Body mass index within the range of 18-35 kg/m^2 (inclusive).

Sex and Contraception/Barrier Requirements

9. Male and female participants are eligible.

The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. Therefore, the reliability of sexual abstinence for female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

A female participant is only eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

Women of non-childbearing potential (WONCBP),

OR

Women of childbearing potential (WOCBP), who:

Agree to remain abstinent (refrain from heterosexual intercourse) or use at least one acceptable contraceptive methods during the treatment period and for at least 28 days after the final dose of study treatment.

The following are acceptable contraceptive methods: bilateral tubal occlusion/ ligation, male sexual partner who is sterilized, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices, male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

Exclusion Criteria

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

Medical Conditions

1. Patients with cirrhosis (F4 fibrosis by Fibroscan®) with significant impairment of liver function (Child Pugh category B or C).
2. Any other autoimmune disease (including overlap syndrome) requiring immunomodulating treatment.
3. History of infection with hepatitis B (hepatitis B surface antigen [HBsAg] positive and/or anti-HBc positive; HBV vaccinated patients are eligible), human immunodeficiency virus (HIV; positive HIV antibody test), active hepatitis C virus (HCV) infection (detectable HCV RNA), detection of replicating CMV or Epstein-Barr virus.
4. Active infections requiring systemic therapy with antibiotic, antiviral or antifungal treatment or febrile illness within 7 days before Day −1.
5. History of primary or acquired immunodeficiency.
6. Female patients: Pregnant or lactating.
7. Symptomatic herpes zoster within 3 months prior to screening.
8. History of active or latent tuberculosis or a positive Quantiferon® Gold test.
9. History of clinically significant severe drug allergies, multiple drug allergies, allergy to any constituent of the product, or intolerance to topical steroids.
10. Lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years and in situ carcinoma of the cervix that was completely removed surgically. Breast cancer within the past 10 years.
11. Significant uncontrolled comorbidity, such as cardiac (e.g., moderate to severe heart failure New York Heart Association [NYHA] Class III/IV), pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders (excluding UC).
12. Any condition or disease detected during the medical interview/physical examination that would render the patient unsuitable for the study, place the patient at undue risk or

interfere with the ability of the patient to complete the study in the opinion of the Investigator.

Prior/Concomitant Therapy

13. CCSs of $<$ 5 mg/day (prednisolone-equivalent dose), or < 2.5 mg CCSs (prednisolone-equivalent dose) plus immune suppressant, or < 3 mg/day budesonide with or without immune suppressant.
14. CCSs $>$ 20 mg/day (prednisolone-equivalent dose) or > 9 mg/day budesonide.
15. NSI daily dose higher than recommended standard of care therapy.
16. T or B cell-depleting therapy (e.g., rituximab) within the last 12 months or T- or B-cell number below normal due to depleting therapy.

Prior/Concurrent Clinical Study Experience

17. Leukocyte apheresis within 12 weeks of screening.
18. Donation of blood or blood products in excess of 500 mL within 3 months prior to screening.
19. Exposure to any investigational treatment within 6 months prior to Day 1.

Laboratory Abnormalities

20. Abnormal hematologic values:
    - Anemia (hemoglobin $<$ 9 g/dL)
    - Leukocytosis (white blood cells $\geq 2 \times$ ULN)
    - Thrombocytopenia (platelet count $<$ 100,000/μL)
    - Thrombocytosis (platelet count $\geq 2 \times$ ULN)
    - Eosinophilia (eosinophil count $\geq 2 \times$ ULN)
21. Abnormal hepatic enzyme or hepatic function values:
    - ALT, AST, or alkaline phosphatase, above normal range
    - Total bilirubin $\geq 2 \times$ ULN
    - International normalized ratio (INR) $\geq$ 1.7
    - Albumin $<$ 3 g/dL
22. Abnormal biochemistry values:
    - IgG above normal range

Other Exclusions

23. History of regular alcohol consumption within 2 months of screening defined as:

    An average weekly intake of $>$ 14 drinks for men or $>$ 7 drinks for women. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine, or 1.5 ounces (45 mL) of 80 proof distilled spirits (equivalent to 40 vol%).
24. Any suspicion or history of illicit drug use.
25. Patients under judicial supervision, guardianship, or curatorship.

NUMBER OF PARTICIPANTS

The study is expected to enroll a maximum of 84 participants (28 participants per arm) in order to observe 45 events. Any patient who satisfies all eligibility criteria and who is randomized will be evaluable. If the enrolment rate or event rate differ from the assumptions used in these calculations, then either the number of participants or the duration of follow-up (or both) may be varied in order to ensure the required number of events is observed.

CONCOMITANT MEDICATIONS

Any medication used by a participant from 30 days prior to screening until the follow-up visit must be recorded in the electronic Case Report Form (eCRF). CCSs and NSIs (e.g., AZA, 6-MP, MMF, others) used 12 months prior to randomization must be recorded in the eCRF. All therapy and/or medication administered to manage AEs should be recorded on the Adverse Event eCRF.

The same information must be recorded for the following concomitant medications taken by a participant during the indicated period prior to screening until the follow-up visit:

Permitted therapies include:

- CCSs and NSIs (e.g., AZA, 6-MP, MMF) used 12 months prior to randomization,
- Pre-medication for the management of injection-related reactions (e.g., anti-histamines),
- Ursodeoxycholic acid (UDCA).

Participants who use the following therapies prior to screening and are on a stable regimen should continue their use:

- Oral contraceptives,
- Hormone-replacement therapy,
- UDCA,
- Maintenance therapy for concomitant diseases.

Participants will taper their CCS therapy for AIH during the first weeks of the study according to the SoA table (see Section 1.3, Table 3). As a general rule, no concomitant medication to treat the underlying disease other than CCSs during tapering will be permitted.

Use of the following therapies will be prohibited during the study:

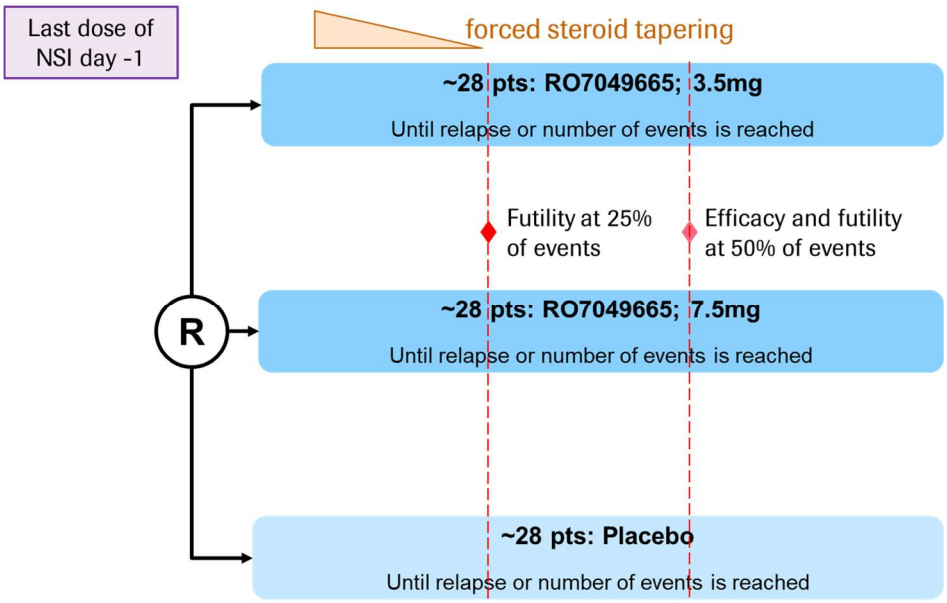
- CCS after tapering has been completed, except topical steroids.
- Any other immune system targeted biological therapy (including but not limited to JAK inhibitors).

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

1.2 SCHEMATIC OF STUDY DESIGN

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

Figure 1 Overview of Study Design



1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities (SoA) is provided in Table 1.

Table 1 Schedule of Activities – Main Table

Version 2022-07-29 Week	Screening	1	2	3	4	5	7	9	11	12	13	15	17	19	21	23	25	27	29 / 33 / 37 / 41 …	31 / 35 / 39 / 43 …	Unscheduled Visit	Early Termination or End of Study	Confirmation of Relapse	Follow Up Visit
Day	D-28 to D-1	1	8	15	22	29	43	57	71	78	85	99	113	127	141	155	169	183	197 / 225 … till relapse	211 / 239 … till relapse	any time assessments as needed		at least 1 week after ALT≥ 2ULN	4 weeks after last dose
Visit Window	no time	±0 days	±0 days	±1 days	±1 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days				±3 days
Informed Consent	x																							
Demography	x																							
Medical History including AIH and other AIDs	x																							
Tuberculosis Screening Test	x																							
Drugs of Abuse + Alcohol Test	x																				x			
Viral testing HBV, HCV, HIV, EBV, CMV	x																				x			
Hormones	x																							
Previous and Concomitant Treatments	x	any time																						
Revised AIH Score at diagnosis	x																							
Simplified AIH Score at diagnosis	x																							
Out-patient visit in clinic	x	x	x	x		x		x	x	x	x		x		x		x		x		x	x	x	x
Home Nurse Visit (optional, else out-patient visit)					x		x					x		x		x		x		x				
Treatment assignment		x																						
Administration of Study Medication		x		x		x	x	x	x		x	x	x	x	x	x	x	x	x	x				
FU phone call 8-24 hrs past injection		x		x		x	x	x	x		x	x	x	x	x	x	x	x	x	x				
Anthropometric Measurements (incl. Weight, Height [height at screening only] and BMI)	x	x	x	x	x	x	x	x	x		x		x		x		x		x		x	x	x	x
Vital Signs	x	x	x	x	x	x	x	x	x		x		x		x		x		x		x	x	x	x
Full physical examination	x	x				x															x	x	x	x
Abbreviated physical examination				x				x		x	x		x		x		x		x		x			
ECG-12 lead	x	x	x																		x	x	x	x
Hematology	x	x	x	x	x	x	x	x	x		x		x		x		x		x		x	x	x	x
Coagulation	x	x	x	x	x	x	x	x	x		x		x		x		x		x		x	x	x	x
Blood Chemistry	x	x	x	x	x	x	x	x	x		x		x		x		x		x		x	x	x	x
Urinalysis	x	x		x		x	x	x	x		x		x		x		x		x		x	x	x	x
Pregnancy Test (WOCBP only, pre-dose)	x	x				x		x			x		x		x		x		x		x			
Fibroscan (A)	x	x															x				x	x	x	x
Liver fibrosis testing (A)	x	x															x				x	x	x	x
Liver Biopsy	x																x - optional				x			
Clinical Genotyping	preferred at day 1 but can be collected any time during the study																							
PK Sample		2	x	x				x	2 (B)	x	x		x		x		2 (B)		x		x	x		x
Blood Flow Cytometry		x	x	x					x	x							x		x (A)		x	x (C)	x	
Soluble PD biomarkers		x	x	x					x	x							x		x (D)		x	x	x	
Soluble Disease Biomarkers		x	x	x					x	x							x		x (D)		x	x	x	
Anti-Drug Antibodies		x	x	x				x	x	x	x		x		x		x		x		x	x	x	x
PRO - PROMIS SF Fatigue 13a		x				x	x (E)				x						x		x (D)		x	x	x	
PRO - SF-12		x					x (E)				x						x		x (D)		x	x	x	
PRO - EQ-5D-5L		x					x (E)				x						x		x (D)		x	x	x	
ISR Questionnaire				x		x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Research Biosample Repository (RBR) Consent	optional - preferred at day 1 but can be collected any time during the study																							
Adverse Events or Intercurrent Illness		any time																						
Injection-Related Reaction (IRR) samples (F)		x	any time as needed																					
Skin Reactivity, Pain and Size Assessment (G)		any time																						

Table 1 Schedule of Activities – Main Table (cont.)

A. Every 24 weeks starting from week 25, e.g., week 49, week 74, etc.
B. The second PK sample can be taken by a mobile nurse, as needed.
C. If not taken within the previous 4 weeks.
D. Every 12 weeks starting from week 25, e.g. week 37, week 49, etc.
E. At the next scheduled visit approximately one week after the last steroid dose, see also Table 3 (tapering scheme).
F. Injection-related reaction (IRR) blood samples will be taken at baseline (Day 1 at pre-dose), and at any time in case of IRR of Grade 2 or above, for the assessment of tryptase, cytokine panel (exploratory safety biomarkers), and total IgE. PK and ADA will also be collected. Baseline samples may only be analyzed in case of IRRs.
G. In case of an adverse event associated with local tolerability and pain.

Table 2 Schedule of Activities – Detailed Table

Day Version 2021-07-29	Schedule Time (h)	PK Sample	Blood Flow Cytometry (whole blood)	Soluble PD biomarkers - EDTA plasma	Soluble Disease Biomarkers - Serum	Anti-Drug Antibodies	Liver fibrosis testing (A)	Fibroscan (A)	ISR Questionnaire every two wks	PRO - PROMIS SF Fatigue 13a	PRO - SF12	PRO - EQ-5D
Screening							x	x				
Day 1	predose	x	x	x	x	x	x	x		x	x	x
Day 1	sampling window 8 - 24 hrs	x										
Day 8	predose	x	x	x	x	x						
Day 15	predose	x	x	x	x	x			x			
Day 29	predose								x	x		
Day 43	predose								x	x (E)	x (E)	x (E)
Day 57	predose	x				x			x			
Day 71	predose	x	x	x	x	x			x			
Day 71	sampling window 8 - 24 hrs (B)	x										
Day 78	predose	x	x	x	x	x						
Day 85	predose	x				x			x	x	x	x
Day 99	predose								x			
Day 113	predose	x				x			x			
Day 127	predose								x			
Day 141	predose	x				x			x			
Day 155	predose								x			
Day 169	predose	x	x	x	x	x	x	x	x	x	x	x
Day 169	sampling window 8 - 24 hrs (B)	x										
Day 183	predose								x			
Day 197, 225	predose	x	x (A)	x (D)	x (D)	x			x	x (D)	x (D)	x (D)
Day 211, 239	predose								x			
Unscheduled Visit	predose	x	x	x	x	x	x	x	x	x	x	x
Early Termination		x	x (C)	x	x	x	x	x	x	x	x	x
Confirmation of Relapse	predose		x	x	x	x	x	x	x	x	x	x
Follow Up Visit		x				x	x	x				

For footnotes, see Table 1.

Table 3 Schedule of Activities – Corticosteroid Tapering Schedule

Maintenance dose (MD) mg/d	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Prednisolone												
≤20 >15	MD	15	10	10	7.5	7.5	5	5	2.5	2.5	0	PRO
≤15 >10	MD	10	10	7.5	7.5	5	5	2.5	2.5	0	PRO	0
≤10 > 7.5	MD	7.5	7.5	5	5	2.5	2.5	0	PRO	0	0	0
≤7.5 >5	MD	5	5	2.5	2.5	0	PRO	0	0	0	0	0
≤5 >2.5	MD	2.5	2.5	0	PRO	0	0	0	0	0	0	0
2.5	MD	0	PRO	0	0	0	0	0	0	0	0	0
Budesonide												
≤9 >6	MD	6	6	6	6	3	3	3	3	0	PRO	0
≤6 >3	MD	3	3	3	3	0	PRO	0	0	0	0	0
3	MD	0	PRO	0	0	0	0	0	0	0	0	0

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PRO – timepoint where PROs are required in relation to CCS treatment end (see SoA Table 1).

2. INTRODUCTION

2.1 STUDY RATIONALE

RO7049665 is a novel dimeric interleukin 2 (IL-2) mutein that is being developed as a therapy for chronic inflammatory and autoimmune conditions, including ulcerative colitis (UC) and autoimmune hepatitis (AIH). It is expected to treat the impaired regulatory T cell (T_{reg}) numbers or function associated with autoimmune diseases without the broad-based immunostimulatory effects of IL-2. Specifically, RO7049665 was engineered to address and overcome the pharmacologic, safety, and functional liabilities of aldesleukin, a recombinant human IL-2 therapy currently approved for the treatment of renal cell carcinoma and malignant melanoma.

Study BP42698 has taken into consideration the experience gained in the healthy volunteer, entry-into-human (EIH), single-ascending dose (SAD) study WP39826 and the ongoing multiple-ascending dose (MAD) study WP40161 in participants with UC. Study BP42698 is the first study where RO7049665 is administered to patients with AIH. The primary objective of this study is to evaluate the effect of RO7049665 on time to relapse following forced corticosteroid (CCS) tapering in participants with CCS-controlled AIH. In addition, secondary objectives are to assess the changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and immunoglobulin (Ig) G (IgG); to investigate the multiple-dose pharmacokinetics (PK) of RO7049665 in this patient population, and to evaluate the safety and tolerability of RO7049665 in participants with AIH. The study results will be used to support further clinical development of RO7049665.

The rationale for the study design is provided in Section 4.

2.2 BACKGROUND

2.2.1 Autoimmune Hepatitis

AIH was first described by Waldenström in 1950 as "*hepatitis sui generis,*" characterized by a long-lasting amenorrhea with polyclonal elevation of IgG, hyperproteinemia, and low serum albumin in young women. Later the autoimmune mechanisms in the pathogenesis of this chronic inflammatory liver disease was identified (Gajdusek and Mackay, 1958).

AIH is a prototypical autoimmune disease characterized by a loss of immune tolerance, robust genetic associations with human leukocyte antigen (HLA) alleles, female predominance, elevated aminotransferase levels, and presence of serum auto-antibodies (Lammert C. et al 2019). In AIH, autoreactive $CD4^+$ and $CD8^+$ T cells break self-tolerance to hepatic autoantigens, potentially as a result of environmental triggers and the inability of T_{regs} to prevent auto-reactivity of conventional T cells. Concurrently, in the absence of effective B-cell regulation, autoreactive B cells produce auto-antibodies.

AIH may present as acute or chronic hepatitis or as well established cirrhosis; in rare cases, it presents as fulminant hepatic failure. Patients experience unspecific symptoms like fatigue, upper abdominal discomfort, mild pruritus, anorexia, myalgia, arthralgia, rashes (including acne), and amenorrhea. Untreated AIH can lead to liver cirrhosis, development of hepatocellular carcinoma, and finally to death (Czaja AJ 2009, Wolf DC, 2019; Heneghan et al., 2013).

AIH is a rare disease with a prevalence of 16 to 18 affected people per 100 000 inhabitants in Europe (EASL 2015). It can affect people of all ages and sexes, though the female to male ratio is approximately four to one (Lowe and John, 2018). AIH is characterized by a large heterogeneity of clinical, laboratory, and histological manifestations and therefore difficult to diagnose. If hypergammaglobulinemia is present, AIH should always be taken into consideration (EASL 2015). A simplified AIH score (Galaski et al. 2020) has been developed to facilitate the diagnosis in patients with histological evidence of hepatitis.

There is currently no approved treatment for AIH. Patients with AIH usually respond rapidly to immunosuppressive treatment (CCS +/- non-specific immunosuppressants [NSIs]) but relapse quickly after its tapering. Most patients need to be on immunosuppressive treatment for extended periods and often for life. Side effects of long-term immunosuppressive treatment can be quite severe and include osteoporosis, muscle wasting, skin manifestations, and endocrine effects like steroid-induced diabetes. Therefore, there is an unmet medical need in patients with AIH to replace the current standard of care (SoC) with a less burdening maintenance (Mack et al. 2019; Dyson et al. 2018; Sebode et al. 2020).

2.2.2 RO7049665

RO7049665 is a novel IL-2 mutein immunocytokine. Compared to aldesleukin, RO7049665 has reduced binding affinity to IL-2 receptor (IL-2R)$\beta\gamma$ present on $CD4^+$ and $CD8^+$ effector T cells (T_{eff}) and natural killer (NK) cells, with no loss of binding affinity to IL-2Rα, a required component of IL-2R$\alpha\beta\gamma$ receptors present at the highest levels on T_{regs}. By virtue of its reduced affinity to IL-2R$\beta\gamma$ receptors and its T_{reg} selectivity, RO7049665 enhances the T_{reg}-supporting function of human IL-2 without the broad-based IL-2R$\beta\gamma$-mediated immunostimulatory effects of IL-2. RO7049665 therefore provides a novel selective immunotherapy to treat autoimmune diseases with an expected improved safety profile compared with that of aldesleukin.

In a human whole blood assay, RO7049665 exhibited greatly reduced potency to induce pro-inflammatory cytokines compared with that of aldesleukin, with 600-fold lower potency for induction of Interferon (IFN)γ, Interleukin 6 (IL-6), tumor necrosis factor (TNF)α, interleukin 1 (IL-1)β, and 5-fold lower potency for induction of interleukin 8 (IL-8). A tissue cross-reactivity study of RO7049665 showed staining patterns consistent with known IL-2R expression profiles.

Observed toxicities in both 4-week and 13-week good laboratory practice (GLP) toxicology studies in cynomolgus monkeys treated with RO7049665 were consistent with increased pharmacological activity of IL-2 and included skin findings (at the injection site and generally), increased heart rate, changes in blood leukocyte numbers (including increased eosinophils as well as microscopic findings of tissue infiltrates), and changes in lymphoid tissues. Findings were dose-dependent and had resolved or were trending to resolution following a 4-week recovery period. At all dose levels tested in both studies, there was no evidence for capillary leak syndrome (CLS), a known toxicity of high dose IL-2 therapy.

Following subcutaneous (SC) administration of RO7049665 in the 13-week GLP toxicology study, exposure to RO7049665 on Day 1 increased less than dose proportionally over the dose range of 0.2 mg/kg to 3 mg/kg. Rapid development of anti-drug antibody (ADA) was observed at a low dose (0.2 mg/kg), leading to almost complete loss of exposure and loss of pharmacodynamic (PD) response by study Day 50 in the majority of animals. The no-observed-adverse-effect level (NOAEL) dose in female animals (that retained exposure to the drug until Day 22) was 0.2 mg/kg weekly, with maximum serum concentration observed (C_{max}) and area under the curve $(AUC)_{0\text{-}168h}$ measured on Day 22 as 254 ng/mL and 8440 ng•h/mL, respectively. At higher doses ($\geq$ 1 mg/kg), a subset of the animals (approximately 50%) did not develop high ADAs and remained exposed until the end of the study but developed generalized rash. Assessment of PD markers and immune-lineage cell counts in the 13 week GLP study confirmed the induction of phosphorylated signal transducer and activator of transcription 5 (pSTAT5) and other markers of activation of T_{regs}, as well as expected changes of lymphocyte populations, including transient reduction followed by an increase of lymphocyte populations (total T cells, T_{regs}, $CD4^+$ T cells, $CD8^+$ T cells, NK cells, and B cells) and monocytes, with the increases of T_{regs} being of greater magnitude than that of other T-cell populations.

2.2.2.1 Previous Clinical Studies

Study WP39826, the first clinical trial where RO7049665 was administered to humans, is completed. The aim of this EIH study was to investigate the safety, tolerability, PK, and PD of SADs of RO7049665 in a healthy male population. A total of 56 participants were administered single doses of RO7049665 or matching placebo injected SC in the abdomen. Additionally RO7049665 is currently being evaluated in the ongoing study WP40161 with patients with UC. To date 36 patients (male and female) have been administered RO7049665 or placebo.

In Study WP39826, a total of nine doses were tested, ranging from 1.5 µg (which was the dose based on the minimum anticipated biological effect level), up to 7500 µg. Thirty-eight participants (67.9%) received one SC injection of RO7049665, and 18 (32.1%) received placebo.

Overall, RO7049665 was well tolerated. A total of 121 treatment-emergent adverse events (TEAEs) were reported across the dose range tested: 94 (77.7%) in the active treatment groups, and 27 (22.3%) in the placebo group. Across all groups, the most frequently reported TEAEs were nasopharyngitis, injection-site erythema, injection-site pruritus, headache, diarrhea, and myalgia. The majority of TEAEs were mild in intensity, with the exception of 5 events (1 event of gastroenteritis, 3 events of food poisoning, and 1 event of influenza-like illness) in 5 participants on active treatment, rated as moderate in intensity but not related to the study treatment by the Investigator of the study. There were no deaths or serious adverse events (SAE), and no withdrawals due to an adverse event (AE). There was no trend or pattern in the AEs observed with increasing doses or between active and placebo groups, with the exception of local injection-site reactions (ISRs; erythema, pruritus), observed in an increasing number of participants proportional to the dose increased. All AEs related to the injection site were mild in intensity and resolved without treatment.

There were no trends observed in vital signs, electrocardiogram (ECG) intervals, or laboratory safety results across the dose range tested.

Immunogenicity was assessed, and positive results for ADAs were observed in a total of 12 participants starting from Cohort 5 (dose of 190 µg). ADAs were of early onset (detected in first samples on Day 8 postdose), generally transient, and exhibited dose dependency with regard to higher titers and higher incidence. The presence of ADAs had no apparent impact on the safety, PK, or PD profiles. ADAs did not reveal neutralizing potential against endogenous IL-2 as assessed in an assay using recombinant human wild type IL-2, which reflects the endogenous counterpart. These analyses concluded that the ADAs were not capable of neutralizing endogenous human IL-2.

Serum RO7049665 concentration reached peak level (C_{max}) approximately 12 hours postdose and declined in an apparent biphasic manner, with a mean apparent terminal phase half-life of approximately 72 to 137 hours (see Table 4). Serum exposure levels of RO7049665 were below or close to the detection limit in the 1.5 µg and 5 µg dose groups and thereafter increased with increasing doses in a highly variable manner. Overall, no obvious deviation from dose-linearity was noted. Sufficient concentration data for reliable estimates of non-compartmental parameters in terms of both AUC and C_{max} was available as of Cohort 6 (650 µg) and above (see Table 4). Although the data showed moderate between-participant variability, no relevant departure from linearity was noted. The mean serum apparent systemic clearance of RO7049665 appeared dose-independent and ranged from 1.4 L/h to 2.2 L/h.

RO7049665 disposition occurred with a mean $T_{1/2}$ of about 5 days; thus, is expected to approach near-complete washout (C_{trough} < 10% of C_{max}) no later than 2 weeks after the last dose. Accordingly, no substantial accumulation in reaching steady state is expected in a biweekly regimen.

At the highest dose of 7500 μg RO7049665, exposure was 33% and 65% of the exposure at the NOAEL (established in female monkeys on Day 22) in terms of C_{max} and $AUC_{0\text{-}168h}$, respectively.

Table 4 Serum Pharmacokinetic Parameters of RO7049665 after Single Subcutaneous Administration

Dose (μg)	n	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{inf} (ng • h/m)	CL/F (L/h)	VZ/F (L)	$T_{1/2}$ (h)
Expressed as Geometric means (%CV)							
650	6	4.55 (49.4)	12.00 (6.00-24.00)	409 (43.1)	1.59 (43.1)	210 (28.2)	91.8 (52)
2200	6	11.0 (58.8)	12.03 (5.98-48.00)	1020 (37.7)	2.16 (37.7)	276 (17)	121 (23.2)
5000	5	46.5 (27.4)	12.00 (12.00-24.00)	2831 (26.9)	1.77 (26.9)	331 (25.6)	130 (18)
7500	6	68.7 (85.6)	12.00 (5.98-12.00	5266 (55.4)	1.42 (55.4)	281 (62.4)	137 (9.3)

AUC_{inf} = area under the serum concentration-time curve extrapolated to infinity; C_{max} = maximum serum concentration observed; CL/F = apparent clearance; ND = not determined; $T_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum concentration; Vz/F = apparent volume of distribution.

a Median (Min–Max).

PD data showed that RO7049665 expanded the T_{reg}-cell pool, thereby delivering proof of pharmacology in a healthy population. The T_{reg} expansion was dose-dependent, and reached an absolute increase of approximately 200 cells/μL at the maximum tested dose of 7500 μg, ranging from 123 cells/μL to 297 cells/μL. This represented a mean fold increase of 5.9 (2.9-7.6) from baseline. The peak was, on average, reached on Day 8, following a drop at 24 hours postdose, and T_{reg} levels were back to baseline values at Follow-up (Day 57). Overall, the estimated therapeutic range of T_{reg} was achieved with the doses of 2200 μg, 5000 μg, and 7500 μg, eliciting a mean increase of 2-fold, 4-fold, and 6-fold, respectively, as compared with baseline.

There was no expansion of NK cells in any dose group, and no significant trends observed in eosinophils. There was no obvious effect on T_{eff} at doses up to 2200 μg. A possible weak trend for increase in T_{eff} count occurred with doses of 5000 μg and 7500 μg, with mean change from baseline on Day 12 reaching up to 1.5-fold increase from baseline.

In the ongoing study WP40161, to date, multiple doses of 3.5 mg and 7.5 mg (to date, 3 cohorts) were safe and well tolerated, and induced dose-dependent T_{reg} expansions up to 5-fold (mean at the highest dose of 7.5 mg) those of baseline.

The most frequently reported AEs were injection site reactions (ISR) and eosinophilia. The majority of AEs reported were mild or moderate (Grade 1 or 2) in intensity except for

a low number of events of severe (Grade 3) intensity, including anemia, eosinophilia and hyperkalemia. No events of CLS were reported. Hypersensitivity and injection related reactions (IRR) have been reported. All events resolved without sequelae or are ongoing. There were no deaths reported to date.

Immunogenicity was assessed, and positive results for ADA were observed in approximately 50% of patients of the study. There were no results to date indicating ADAs with neutralizing potential against endogenous IL-2.

No significant abnormalities on vital signs or ECG intervals were reported to date and besides the changes on eosinophils, no significant laboratory safety results have been noted in patients with ulcerative colitis receiving 3.5 mg and 7.5 mg of RO7049665.

Detailed descriptions of the chemistry, pharmacology, PK, efficacy, and safety of RO7049665 are provided in the Investigator's Brochure RO7049665.

2.3 BENEFIT/RISK ASSESSMENT

As mentioned in Section 2.2.1, AIH is a chronic autoimmune disease of unknown cause, characterized by continuing hepatocellular inflammation and necrosis; it has a tendency to progress to cirrhosis. Some patients go on to develop signs and symptoms of chronic liver disease, while others rapidly progress to acute liver failure, as marked by coagulopathy and jaundice (Wolf DC, 2019). There is no registered treatment for AIH. SoC is CCS, possibly with the addition of NSIs such as, but not limited to, azathioprine (AZA), 6-mercaptopurine (6-MP) mycophenolate-mofetil (MMF) methotrexate, cyclosporine, or tacrolimus. While the vast majority of patients are responsive to CCSs, 80% of patients relapse when the CCS and /or immunosuppressive treatment is withdrawn (van Gerven NM et al. 2013). Untreated AIH has a high mortality rate due to the development of liver cirrhosis. Thus, most patients with AIH require lifelong CCS and/or immunosuppressant treatment and suffer from the side effects of chronic treatment, including osteoporosis (particularly worrisome, as AIH is common in young women), skin effects, depression, diabetes and metabolic syndrome, infection risk, etc.

The hallmark laboratory findings in AIH are elevated liver enzymes (notably ALT) and elevated serum Ig levels, primarily IgG. ALT and IgG are also the recognized disease activity markers, and the treatment goal is normalization of these two markers (known as "biochemical remission"). In most patients, this can be achieved quickly by induction of high-dose CCS therapy followed by the addition of NSIs. After response to induction therapy, CCS dose is reduced in a stepwise fashion. Complete withdrawal of immunosuppressive therapy is tried after approximately 2 years of stable remission (EASL, 2015). However, it is rarely successful; > 80% of patients require re-instigation of CCS treatment (van Gerven NM et al. 2013). Patients who relapse twice usually need to stay on immunosuppressive treatment for the rest of their life (EASL, 2015).

RO7049665 represents a potential novel therapy for AIH aiming at long-term, CCS-free remission.

Study BP42698 is the first study involving dosing of RO7049665 in participants with AIH. At the time of the commencement of Study BP42698, the safety data in healthy volunteers from the EIH Study WP39826 are available, as are some preliminary data from the MAD study WP40161 in participants with UC (see Section 2.2.2.1). Potential risks have been defined on the basis of clinical experience in healthy volunteers and preliminary data from patients with UC, non-clinical pharmacology and toxicology data in the relevant animal species, and theoretical risks based on expected PD effects and the safety profile of aldesleukin. The doses planned for Arm 1 (3.5 mg) and Arm 2 (7.5 mg) are being assessed in study WP40161.

The eligibility criteria, design, and procedures adopted are considered appropriate for the safe conduct of the study. Participants will be closely monitored for safety.

Identified potential risks and plans for their mitigation are as follows:

- Excessive interleukin-2 effects
- Hypersensitivity
- ADA formation
- Increased T_{regs} causing immunosuppression
- ISRs
- Heart rate and 12-lead ECG parameters

For further details, see the RO7049665 Investigator Brochure.

Safety monitoring and risk mitigation measures listed below will be implemented:

- Participants will be monitored closely throughout the study for their well-being by a phone call following the administration of each dose.
- Assessments of ADA development, their neutralizing capability and the impact on continued dosing are scheduled throughout the study.
    - Study level stopping criteria relating to hypersensitivity reactions and development of neutralizing antibodies to endogenous human IL-2 (see Section 4.1.3).
    - Signs and symptoms of autoimmune diseases will be monitored and treated according to standard of care.

- Procedure-related Risks

  The procedures performed include an optional liver biopsy at 6 months to assess the inflammation and gain insight on immune cells in the liver tissue, SC injections, and blood draws. The risks associated with liver biopsies include bleeding, pain, and injury to adjacent organs and infection. SC injections may produce a local inflammatory reaction, which can range from a slight irritation to infection or possible necrosis. The risks associated with blood draws include hematoma, and rarely injury to neurovascular structures.

- Risks Related to Concomitant Medications

  Risks of CCS and RO7049665 Adjunctive Therapy

  Long-term use of CCSs is associated with pleiotropic effects, which are well described (Ford et al. 2011). An increased susceptibility to infection is a known side effect. Addition of RO7049665 could theoretically further increase the risk of infection. Current SoC includes the addition of other immune-modulating therapeutics on a background of CCS therapy, with the goal of therapy being to discontinue CCSs, such as in this study. Participants in this study will stop other immunosuppressive treatment (if any) before entry into the study (Day –1) and taper their steroid dose during the first weeks (see the tapering schedule Section 1.3, Table 3) while starting with RO7049665.

  To avoid risks associated with immediate withdrawal of CCS, they will be tapered slowly (see the tapering schedule Section 1.3, Table 3).

- Risk related to being randomized to placebo

  Participants eligible for this trial are patients with AIH in stable remission who are ready for withdrawal of immunosuppressive treatment in the judgment of the Investigator. The chance of being randomized to placebo in this study is 1 in 3. Patients in the placebo arm would be treated very similarly to the EASL-recommended patient management—i.e., stepwise withdrawal of immunosuppressive treatment. Being monitored more frequently during the study offers the participants the benefit of early detection of a possible relapse justifying withdrawal also of combination therapy of CCS plus NSIs.

Participants will receive the randomized dose of RO7049665 or placebo every 2 weeks (Q2W) until they experience relapse or the study is closed (for trial design please refer to 4.1). Participants will be monitored for at least one hour in the clinical research unit *or at home* after receipt of the first doses administered and receive a follow-up call 8-24 hours postdose *from the site*. To ensure appropriate safety monitoring, the participants will receive the first study treatment injections at the clinical research unit. As of week 7, participants may have the study treatment administered at home by a nurse. If the study treatment is administered at the patient's home, the nurse will stay for an hour after the administration.

Furthermore, following the outbreak of coronavirus (COVID-19 or SARS CoV2, declared as a global pandemic by the World Health Organization [WHO]), the Sponsor will provide the sites with guidance on the reporting of AEs and the capturing of COVID-19 test result data. There is currently no identified impact of COVID-19 on the data of the ongoing study WP40161, or on the known benefit-risk profile of RO7049665.

Overall, the expected benefits of RO7049665 in the treatment of autoimmune conditions are greater than the expected risks. The level of risk for participants with AIH is considered acceptable as it is mitigated by careful monitoring, careful dose selection,

and study-stopping criteria (Section 4.1.2 and Section 4.1.3). More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of RO7049665 is provided in the IB.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The objectives and corresponding endpoints are provided in Table 5.

Table 5 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of RO7049665 on time to relapse following forced CCS tapering as measured by the hazard ratio between 7.5 mg RO7049665 and placebo.	• Time to relapse from randomization.
Secondary	
• To assess changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and IgG over time and by dose.	• ALT, AST, and IgG (for both Δ, absolute and relative [ULN]) over time.
• To evaluate the effect of RO7049665 on time to relapse following forced CCS tapering as measured by the hazard ratio between 3.5 mg RO7049665 and placebo.	• Time to relapse from randomization.
• To evaluate the safety and tolerability of RO7049665 in participants with AIH.	• Incidence and severity of adverse events. • Changes in vital signs, physical examination, ECG parameters, and safety laboratory parameters. • ADA emergence and neutralizing potential.

Tertiary/Exploratory	
• Assess changes in auto-antibodies.	• Titers for anti-nuclear antibodies (ANA), and/or anti-smooth muscle antibodies (SMA).
• Assess changes in patient's self-reported health-related quality of life	• Change in health-related quality of life as measured by SF-12.
• Assess changes in fatigue • Describe health utility state.	• Change in fatigue, as measured by PROMIS Fatigue SF 13a scale. • Health utility score as measured by EQ-5D-5L.
• Assess changes in inflammatory and anti-inflammatory cytokines.	• Inflammatory and anti-inflammatory cytokines.
• Assess changes in liver histology and fibrosis.	• Fibroscan®, liver fibrosis markers, liver histology.
• To assess PD biomarkers (e.g., systemic T_{reg}, T_{eff}, T_{fh}, B cells, sCD25 and in tissue as available) and correlate with efficacy parameters (modeling and simulation).	• For example: T_{reg}, T_{eff}, T_{fh} and B-cell counts and sCD25 in peripheral blood and tissue as available.
• To collect blood samples for measurement of RO7049665 serum concentrations.	• RO7049665 serum concentrations.

3.1 PRIMARY ESTIMAND

The primary question of scientific interest is "Does administration of RO7049665 to participants with confirmed AIH and in stable biochemical remission $\geq$ 2 years *(or less if according to local clinical practice)* and on stable immunosuppressive treatment ≥ *3* months *prior to randomization (and no dose increase within the previous 6 months prior to randomization)* affect the time to relapse following forced CCS tapering?" The following sections describe the components of the corresponding estimand.

For details on the study population, see Section 5.

3.1.1 Treatment

The treatment of interest is treatment with RO7049665. Each dose of RO7049665 used in this study will be analyzed separately. Use of prohibited concomitant medications and missed doses will be regarded as intercurrent events and will be handled in ways described in Section 3.1.3.

3.1.2 Endpoint

The patient-level endpoint that provides information about the question of scientific interest is the number of days from randomization to relapse. A participant will be considered to have relapsed the first time they meet the criteria given in Section 8.1 at a

post-baseline study visit, whether the visit is scheduled or unscheduled. If the relapse requires confirmation at a subsequent visit, the date of relapse will be the date of the first set of tests, if confirmed. The sensitivity analyses below will examine the effect of how missing confirmatory tests are handled and the impacts on the results of the trial.

3.1.3 Intercurrent Events

The following intercurrent events will be handled using a treatment policy strategy. That is, the primary endpoint will be defined to be the earliest of the time to relapse as described in Section 8.1 and the time at which any of the events defined below occur.

Table 6 Intercurrent Events and the Statistical Treatment

Permanent discontinuation of study medication unrelated to treatment.	Censored
Permanent discontinuation of study medication related to treatment.	Estimand event
Temporary discontinuation of study medication regardless of relationship to treatment will be discussed by the Sponsor and the Investigator to determine whether patient can stay in the study and restart treatment (see Section 7.1.1).	In case of permanent discontinuation, see rows 1 and 2.
Initiation of treatment with any systemic CCSs (not related to AIH), or any other prohibited concomitant medication listed in Section 6.5.2.	Censored
Death due to any cause.	Censored
Liver transplant.	Censored
CCS increase during tapering or reintroduction related to AIH.	Estimand event

In the primary analysis of the primary estimand, participants who experience any of these intercurrent events will have a response status as indicated in Table 6 at the time of their earliest intercurrent event. Other strategies will be adopted in sensitivity analyses (see Section 3.1.5).

Participants who neither relapse nor experience any of the intercurrent events will be regarded as censored on the date of their last known follow-up.

3.1.4 Summary Measure

The summary measure used to assess the effect of RO7049665 will be the hazard ratio for time to relapse between the relevant RO7049665 group and the SoC group, as

calculated by a Cox proportional hazards model with terms for treatment arm, sex, and prednisolone-equivalent CCS dose at baseline. If inclusion of any model term leads to model instability, then the terms included in the model may be modified.

3.1.5 Sensitivity Analyses

The most likely cause of “missing” confirmation of relapse is the absence of a confirmatory laboratory test results. Therefore, the first sensitivity analysis will define relapse to have occurred on the date of the tests that triggered the need for a subsequent confirmation, regardless of the result of that confirmation. The status of participants whose laboratory test results indicate definitive relapse without the need for confirmation will be unchanged. Moreover, if exactly one of the values for ALT or IgG is missing at a given visit, this analysis will assume that the missing test meets the criterion for retest, and therefore that the participant will have relapsed at that visit.

Additional sensitivity analyses will regard all intercurrent events listed above as relapses rather than as censorings and regard all intercurrent events listed above as censorings rather than as events.

The fourth and final sensitivity analysis will use multiple imputation to replace any missing laboratory test result with values selected at random from other participants in the study, matched for sex and prednisolone-equivalent CCS dose. Further details of the methodology used will be documented in the study electronic Trial Master File (eTMF).

4. STUDY DESIGN

4.1 OVERALL DESIGN

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

Study BP42698 is a 3-parallel arm (two dose levels of RO7049665 versus placebo), randomized, placebo-controlled, double-blind, event-driven, phase 2 study to assess efficacy of RO7049665 over placebo in patients with AIH in stable biochemical remission.

Two dose levels will be assessed, 3.5 mg RO7049665 (SC. Q2W) and 7.5 mg RO7049665 (SC, Q2W) and matching placebo.

This is an event-driven study, which means that participants stay in the study and on treatment until the participant experiences an event, the necessary number of events is reached, the participant stops for other reasons or withdraws consent, or the study ends.

All participants in the study will have been diagnosed with AIH previously and will have responded well to treatment with CCSs $\pm$ NSIs. It will be the first attempt to taper out CCS completely $within\ the\ last\ 3\ years$ (see inclusion criteria Section 5.1). At study entry, the disease status of the participants should allow for a stepwise removal of all

immunosuppressive treatment according to *local guidelines or practice. If no local guidelines exist, EASL* guidelines *should be applied* (EASL 2015: *"Treatment should be continued for at least three years and for at least 24 months after complete normalisation of serum transaminases and IgG levels (biochemical remission). […] In patients with continued histological disease activity (HAI >3), immunosuppressive treatment should not be discontinued, as relapse is almost certain to occur. […] A trial of treatment withdrawal should be undertaken by stepwise reduction of immunosuppressive agents, and patients monitored closely."*). Participants will start with study treatment on Day 1 and start tapering CCS use from Day 8 onwards (see tapering schedule, Section 1.3, Table 3) to allow for complete CCS withdrawal within a maximum of 12 weeks, depending on the starting dose. Last dose of NSIs, if any, will be taken on Day −1.

Randomization in a 1:1:1 fashion will occur after patient eligibility is confirmed and before the first dose of study treatment is administered. Randomization will be stratified by equivalent prednisolone dose (≤ 7.5 mg daily versus > 7.5 mg daily or dual therapy [CCS any dose, plus NSI]).

The study is powered to detect a statistically significant difference between one treatment arm and placebo with a sample size of total 84 participants or 28 participants per arm after a total of 45 events are observed (see Section 9.2).

Two interim analyses are planned. The first is planned for futility once 25% of events (i.e., 12 events) are observed. The second interim analysis for efficacy and futility is planned once 50% of events (i.e., 23 events) are observed.

4.1.1 Length of the Study

The study is anticipated to run for approximately 25 months (i.e., 19 months' recruitment and 6 months' follow-up), until the necessary number of events is observed. If recruitment and/or the event rate is faster or slower, then the duration of the study could be longer or shorter. It is not possible to estimate the duration of the study for an individual patient as this is an event-driven study; the occurrence of an event cannot be reliably estimated for an individual patient.

Participants will be monitored for at least one hour in the clinical research unit *or at home* after receipt of the first doses administered and receive a follow-up call 8-24 hours postdose *from the site. If the study treatment is administered at the patient's home, the nurse will stay for an hour after the administration.* To ensure appropriate safety monitoring, the participants will receive the first study treatment injections at the clinical research unit.

Study periods are divided as follows:

- Screening: Up to 28 days.
- Treatment period: Day 1 to relapse or final number of events is observed.

- Safety follow-up: 4 weeks after last administration of study treatment.
- End of study visit: Follow-up visit 28 days after last dose of study treatment. In the event that a participant is enrolled into an open-label extension (OLE) study, the follow-up visit will not apply and the last visit within the treatment period will be considered as the end of study visit.

4.1.2 Stopping-rules Criteria

The study will stop if either of the interim analyses recommends stopping for success. If any interim recommends stopping for futility, the Sponsor's project team will make the actual decision whether to stop or continue the study. This process is mandated by the binding nature of the success boundary and the non-binding nature of the futility boundary defined in Section 9.2. Reasons for continuing the study after a futility recommendation could include, but are not limited to, an efficacy effect that is smaller than assumed in the sample size calculation but still of clinical relevance, or evidence of potential benefit not considered in the primary efficacy analysis.

The dosing in the study will be suspended if any of the conditions below occur in participants treated with RO7049665:

- Clinically manifest secondary (reactive) hypereosinophilia (HER) in $>$ 3 participants.
- Grade 3 hypersensitivity reaction (as per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v. 5.0) in $>$ 1 participant considered related to RO7049665.
- Local ISRs leading to treatment discontinuation in $>$ 5 participants, considered related to RO7049665.
- ADA with neutralizing potential against endogenous IL-2 in $\geq$ 1 participant.
- Other findings (e.g., presence of clinically manifest safety findings in treatment arms typically associated with therapeutic IL-2 doses as per aldesleukin label, other AEs or lab abnormalities) that, at the joint discretion of the Sponsor's lead clinical scientist and safety science leader, the Sponsor's IMC and the Investigators, indicate that dosing should be stopped.

4.1.3 Individual Stopping Criteria

Dosing will be stopped in a given individual participant if the following circumstances occur:

- Grade 3 or greater severe AE or SAE considered related to study treatment, including but not limited to:
    - Hypersensitivity reaction which is considered related to study treatment and believed to pose an unacceptable risk if the dose is repeated.
    - CLS including severe, clinically significant respiratory distress syndrome, edema, effusions, or decrease in blood pressure (BP).

- Grade 3 or higher injection-related reaction (i.e., cytokine release syndrome and severe, acute influenza-like syndrome).
- Disease relapse signifying study treatment failure (See Section 7).
- Other findings that, at the discretion of the Investigator, indicate that dosing should be stopped.

Study closure information is provided in Section 4, Appendix 1.

4.1.4 Communication Strategy

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.

4.1.5 Administrative Structure

In order to keep the study personnel blinded during interim analyses, an Internal Monitoring Committee (IMC) will be established.

The unblinded IMC will review the results of each interim analysis and recommend to the study team whether the study should stop, continue, or be modified.

The IMC is a dedicated group of selected Sponsor representatives, who will be independent from the project and review the safety and efficacy data of the study, as well as the interim analyses. The roles, responsibilities, membership, scope of activities, time of meetings, and communication plan for the IMC will be documented in an appropriate charter.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

4.2.1 Rationale for Study Population

AIH is a rare and chronic disease without approved treatment. SoC consists of CCSs +/- NSIs. Untreated, the disease leads to death within 10 years of diagnosis mainly due to liver cirrhosis. Treatment with SoC enables patients with AIH to lead a nearly normal life with a normal life expectancy (Heneghan et al 2013).

Nevertheless, lifelong CCS/immunosuppressant treatment poses considerable burden on patients with AIH, sometimes with severe side effects like osteoporosis, muscle wasting, skin manifestations, and endocrine effects like steroid-induced diabetes (Heneghan et al 2013).

Treatment guidelines (EASL 2015) therefore recommend tapering patients off CCS treatment and (if possible) other immunosuppressive treatment, in order to relieve treatment-related side effects once the patients have reached biochemical remission and the liver shows no sign of inflammation. Withdrawal of SoC unfortunately leads more often than not to disease relapse (i.e., > 80% as reported by van Gerven et al. 2013). Relapsing patients will usually respond again to CCS treatment, require (in most cases) a higher dose, and have a longer duration to response (van Gerven et al. 2013). After the second relapse, it is recommended to keep patients on lifelong immunosuppressive treatment.

This study is conducted in patients with AIH currently on immunosuppressive treatment prior to their first attempt to taper CCS/NSIs completely $within\ the\ last\ 3\ years$ and who have an unmet medical need for a treatment option beyond CCSs/NSIs.

4.2.2 Rationale for Control Arm

RO7049665 will be compared with placebo, with participants randomized in a 1:1:1 ratio to receive one of two doses of RO7049665 or placebo. We will employ a blinded placebo arm to derive a preliminary assessment of the efficacy of the different doses of RO7049665 in participants with AIH in stable remission and for establishing drug-relatedness of AEs. A placebo arm will similarly inform the analysis of key biomarkers. As we are studying participants with a well-controlled but chronic disease, it will be critical to distinguish disease-related complications from intervention associated safety signals, as well as study treatment-related changes in leukocyte and cytokine biomarkers. In order to get a fair understanding of the efficacy of RO7049665 in AIH, it is important to establish the effect over placebo (i.e., to rule out a placebo effect).

Current $EASL$ treatment guidelines $(EASL\ 2015)$ propose withdrawal of CCS treatment once stable biochemical remission of more than two years without signs of inflammation (HAI ≤ 3) has been achieved in order to remove the risk of CCS-related AEs. There is no approved treatment for patients with AIH following withdrawal of CCSs, and RO7049665 is an investigational drug with no established benefit. Therefore, placebo is an appropriate control treatment. Placebo injections are used purely to preserve the blind.

4.2.3 Rationale for Biomarker Assessments

Key objectives of the mandatory biomarker strategy are to:

- confirm and further investigate the expected effect of drug on target cells (expansion of T_{regs} in number)
- identify a safe dose at which the target PD effect can be observed
- confirm the magnitude and kinetics of this effect after multiple dosing and in the particular study population
- correlate a PD effect with clinical outcome

- characterize the expected target PD effects
- monitor biomarkers for unwanted events such as expansion of effector cells (T_{eff} cells, NK cells, and eosinophils)

These assessments are expected to add valuable information towards an estimate of the therapeutic window, patient selection, and prediction of clinical response.

Additional objectives of the mandatory biomarker assessments are: (1) to investigate if systemic PD effects can be measured as surrogate markers for predicting relapse; (2) to identify which of the candidate systemic biomarkers shows highest correlation to tissue effects (as available); (3) to determine if any systemic or tissue biomarkers can predict efficacy.

A fresh or historical liver biopsy is required before randomization. Provided no worsening of disease has occurred, a historical biopsy taken no more than 12 months prior to randomization is acceptable. A formalin-fixed paraffin embedded (FFPE) block has to be sent to the Sponsor if available. It will be used to characterize immune cell infiltration and histologic appearance. Additional measurements which may be performed on liver biopsy-derived material are whole (spatial) transcriptome or targeted gene expression analyses. An optional liver biopsy at 6 months of treatment will provide the opportunity to assess changes in tissue markers from baseline. The objective of these measurements is to confirm the translation of changes in T cell subsets from blood to tissue and to identify further mechanistic markers such as changes in inflammatory signatures or markers of tissue healing.

Blood samples will be collected to quantify relative and absolute WBC counts (including B cells, T cells, NK cells, and eosinophils). Furthermore, markers for quantification and characterization of T_{regs} and T_{eff} subsets including, but not limited to CD3, CD4, CD8, CD127, CD25, and FoxP3 will be determined.

Serum and plasma samples will be collected to measure cytokines or other soluble biomarkers mechanistically linked to RO7049665's mode of action or the disease. In addition, exploratory safety biomarkers may be measured in an ad-hoc fashion, (e.g., in participants experiencing symptoms associated with injection-related reactions).

Clinical blood genotyping data may be used to explore whether genotype may correlate with efficacy, influence the magnitude of PD effects, or impact the safety of RO7049665.

Exploratory disease biomarkers in serum samples will be tested for their ability to stratify participants and to evaluate their potential for non-invasive response to treatment monitoring.

Additional PD biomarkers and methods to obtain further confidence on the mechanism of action of RO7049665 in participants may be tested. Such assessments may include, but are not limited to, determining specific methylation signatures in blood or liver

biopsies to quantify T_{reg} or T_{eff} subsets and possibly the functionality of such. The purpose of this assessment is to explore alternative T cell subset quantification methods and to understand their potential usefulness for replacing established methods with limited throughput and logistical challenges in later stages of clinical development.

4.3 JUSTIFICATION FOR DOSE

The doses are based on data from the EIH study (WP39826) in healthy volunteers and the ongoing MAD WP40161 study in participants with UC. The therapeutic range of RO7049665 is unknown; however, the estimated therapeutic range of T_{reg} was achieved with the doses of 2200 µg, 5000 µg, and 7500 µg, eliciting a mean increase of 2-, 4-, and 6-fold, respectively, as compared with baseline without stimulating expansion of effector T cells (T_{eff} ; see the RO7049665 Investigator Brochure). In AIH, the intrahepatic T_{reg}/T_{eff} ratio appears to be a determinant of disease progression, because patients reaching biochemical remission have higher intrahepatic T_{reg}/CD8 and T_{reg}/B cell ratios, whereas this ratio remains constant in the liver of untreated patients with AIH (Taubert et al. 2014). Also, the disproportional decrease of intrahepatic T_{reg} during SoC immunosuppressive therapy might explain the high relapse rates after discontinuation of immunosuppression. Thus, intrahepatic immunoregulation through T_{reg} expansion may be better suited for long-term control of AIH.

Data from WP39826 demonstrated 4-fold expansion of T_{reg} cells in healthy volunteers after a single 5-mg dose of RO7049665 (mean peak T_{reg} expansion to 155.2 cells/µL) and a mean 5.8-fold expansion of T_{reg} cells after a single 7.5-mg dose (with a mean peak of approximately 200 cells/µL [range 123 – 297]). The 2.2 mg single dose in the SAD study elicited a mean 2-fold increase in T_{reg} cells; therefore, the lower dose of 3.5 mg in Study BP42698 is expected to produce a measurable PD effect (specifically, the expansion of T_{reg} cells), but the overall expansion is projected to be at the lower end of the hypothesized therapeutic target.

Single doses at these dose levels were safe and well tolerated in healthy volunteers with no SAEs and no DLAEs, with limited expansion of T_{eff} and eosinophils and no observed effect on NK cells. The maximum T_{reg} expansion was observed at Day 8 following dosing. Similar results could be preliminarily confirmed in the MAD study WP40161.

Further details are provided in the RO7049665 Investigator's Brochure.

4.4 END OF STUDY DEFINITION

The goal of the study is achieved when any of the interim analyses results in a decision to stop the study, when the required number of events is reached, or if any of the stopping rules apply. At this point, the study will be unblinded.

An individual participant has completed the study if he/she has completed all scheduled procedures as shown in the SoA (see Section 1.3).

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur approximately 4 weeks after study closure when the final follow-up visit is conducted. Study closure can occur either after:

- The first interim analysis for futility, or
- The second interim analysis for futility or efficacy, or
- 45 events are observed, or
- Early study termination.

The Sponsor may set up an OLE study if RO7049665 development continues. Participants not having had a relapse at study closure may have the option to enter the OLE study. For participants entering a possibly available OLE study, the last regular visit will count as last observation in Study BP42698. Participants not entering the OLE study will have a last observation 4 weeks after the last dose of RO7049665 or placebo.

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants of this study are patients with biopsy-proven diagnosis of AIH, with no evidence of cirrhosis with significant impairment of liver function stage (e.g., Child Pugh B or C). Patients must be in biochemical remission for at least 2 years *(or less if according to the local practice)*, be on stable treatment (CCSs ± NSIs) for at least *3* months prior to *randomization (and who have not had a dose increase 6 months prior to randomization)*, and show no signs of inflammation (HAI ≤3) on a liver biopsy taken no more than 12 months prior to randomization.

This study will recruit approximately 84 female and male participants diagnosed with AIH who are between 18 and 75 years of age, inclusive, and satisfy all of the inclusion and exclusion criteria.

Prospective approval of protocol deviations, 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. Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonisation (ICH) and local regulations.

Age

2. Between 18 to 75 years of age, inclusive, at the time of signing the informed consent.

Type of Participants and Disease Characteristics

3. Patients with a definite diagnosis of AIH (type 1, 2 and 3) as per simplified or revised original diagnostic criteria (including response to CCSs) (Hennes et al 2008).
4. Patients who have been in biochemical remission (complete normalization of serum transaminases and IgG levels *[if IgG is measured, as according to local practice]*) for ≥ 2 years *(or less if according to the local practice)* prior to randomization. *At least two measurements of IgG levels within normal range at least two weeks apart need to be available before randomization.*
5. Patients who have been on stable treatment (CCSs ± NSIs) for at least *3* months prior to randomization *and who have not had a dose increase in the previous 6 months prior to randomization.*
6. No signs of liver inflammation (HAI ≤ 3) on a liver biopsy taken no more than 12 months prior to randomization.
7. Patients with AIH who have previously not attempted *(or not attempted in the last 3 years, if this is the local practice)* to taper CCS to 0 mg/day.

Weight

8. Body mass index (BMI) within the range of 18-35 kg/m^2 (inclusive).

Sex and Contraception/Barrier Requirements

9. Male and female participants are eligible.

   The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. Therefore, the reliability of sexual abstinence for female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

   A female participant is only eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

- Women of non-childbearing potential (WONCBP),

  OR

- Women of childbearing potential (WOCBP), who:

  Agree to remain abstinent (refrain from heterosexual intercourse) or use at least one acceptable contraceptive method during the treatment period and for at least 28 days after the final dose of study treatment.

The following are acceptable contraceptive methods: bilateral tubal occlusion/ ligation, male sexual partner who is sterilized, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices, male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide (see Appendix 5).

5.2 EXCLUSION CRITERIA

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

Medical Conditions

1. Patients with cirrhosis (F4 fibrosis by Fibroscan®) with significant impairment of liver function (Child Pugh category B or C).
2. Any other autoimmune disease (including overlap syndrome) requiring immunomodulating treatment.
3. History of infection with hepatitis B (HBsAg positive and/or anti-HBc positive; HBV vaccinated patients are eligible), human immunodeficiency virus (HIV; positive HIV antibody test), active hepatitis C virus (HCV) infection (detectable HCV RNA), detection of replicating CMV or Epstein-Barr virus (EBV).
4. Active infections requiring systemic therapy with antibiotic, antiviral, or antifungal treatment or febrile illness within 7 days before Day −1.
5. History of primary or acquired immunodeficiency.
6. Female patients: Pregnant or lactating.
7. Symptomatic herpes zoster within 3 months prior to screening.
8. History of active or latent tuberculosis or a positive Quantiferon® Gold test.
9. History of clinically significant severe drug allergies, multiple drug allergies, allergy to any constituent of the product, or intolerance to topical steroids.
10. Lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years and in situ carcinoma of the cervix that was completely removed surgically. Breast cancer within the past 10 years.
11. Significant uncontrolled comorbidity, such as cardiac (e.g., moderate to severe heart failure New York Heart Association [NYHA] Class III/IV), pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders (excluding UC).
12. Any condition or disease detected during the medical interview/physical examination that would render the patient unsuitable for the study, place the patient at undue risk, or interfere with the ability of the patient to complete the study in the opinion of the Investigator.

Prior/Concomitant Therapy

13. CCSs of $<$ 5 mg/day (prednisolone-equivalent dose), or < 2.5 mg CCSs (prednisolone-equivalent dose) plus immune suppressant, or < 3 mg/day budesonide with or without immune suppressant.
14. CCSs $>$ 20 mg/day (prednisolone-equivalent dose) or > 9 mg/day budesonide.
15. NSI daily dose higher than recommended standard of care therapy.
16. T or B cell-depleting therapy (e.g., rituximab) within the last 12 months or T- or B-cell number below normal due to depleting therapy.

Prior/Concurrent Clinical Study Experience

17. Leukocyte apheresis within 12 weeks of screening.
18. Donation of blood or blood products in excess of 500 mL within 3 months prior to screening.
19. Exposure to any investigational treatment within 6 months prior to Day 1.

Laboratory Abnormalities

20. Abnormal hematologic values:
    - Anemia (hemoglobin $<$ 9 g/dL)
    - Leukocytosis (white blood cells $\geq 2 \times$ upper limit of normal [ULN])
    - Thrombocytopenia (platelet count $<$ 100,000/μL)
    - Thrombocytosis (platelet count $\geq 2 \times$ ULN)
    - Eosinophilia (eosinophil count $\geq 2 \times$ ULN)
21. Abnormal hepatic enzyme or hepatic function values:
    - ALT, AST, or alkaline phosphatase, above normal range
    - Total bilirubin $\geq 2 \times$ ULN
    - International normalized ratio (INR) $\geq$ 1.7
    - Albumin $<$ 3 g/dL
22. Abnormal biochemistry values:
    - IgG above normal range

Other Exclusions

23. History of regular alcohol consumption within 2 months of screening defined as:

    An average weekly intake of $>$ 14 drinks for men or $>$ 7 drinks for women. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine, or 1.5 ounces (45 mL) of 80 proof distilled spirits (equivalent to 40 vol%).

24. Any suspicion or history of illicit drug use.

25. Patients under judicial supervision, guardianship, or curatorship.

5.3 LIFESTYLE CONSIDERATIONS

This section is not applicable for this study.

5.4 SCREEN FAILURES

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

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) may be re-screened up to three times if it is thought that the reason for failure is transient in nature.

Re-screened participants should be assigned the same participant number as for the initial screening.

For re-screened participants, the following specific criteria must be met:

- Results of a liver biopsy taken within 12 months of randomization must be available (see criteria for biopsy under Section 4.2.3).
- Testing for HBV, HIV, HCV, CMV, and EBV and latent tuberculosis infection need not be repeated if they have been already done within 6 months and their results were negative.
- WOCBP must repeat pregnancy testing.
- Screening laboratory evaluations beyond those itemized above must be completed within 28 days of the first dosing.

6. TREATMENTS

Study intervention is defined as any investigational product (including placebo) or marketed product intended to be administered to a study participant according to the study protocol.

The investigational medicinal products (IMPs) for this study are RO7049665 or matching placebo. All IMPs required for completion of this study will be provided by the Sponsor. The first three doses of study treatment will be administered by the investigational staff (i.e., Investigator or study nurse) at the study center under supervision of the Investigator. Administration of study treatment should be done in the abdomen. Once the safe administration of study treatment is confirmed, it is at the discretion of the

Investigator whether to allow administration of study treatment at the participant's home by a home nurse.

Corticosteroids are considered non-investigational medicinal products (NIMPs).

Cases of overdose and medication error, along with any associated AEs, have to be reported as described in Section 5.2, Appendix 2.

6.1 TREATMENTS ADMINISTERED

The treatments administered are summarized in Table 7. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

Please see the IB(s) and pharmacy manual for more details.

Table 7 Summary of Treatments Administered

Study Treatment Name:	RO7049665	Placebo
IMP and NIMP:	IMP	IMP
Dosage Formulation:	Solution for injection	Solution for injection
Unit Dose Strength:	5.0 mg/mL	N/A
Dose:	3.5 mg or 7.5 mg	N/A
Route of Administration:	SC injection	SC injection
Dosing Instructions:	RO7049665 must be prepared for dosing under appropriate aseptic conditions and should be used immediately. The solution for injection must be filtered prior to use.	Placebo must be prepared for dosing under appropriate aseptic conditions and should be used immediately. The solution for injection must be filtered prior to use.
Packaging and Labeling:	RO7049665 and placebo will be provided in 2 mL colorless glass vials. Each vial will be labeled as required per country requirement.	
Storage Conditions:	For RO7049665 and placebo, if not used immediately, the total storage time of the dose solution prior to administration should not exceed 24 hours to limit the risk of microbial growth in case of accidental contamination. The recommended storage condition for the dose solution is 2°C to 8°C, protect from light, but dose solutions may be stored at room temperature for up to a maximum of 4 hours.	
Manufacturer:	F. Hoffmann-La Roche, Ltd.	F. Hoffmann-La Roche, Ltd.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study treatment packaging will be overseen by the Sponsor's clinical study 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 the Sponsor's standard and local regulations.

The study site should follow all instructions included with each shipment of IMP. The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced. The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs 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 staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

The study site (i.e., Investigator or other authorized personnel [e.g., pharmacist or home nurse]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol. 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 Interactive Voice/Web Response System (IxRS) 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 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 staff.

The Investigator 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 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. Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and RO7049665 Investigator's Brochure for information on IMP formulation, IMP handling, including preparation and storage, and accountability.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

Randomization will occur once all eligibility criteria have been satisfied, and time to event will be measured in days from the date of randomization. The randomization will be stratified as described in Section 4.1.

All participants will be centrally assigned to randomized study treatment using an IxRS. Before the study is initiated, the telephone number and call-in directions for the IxRS and/or the login information and directions for the IxRS will be provided to each site.

The randomization numbers will be generated by the Sponsor or its designee. The randomization list will be made available to the individual responsible for PK/PD sample bioanalysis, and to statisticians or programmers at Roche. PK/PD data can be received and cleaned on an ongoing basis. The data will be handled and cleaned in a restricted area which is not accessible by any blinded study management team member.

Study treatment will be administered at the study visits indicated in the SoA (Section 1.3).

6.3.2 Blinding

Interim analyses will be conducted by a group independent of the study team and decisions flowing from the results of the interim analyses will be communicated in a blinded fashion.

PK/PD data can be received and cleaned on an ongoing basis. The data will be handled and cleaned in a restricted area which is not accessible by any blinded study management team member.

If unblinding is necessary for participant management (in the case of an SAE), the Investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the Investigator wishes to know the identity of the study treatment for any other reason, he/she should contact the Medical Monitor directly. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a SAE).

The randomization schedule will not be made available to any member of the core study team. The randomization schedule may be made available to members of the extended study team on the basis of operational need. Reasons for providing access to the randomization list include, but is not limited to, support for the functions of the IMC and PK. The names and responsibilities of all those to whom the randomization schedule is released will be documented in the eTMF along with the date of release. As per Health Authority reporting requirements, the Sponsor will break the treatment code for all unexpected SAEs (see Section 8.3.4) that are considered by the Investigator to be related to study treatment.

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

In case participants experience a relapse of their disease (see Table 8, Section 8.1) treatment, mainly high dose CCS and/or other NSIs, may be provided by the study site.

Participants who experience an AE will be followed up for safety (see Section 8.3.1).

6.5.1 Permitted Therapy

Any medication (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant from 30 days prior to 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 same information must be recorded in the eCRF for the following concomitant medications taken by a participant during the indicated period prior to screening until the follow-up visit:

- CCSs and NSIs (e.g., AZA, 6-MP, MMF) used 12 months prior to randomization.

- Pre-medication for the management injection-related reactions (e.g., anti-histamines).
- Ursodeoxycholic acid (UDCA).

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

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

- Participants who use the following therapies prior to screening and are on a stable regimen should continue their use:
  - Oral contraceptives,
  - Hormone-replacement therapy,
  - UDCA,
  - Maintenance therapy for concomitant diseases.
- Participants will taper their CCS therapy for AIH during the first weeks of the study according to the SoA table (see Section 1.3, Table 3).

6.5.2 Prohibited Therapy

As a general rule, no concomitant medication to treat the underlying disease other than CCSs during tapering will be permitted.

Use of the following therapies will be prohibited during the study:

- CCS after tapering has been completed, except topical steroids.
- Any other immune system targeted biological therapy (including but not limited to JAK inhibitors).

6.6 DOSE MODIFICATION

No dosage modification of RO7049665 is permitted for any participant in the study. Study treatment may be temporarily halted and restarted, as described in Sections 7.1.1.

6.7 TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not commit to provide study treatment or other study interventions to participants after conclusion of the study or any earlier participant withdrawal. The Sponsor will evaluate the appropriateness of continuing to provide study treatment to participants after evaluating the primary efficacy outcome measure and safety data gathered in the study; these analyses may be conducted prior to completion of the study. If these data are medically significant, the Sponsor may decide to open an OLE study to participants. This OLE study might continue until study treatment is

commercially available to the participating participants in their countries, or until the Sponsor ceases producing or studying the study treatment.

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

An excessive rate of withdrawals (either participants discontinuing study treatment or 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

For data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed see the SoA (Section 1.3).

Reasons for discontinuation of study treatment (or withdrawal from the study) may include, but are not limited to, the following:

- Participant withdrawal of consent at any time.
- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study.
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant.
- Pregnancy.
- Disease relapse (See Section 8.1).
- Any event that meets stopping criteria defined in Section 4.1.3.

Every effort should be made to obtain information on participants who withdraw from the study but have not withdrawn consent. Participants who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 8.11.3) and may undergo follow-up assessments (see Section 8.11.4), unless the participant withdrew consent. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

7.1.1 Temporary Interruption

Before permanently discontinuing study treatment (regardless of whether initiated by the participant, the Investigator or Sponsor), an interruption should be considered. Participants who have had study treatment temporarily interrupted should be considered

to restart as soon as medically justified in the opinion of the Investigator after discussion with the Sponsor. If more than one study treatment administration throughout the study is omitted, restarting administration needs to be discussed and agreed with the Sponsor.

If RO7049665 administration is delayed by more than 7 days from the schedule administration date, the dose will then be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose of RO7049665 will not be made up.

A dosing delay of ± 2 days (e.g., due to holidays or bad weather conditions) after the fourth dosing will not be counted as a protocol violation.

When study treatment is paused, assessments will continue as per SoA, if possible (see Section 1.3).

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. A participant's withdrawal from this study does not, by itself, constitute withdrawal of samples donated to the Research Biosample Repository (RBR).

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

For data to be collected at the time of study discontinuation and at safety and follow-up visits, and for any further evaluations that need to be completed see SoA (Section 1.3).

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 timepoints 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 that the procedure met the protocol-specified criteria and was performed within the time-frame defined in the SoA (Section 1.3).

Samples for laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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

8.1 EFFICACY ASSESSMENTS

The primary efficacy endpoint of this study is time from randomization to relapse. Relapse is defined in Table 8. ALT and IgG will be assessed centrally according to the SoA (see Section 1.3). If a value exceeds the defined threshold, the site will be notified immediately, and a confirmatory sample will be taken no less than 7 days after the sample showing exceeding the threshold the first time. If the values returned to below the threshold in the repeat measurement, the participant can continue in the study. If the values still exceed the threshold, the participant can be either re-tested (as described in Table 8) or will be counted as having a relapse and leave the study, depending on the test results. SoC should be started as soon as relapse is confirmed.

If CCSs are increased during tapering or re-introduced because of AIH flare as per Investigator assessment (e.g., ALT > 1 and < 2 for extended period or biopsy finding), the incidence will be counted as an event, and the respective participant should stop study treatment.

Changes in ALT, AST, and IgG will be assessed according to the SoA (Section 1.3).

Table 8 Decision Tree for ALT or IgG Increase

ALT ≥ 2 × ULN < 5 × ULN	Confirm +7 days	– If < 2 × ULN ➔ return to normal schedule – If ≥ 2 × ULN and < 3 × ULN ➔ retest + 7 days ➔ if not < 2 x ULN = relapse: end of study – If ≥ 3 × ULN ➔ relapse: end of study
ALT ≥ 5 × ULN	Relapse: end of study	
IgG > 1 × ULN < 1.5×ULN	Confirm +14 days	– If ≤ 1 × ULN ➔ return to normal schedule – If > 1 × ULN and < 1.5 × ULN ➔ retest + 14 days; if > 1 × ULN ➔ relapse: end of study – If ≥ 1.5 × ULN ➔ relapse; end of study
IgG ≥ 1.5 × ULN	Relapse: end of study	

Study treatment continues as per SoA (see Section 1.3) until relapse criteria are met.

8.1.1 Clinical Outcome Assessments

8.1.1.1 Efficacy Assessments Completed by Participant or Clinician at Site Visits

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Clinical outcome assessments (COAs) will be completed during site visits as per the SoA (see Section 1.3), using electronic patient reported outcomes (PROs). A description of each and its associated endpoint is described below.

EQ-5D Questionnaire

The EuroQol 5-Dimension Questionnaire 5-level version (EQ-5D-5L; see Appendix 6) is a self-reported health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (EuroQol Group 1990; Brooks 1996; Herdman et al 2011; Janssen et al 2013). There are two components to the EuroQol EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. Published weighing systems allow for creation of a single summary score. Overall, scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D-5L will be utilized in this study for economic modeling.

SF-12v2

The SF-12v2 (see Appendix 6) will be used to assess patient's health-related quality of life (QoL) (Ware et al. 1996).

The 12-item questionnaire consists of **eight** domains:

- Physical functioning (2 items)
- Role-physical (2 items)
- Bodily pain (1 item)
- General health (1 item)
- Vitality (1 item)
- Social functioning (1 item)
- Role-emotional (2 items)
- Mental health (2 items)

The SF-12v2 has a recall specification of 4 weeks, and items are assessed on 3- to 5-point Likert scales. A higher score indicates better health. The SF-12v2 health survey will be used in this study to assess health-related QoL and for economic modeling.

PROMIS Fatigue – Short Form 13a (FACIT-Fatigue)

The FACIT-Fatigue is a 13-item scale developed as a measure of fatigue with a recall period of the preceding 7 days.

Items are assessed on a 5-point Likert scale, with responses ranging from 1 "not at all" to 5 "very much." The total raw score is the sum of the values of each scored question and ranges from 13 to 65. Scores will also be transformed to a PROMIS T-score that has been calibrated so that a score of 50 is comparable to the "average" fatigue in the general population and a standard deviation of 10. The T-scores range from 30.3 to 83.5 with a higher score being associated with worse fatigue (scoring manual; see Appendix 6).

During clinic visits, COA instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

8.2 SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AEs of special interest (NSAESI); measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs; 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, neurological, and musculoskeletal systems; in addition to head; eyes; ears; nose; throat; neck; and lymph node systems. Height and weight will also be measured and recorded. Further examination of other body systems may be performed at the Investigator’s discretion.

An abbreviated physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological, and neurological systems; and measurement of body weight.

A complete or abbreviated physical examination will be performed at the timepoints specified in the SoA (Section 1.3) by trained medical personnel at the study center. Attention should be paid to signs and symptoms suggestive of type 3 hypersensitivity reactions.

The BMI will be calculated. Height will be recorded at screening only. Body weight will be recorded at screening and at all subsequent physical examinations and as clinically indicated.

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

Changes from baseline abnormalities should be recorded in participant's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

8.2.2 Vital Signs

BP, pulse rate, body temperature (*forehead,* tympanic or oral) and respiratory rate will be assessed at the timepoints specified in the SoA (Section 1.3).

BP 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 same arm should be used for all BP measurements.

BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Three readings of BP and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

Single measurements of the other vital signs will be taken before blood collection for laboratory tests but after ECG collection when scheduled at the same timepoint.

The timings of assessments may be amended or the number of assessments increased during study conduct on the basis of emerging data in order to allow for optimal characterization of the effect profile.

8.2.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine. Measurements of PR, QRS complex (QRS), QT, and QTc intervals may be performed by the instrument or calculated using an external tool.

At each timepoint at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession but no more than 5 minutes apart. The full set of triplicates should be completed in less than 10 minutes.

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 as 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. QTcF (Fridericia's correction) and RR will be calculated and recorded on the eCRF. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

8.2.4 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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- 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 CRF/Clinical Trial Adverse Event/Special Situations Form.

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 laboratory results at screening is considered uncertain, screening laboratory 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.

Samples collected before dosing or from participants on placebo are to be taken as a precautionary measure and may not be analyzed in the first instance.

8.2.5 Safety Biomarker Assessments

Quantitative changes in T_{reg}, T_{eff}, NK cells, and eosinophils will be evaluated as exploratory safety biomarkers. Cytokines, including but not limited to, IL-6, IL-8, TNF-α, or IL-1β may be measured as exploratory safety biomarkers ad hoc in participants experiencing symptoms associated with IRRs. These assessments are described in Section 8.7.

Total IgE, tryptase, safety cytokines, and further exploratory safety biomarkers may be tested in case of participants experiencing signs and symptoms associated with IRRs (IRR samples; see Section 1.3). This includes hypersensitivity reactions.

8.2.6 Local Pain and Skin Reactivity Assessments

Local pain and ISRs (e.g., burning, bleeding, itching, bruising, redness, hive formation, or other) may be assessed at any time in the study.

Participants will be asked an additional set of questions via an ISR questionnaire (see Appendix 6) to capture self-reported experiences of ISRs.

8.2.7 Medical History and Demographic Data

Medical history includes clinically significant diseases (including AIH and other AIDs), surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 14 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 SAE can be found in Appendix 2. The NSAESI are discussed in Section 8.3.6.

The Investigator and any qualified designees are responsible for ensuring that all AEs (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 AEs 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.

Investigators will seek information on AEs at each participant's contact. All AEs, 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 detailed below.

After informed consent has been obtained **but prior to initiation of study treatment**, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies). Any other AE should not be reported.

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until the follow-up visit, which is scheduled 28 days after last dose of study treatment.

Post-study AEs and SAEs: The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period (e.g., follow-up visit).

However, if the Investigator learns of any SAE (including a death) or other AEs 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 AE 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 up each AE 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 SAEs considered to be related to study treatment or study-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (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 SAEs, NSAESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional event 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 event.

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 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 IEC; 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. Details will be available separately.

8.3.5 Pregnancy

WOCBP will be instructed to immediately inform the Investigator if they become pregnant during the study or within 28 days after the final dose of study treatment.

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

NSAESIs 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).

NSAESIs 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 participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.
- NCI CTCAE (v5.0) ≥ Grade 2 IRRs and any hypersensitivity.

8.3.7 Management of Specific Adverse Events

Treatment of AEs will be considered on a case-by-case basis according to local standard of care.

IRRs have been reported with the first or second infusion/injection (e.g., of biologic therapies) and tend to be dose-related. Such reactions typically occur during, shortly after or within 24 hours after study treatment administration.

“IRR” is a basket term including other terms such as anaphylaxis, anaphylactoid reactions, complement activation-related pseudoallergy, and cytokine release syndrome. Combinations of IRR types may occur in the same patient (Doesseger et al. 2015). A localized ISR is not by itself considered an IRR.

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 compound (e.g., biologic therapy).

The participant should be monitored until complete resolution of the symptoms and treated as clinically indicated.

An IRR blood sample will be taken in all participants at baseline (Day 1 at pre-dose) (see Section 1.3). In case a Grade ≥ 2 IRR occurs, unscheduled PK and IRR samples will be collected and analyzed. The baseline samples of all participants may be analyzed as appropriate.

In case of signs/symptoms of IRRs in a given arm, IRR risk mitigation steps may be implemented in the remaining participants of the dose level. In order to reduce the occurrence and potential impact of IRRs, pre-medication (e.g., anti-histamine) may be applied after discussion between the Sponsor Clinical Pharmacologist, the Investigator, the safety science leader, and the Medical Monitor(s).

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 AE unless it results in untoward medical effects (see Sections 5 and 5.2 of Appendix 2 for further details).

Decisions regarding dose-interruptions or modifications (if applicable) will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

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. Document the quantity of the excess dose in the eCRF.

8.5 PHARMACOKINETICS

Mandatory blood samples to evaluate serum concentrations of RO7049665 will be collected at on-treatment visits as specified in the SoA (see Section 1.3). The date and time of each sample collection will be recorded in the eCRF. Serum concentrations of RO7049665 will be measured by specific and validated enzyme-linked immunosorbent assay methods.

During the course of the study, PK sampling timepoints may be modified on the basis of emerging data to ensure the PK of RO7049665 can be adequately characterized. Additional PK samples will be taken at the time of treatment discontinuation, if the participant experiences an injection-related AE (such as an IRR).

- Placebo-treated participants may not be analyzed in the first instance, but retained for subsequent analysis if appropriate.
- If required, remaining PK samples, or any remaining volume of blood samples, may also be used for assay development/validation experiments and ADA characterization.

The PK samples will be destroyed 5 years after the date of final clinical study report (CSR). Details on sampling procedures, sample storage, and shipment are given in the sample documentation.

Genetic analyses will not be performed on these samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

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

For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.9).

8.6 IMMUNOGENICITY ASSESSMENTS

As RO7049665 is a fusion protein that consists of two human IL-2 muteins covalently linked to a human monoclonal antibody there is a risk that ADAs could develop (see Section 2.3).

The date and time of each sample will be recorded in the eCRF. Additional samples will be taken in participants with clinical signs of hypersensitivity reaction for ADA evaluation *(*see SoA Section 1.3*)*. In each case, for each collected ADA sample, a corresponding PK sample will be collected at the same timepoint for the determination of the RO7049665 concentration.

Validated ADA assays will be employed to detect ADAs against RO7049665 (in serum). Samples which are positive for ADA will be further characterized and their neutralizing capability for endogenous IL-2 will be assessed using the neutralizing antibody assay.

If required, remaining ADA samples may also be used for assay development/validation experiments, further ADA characterization, for compound-related exploratory analyses, or to help develop further blood tests, after they are used for the mentioned intended uses. For exploratory purposes, such as epitope characterization or IgG-IgM-isotyping, samples may be analyzed by assays which are not fully validated.

The ADA serum samples will be destroyed 5 years after the date of final CSR. For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.9).

Samples from placebo-treated participants may not be analyzed in the first instance but may be retained for subsequent analysis if appropriate.

Details on sampling procedures, sample storage, and shipment are documented in the sample documentation.

8.7 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

A fit for purpose biomarker strategy (Section 4.2.3) will be implemented, monitoring several key biomarker types.

Systemic PD will be assessed in the expected target cell population (T_{regs}), with the aim of reconfirming and further characterizing the dose-dependent effects of the drug in this study population. For consistency, the same technology as in prior clinical studies (flow cytometry) will be employed. In addition to the desired selective expansion of target cells, changes in other cell types of interest (including but not limited to T_{effs}, NK cells, T_{fhs}, B cells) will be monitored, thereby corroborating the mode of action (MoA) and potentially informing dose selection and clinical response.

When possible (paired baseline and on-treatment liver biopsies available), liver tissue changes in regulatory and effector T cells will also be measured. This will enable the assessment of tissue PD effects, their comparison with systemic PD observations as well as a preliminary evaluation of intrahepatic T_{reg}/T_{eff} ratio as a response predictive biomarker. Tissue infiltrating lymphocytes will most likely be assessed by immunohistochemistry (IHC), given the availability of historical liver biopsies at baseline, as opposed to fresh samples amenable for flow cytometry. In addition, (spatial) gene expression analyses (targeted genes or whole transcriptome) may be performed on liver biopsy-derived material for enhanced insights into MoA and activated pathways.

Select exploratory serum and/or plasma disease biomarkers will be tested for their diagnostic (e.g., auto-antibodies, anti-nuclear antibodies [ANA], smooth muscle

antibodies (SMA), LKM-1, anti-LC1, anti-SLA/LP, anti-LC1, anti-LKM3) (Galaski et al. 2020) or progression monitoring value (e.g., IgG, IgA, IgM).

Several soluble PD markers will be monitored, including but not limited to, sCD25, cytokines either mechanistically linked to the study treatment MoA (IL-5, IL-6, IL-10, TNF-α, and potential others) as well as cytokines or chemokines hypothesized to either have patient stratification potential (e.g., baseline IL-2) or an ability to be used as non-invasive response to treatment markers (e.g., CXCL10).

Non-invasive markers of liver fibrosis and steatosis will also be measured in the periphery to support MoA and provide supportive evidence for their use as surrogate liver function assessments. These may include but are not limited to composite scores of liver fibrosis.

Additional PD biomarkers and methods to obtain further confidence on the mechanism of action of RO7049665 in participants may be tested, including but not limited to epigenetic signatures of T-cell subsets, e.g., T cell-specific demethylation region.

8.7.1 Genetic and Genomic Analyses

8.7.1.1 Clinical Genotyping

A mandatory whole blood sample will be taken for DNA extraction from every participant in all countries where this assessment is permitted (see SoA Section 1.3).

The DNA may be used for, but analysis is not limited to:

- Genetic variants of the IL-2 gene or other genes encoding proteins involved in IL-2 mediated signal transduction.
- Genetic variants of pathways related to AIH or other autoimmune diseases.
- Genes coding for human leukocyte antigens (i.e., HLA gene family).

Data arising from all biosamples, including samples for analyses of inherited DNA, will be subject to the confidentiality standards described in Section 1.4, Appendix 1. For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.9).

8.8 PHARMACODYNAMICS AND BIOMARKER SAMPLES

Samples will be collected for biomarker assessments at the time points specified in the Schedules of Activities (Section 1.3). Biomarkers will be evaluated as described in Section 8.7**.**

The samples may also be used for research purposes to identify biomarkers useful for predicting and monitoring response to and safety of RO7049665, assess PD effects of

RO7049665, and investigate mechanism of therapy resistance. Additional markers may be measured in the case that a strong scientific rationale develops.

Based on continuous analysis of the data in this study and other studies, any sample type and/or analysis 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.

Unless otherwise specified below, samples (including blood, slides, extracts, etc.) will be destroyed no later than 5 years after the final CSR. For participants who consent to RBR, leftover samples will be transferred to RBR (Section 8.9).

Any remaining blood/tissue, or appropriate, sample type after the specified analyses may also be used for additional (assay) validation experiments. Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to IL-2, T cell subsets and autoimmune diseases.

Details on processes for collection and shipment of these samples can be found in separate sample documentation.

8.8.1 Mandatory Samples

The following samples for PD and biomarker research are required and will be collected from all participants:

8.8.1.1 Blood Sampling

Blood samples will be collected for the following assessments:

- To quantify relative and absolute WBC counts (T cells, B cells, NK cells, eosinophils) by flow cytometry as well as to complete white blood count differential. Tests may include (but are not limited to) markers for quantification and characterization of T_{reg} and T_{eff} cell subsets CD3, CD4, CD8, CD25, CD127 and FoxP3.
- A mandatory whole blood sample will be taken for DNA extraction and clinical genotyping from every participant. If the sample is missed on Day 1, it can be collected at any other scheduled visit.

8.8.1.2 Tissue Sampling

A fresh or historical liver biopsy is required prior to baseline. Provided no worsening of disease has occurred, a historical biopsy taken no more than 12 months prior to randomization is acceptable. If a FFPE block is available, it is mandatory to provide it to the Sponsor. An optional liver biopsy sample will be taken at 6 months after treatment initiation.

The purpose is to conduct the following assessments:

- Characterization of infiltrating WBCs by histology (hematoxylin and eosin-staining) and immunohistochemistry (IHC). IHC markers tested may include but are not limited to CD3, CD4, CD8, and FoxP3.

- RNA extraction on biopsy samples may be performed in order to undertake optional whole or targeted transcriptome gene expression analysis with or without spatial resolution.
- Methylation signature changes induced by the study treatment indicative of quantitative and specific changes of T-cell subsets may be assessed.

8.8.1.3 Serum and Plasma Samples

Serum and plasma samples will be collected for the following assessments:

- To measure cytokines mechanistically linked with the study treatment's mode of action. Soluble biomarkers considered for testing include, but are not limited to IL-5, IL-6, IL-10.
- To measure cytokines or chemokines with stratification (baseline IL-2) or treatment response potential (CXCL10).
- To measure disease biomarkers including but not limited to auto-antibodies (e.g. ANA, SMA) or immunoglobulins (e.g., IgG, IgA, IgM).
- To measure non-invasive markers of liver fibrosis, e.g. but not limited to: α-2-macroglobulin, haptoglobin, apolipoprotein A1, hyaluronic acid, procollagen III amino-terminal peptide (PIIINP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1).
- Additional soluble biomarkers to obtain further confidence on mechanism of action of RO7049665 in humans, PD or disease markers may also be tested.

8.8.1.4 Optional Samples

An optional liver biopsy may be taken (see Section 8.8.1.2).

The ICF will contain a separate section with a separate signature field that addresses the use of optional samples.

8.9 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

8.9.1 Overview of the Research Biosample Repository

The Roche RBR is a centrally administered group of facilities for the long-term storage of human biologic samples, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage and analysis of the RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Collected RBR samples will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy or progressive disease.
- To identify safety biomarkers that are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation.

- To increase knowledge and understanding of disease biology and drug safety.
- To study treatment response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

8.9.2 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7049665, diseases or drug safety:

- Leftover plasma samples
- Leftover serum samples
- Leftover blood samples
- Leftover liver tissue samples
- Leftover blood samples for DNA extraction
- Leftover PBMCs prepared from blood

Samples collected for DNA extraction include, but is not limited to, genomic analysis and may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing, or other genomic analysis methods like spatial transcriptomics or other methods developed in the future.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

Participants will not be identified by name or any other personally identifying information. Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For all samples, dates of consent and sample collection should be recorded on the associated RBR page of the eCRF. Details on processes for collection and shipment of these samples can be found in separate sample documentation.

RBR samples will be stored and used until no longer needed or until they are exhausted. The RBR storage period will be in accordance with the IRB/IEC‑approved Informed Consent Form and applicable laws (e.g., Health Authority requirements).

The repository samples will be subject to the confidentiality standards (as described under Confidentiality and in Appendix 1).

8.10 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

For Health Economics/Medical Resource Utilization and Health Economics parameters see Section 8.1.1.1.

8.11 TIMING OF STUDY ASSESSMENTS

8.11.1 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. 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 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 within 28 days prior to Day 1, unless otherwise specified.

8.11.2 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 (Section 1.3). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the SoAs. COAs (Section 8.1.1) should be performed prior to the completion of other study assessments.

8.11.3 Assessments at Study Completion/Early Termination Visit

Participants who complete the study (defined as relapse) or discontinue from the study early will be asked to return to the clinic 28 days ± 3 days after the final dose of study treatment for a follow-up visit.

8.11.4 Follow-Up Assessments

After the follow-up visit, AEs should be followed as outlined in the SoA (Section 1.3) and in Sections 8.3.1 and 8.3.3.

8.11.5 Assessments at Unscheduled Visits

For activities that are required to be performed in case of an unscheduled visit, refer to the SoA (Section 1.3).

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The hypothesis associated with the primary estimand (see Section 3.1) for this study is that the hazard ratio (HR) for the risk of relapse in the 7.5 mg RO7049665 compared with that of placebo is less than 1. In other words, that 7.5 mg RO7049665 increases the time to relapse following forced tapering of CCS/± NSI therapy in participants with confirmed AIH who have been in stable biochemical remission for at least two years *(or less if according to the local practice)* and on stable AIH treatment for *at least 3 months prior to randomization (and who have not had a dose increase 6 months prior to randomization)*.

Six months after the start of CCS tapering, the relapse rate on placebo is assumed to be 45% (van Gerven 2013). It is estimated that treatment with RO7049665 will reduce the relapse rate to 15%. Under the assumption of exponential times to relapse, these six-month relapse rates imply mean times to relapse of 10.0 months in the placebo arm and 36.9 months in the treatment arm, leading to a reference hazard ratio of 0.272.

The hypotheses formally tested in this study are

$$H_0: HR = 1 \text{ vs } H_1: HR < 1$$

9.2 SAMPLE SIZE DETERMINATION

The sample size for this study is based on independent pairwise comparisons of each RO7049665 group—i.e., high dose (7.5 mg) and low dose (3.5 mg) with placebo. The total sample size required is obtained by multiplying the appropriate per-group size by three. Methods for the control of the family-wise error rate are described both in this section and in Section 9.3.

The reference treatment effect is 0.272. The study will use an overall one-sided type 1 error rate (significance level) of 2.5%. A power of 90% against the reference treatment effect is required.

There will be one opportunity to stop for success before the end of the study, at 50% information. An O'Brien-Fleming-like alpha-spending rule will preserve the type 1 error rate. The success boundary will be binding.

There will be two opportunities to stop for futility before the end of the study: once at 25% information (i.e., when 25% of the maximum number of events have occurred) and once at 50% information (i.e. when 50% of the maximum number of events have occurred). A Pocock-like beta-spending rule will preserve power of the study. The futility boundary will be non-binding.

If the proportional hazards assumption holds, these assumptions imply that 29.1 events (i.e., 30 events for all practical purposes) in the placebo and 7.5 mg RO7049665 arms combined are required to achieve the desired power and significance levels.

Under the assumption that recruitment to the study will take approximately 19 months, that sites will be activated at uniform rate for six months, after which recruitment will plateau, and that follow-up should continue for at most 6 months after the last patient to enter the study is randomized, then recruitment of 28 participants per arm will generate the required number of events.

Table 9 Summary of the Group Sequential Design

Stage	***Interim 1***	***Interim 2***	***End of study***
Information rate	25%	50%	100%
Efficacy boundary (z-value scale)	∞	2.963	1.969
Futility boundary (z-value scale)	−0.046	0.738	
Number of subjects [a,c]	31	47	56
Cumulative number of events [a]	7.3	14.5	29.1
Analysis time [b,c]	11.7	16.3	25.0
Cumulative alpha spent	<0.0001	0.0015	0.025
Cumulative power	<0.0001	0.3159	0.9000
One-sided local significance level	N/A	0.0015	0.0245[d]
Efficacy boundary (t)	N/A	0.211	0.482
Futility boundary (t)	1.035	0.679	
Overall exit probability (under H0)	0.4815	0.3136	
Exit probability for efficacy (under H0)	<0.0001	0.0015	
Exit probability for efficacy (under H1)	<0.0001	0.3159	
Exit probability for futility (under H0)	0.4815	0.3121	

a: For the two arms (the placebo arm and one of the RO7049665 arms) in question.
b: Months after FPFV.
c: Estimate.
d: The hazard ratio that gives rise to a p-value of 0.0245 at the end of study analysis is approximately 0.594. This is the minimum detectable difference for the study and, assuming a mean time to relapse of 10.0 months in the placebo arm, corresponds to a mean time to relapse of 16.9 months on RO7049665.

Thus, the study is expected to recruit 3 × 28 = 84 participants in total and run for no longer than 25 months from FPFV to LPLV. If the enrolment rate or event rate differ from the assumptions used in these calculations, then either the number of participants or the duration of follow-up (or both) may be varied in order to ensure that the required number of events is observed.

Sample size calculations were performed using R package version 2.0.6 (Wassmer and Pahlke, 2019). Details are filed in the study electronic Trial Master File (eTMF).

9.3 MULTIPLICITY

There are three sources of multiplicity in this study: multiplicity due to interim analyses, multiplicity due to multiple doses, and multiplicity due to multiple endpoints.

The overall type 1 error rate for the study is protected against multiplicity due to interim analyses, because of the alpha- and beta-spending rules described in the preceding section.

The overall type 1 error rate for the study will be protected against multiplicity due to multiple doses by using a step-down, or gatekeeper, procedure. The statistical significance of the difference in response between the 3.5 mg RO7049665 group and the placebo group will be assessed if and only if the corresponding difference between the 7.5 mg RO7049665 and placebo has already been shown to be statistically significant.

The study has a single primary endpoint, corresponding to the single primary estimand. All other endpoints are secondary or exploratory. Therefore, no adjustment to nominal p-values will be made to protect the overall type 1 error rate for the study against multiplicity of endpoints.

9.4 ANALYSES SETS

For purposes of analysis, the following analysis sets are defined in Table 10.

Table 10 Analysis Sets

Analysis set	Description
Intent-to-treat	All randomized participants will be included in the intent-to-treat analysis set.
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.
Immunogenicity	Participants who had at least one pre-dose or at least one postdose ADA assessment will be included and analyzed according to the treatment they actually received or were allocated to receive. The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.
PK	Participants who had at least one pre-dose or at least one evaluable postdose PK sample will be included and analyzed according to the treatment they actually received.

Note: The analysis set for the primary estimand is defined by the estimand itself. However, unless there are any participants who are misdiagnosed and who subsequently enter the study (or other unlikely protocol violations), the intent-to-treat analysis set will be identical to the population for the primary estimand.

9.5 STATISTICAL ANALYSES

9.5.1 Demographics and Baseline Characteristics

Summaries for categorical baseline variables will include counts and frequencies. Summaries for continuous baseline variables will include counts, means, and standard deviations. Participants in the ITT analysis set will contribute to baseline summaries.

For each variable, the “baseline value” will be the last non-missing value obtained prior to the first administration of study treatment.

9.5.2 Efficacy and Pharmacodynamic Analyses

9.5.2.1 Primary Estimand

The hazard ratio will be derived from a Cox proportional hazards model for time until relapse with fixed effects for treatment arm, sex, and CCS use, expressed as equivalent prednisolone dose. The raw and median unbiased point estimates for the HR will be

presented together with associated confidence intervals and p-value. The estimated 6-month relapse rates for each arm will be presented, together with associated confidence intervals. Kaplan-Meier curves and the associated confidence intervals will be graphed.

Refer to Sections 3.1.3 and 8.1 for definitions of censoring and relapse.

9.5.2.2 Secondary Endpoints

No formal hypothesis testing will be conducted for any secondary endpoint.

Changes in ALT and IgG

Values of ALT and IgG (both absolute and relative to ULN) will be plotted over time, grouped by treatment arm. Values (both absolute and relative to ULN) and changes from baseline will be tabulated.

For the safety analyses, see Section 9.5.3.

9.5.2.3 Exploratory Endpoints

Clinical Outcome Assessment

Absolute values and changes from baseline for PRO data will be tabulated by visit and treatment group. Where appropriate, both the overall and individual domain scores will be summarized (see Section 8.1.1 for further details).

Auto-antibodies

Absolute values and changes from baseline will be tabulated by visit and treatment group.

- Titers of auto-antibodies specific for type 1, 2, or 3 AIH.
- Titers for ANAs and/or anti-smooth muscle antibodies.

Cytokines

Absolute values and changes from baseline of inflammatory and anti-inflammatory cytokines will be tabulated by visit and treatment group.

Liver-residing Regulatory T-cells

Absolute values and changes from baseline of liver-residing T_{reg} and T_{eff} cells and the T_{reg}/T_{eff} ratio will be tabulated by visit and treatment group.

Liver Fibrosis

Raw Fibroscan® results (controlled attenuation parameter [CAP] scores in dB/m and pressure readings in kPa) will be tabulated by visit and treatment group, together with derived steatosis grades and fibrosis scores.

Component laboratory test results (alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, Total bilirubin, ALT, hyaluronic acid, PIIINP and TIMP-1) will be tabulated by

visit and treatment group. If calculated, derived liver fibrosis test scores will be tabulated by visit and treatment group. If at least one required laboratory test result is not available at a visit, the derived test score will also be missing: there will be no imputation of missing laboratory test results.

Liver fibrosis scores from histology will be tabulated by visit and treatment group. Other liver histology findings will be presented in listings.

IgA and IgM

Absolute values and changes from baseline of total IgA and total IgM will be tabulated by visit and treatment group.

Pharmacodynamic Markers

- Systemic T_{reg}, T_{eff}, T_{fh}, B cells, sCD25 and in tissue may be used for modeling and simulation together with efficacy parameters.
- Absolute values and changes from baseline of T_{reg}, T_{eff}, $T_{fh,}$ and B-cell counts in peripheral blood and tissue will be plotted over time, grouped by treatment group, and tabulated by visit and treatment group.

9.5.3 Safety Analyses

All safety analyses (see Table 11) will be based on the safety analysis population grouped according to the treatment assigned at randomization (see Table 10).

Table 11 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for AEs will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level. Incidence, nature and severity of AEs, number of participants with SAEs, treatment-related SAEs, SAEs leading to discontinuation, treatment-related AEs, or AEs leading to discontinuation will be tabulated.
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 outputs with flagging of abnormal results. In addition, tabular summaries will be used, as appropriate. Laboratory data not reported in SI units will be converted to SI units before processing.
Vital signs	Vital signs data and weight data will be presented 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 using appropriate outputs, with flagging of values outside the normal ranges and abnormalities. In addition, tabular summaries will be used, as appropriate.
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 using appropriate outputs.

9.5.4 Pharmacokinetic Analyses

RO7049665 concentration data will be pooled with data from other studies for population PK and PK/PD modeling. The methods and results of that population modeling will be reported separately.

9.5.5 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 treatment administration (post-baseline incidence during both the treatment and follow-up periods) will be summarized.

The following definition applies to post-baseline samples:

- Participants are considered to be ADA positive if they are ADA negative at baseline but develop an ADA response following study treatment 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 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 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.

9.6 INTERIM ANALYSES

Formal interim analyses form an integral part of the analytical strategy for this study and are defined in Section 9.2. During the conduct of each interim analysis, the study team will remain blind to the results of the interim analysis. The interim analysis will be conducted by the statistician who is a member of the study IMC and independent from the study team and its results reviewed by the IMC as a whole.

It is unlikely that the interim (or final) analyses will be conducted precisely at the information fractions assumed in the sample size calculation. In this case, the stopping boundaries for both success and futility will be adjusted to take account of the actual information fractions at which the interim (and final) analyses were actually conducted while at the same time protecting the overall type 1 and type 2 errors of the study.

A further complication is that the planned timing of each interim analysis depends on the number of relapses observed in the 7.5 mg RO7049665 and placebo groups combined. This is a double-blind, three-arm study, so this number cannot be known without breaking the blind on a regular basis. Therefore, the timing of the interims will be estimated by looking at the number of relapses in the study as a whole, with conduct of the interims and the final analysis when the total number of relapses is expected to be 1.5 times greater than the number of events given in Section 9.2; that is, when 12, 23, and 45 events have been observed in the whole study.

The IMC charter will describe the planned interim analyses in detail.

9.7 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed. Data for study treatment 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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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes standard appendices such as

- Appendix 1 (Regulatory, Ethical and Study Oversight Considerations),
- Appendix 2 (AE: Definitions, Reporting, Procedures for Evaluating, Follow-up, and Reporting)
- Appendix 3 (Procedures of Recording Adverse Events),
- Appendix 4 (Clinical Laboratory Tests),
- Appendix 5 (Contraceptive Guidance and Collection of Pregnancy Information).
- Appendix 6 (Patient-Reported Outcome [PRO] Assessments)

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 s 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 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.

The ICFs must be signed and dated by the participant 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 ICFs 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 ICFs must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

If the ICFs are revised (through an amendment or an addendum) while a participant is participating in the study, the participant may be re-consented by signing the most current version of the ICFs or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised ICFs, 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 ICFs for continued participation in the study. The study team will provide guidance for which participants need to re-consent in the event of an update to the ICF.

A copy of each signed ICF must be provided to the participant. All signed and dated ICFs 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.

Participants who are re-screened are required to sign a new ICF.

Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the RBR. The Investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their samples at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant’s agreement to provide optional RBR samples. Participants who decline to participate will not provide a separate signature.

The Investigator should document whether or not the participant has given consent to participate by completing the RBR Sample Informed Consent eCRF.

In the event of death or loss of competence of a participant who is participating in the research, the participant's samples and data will continue to be used as part of the RBR.

Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site

Withdrawal from the Research Biosample Repository

Participants who give consent to provide samples for the RBR have the right to withdraw their samples at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her samples, the Investigator must inform the Medical Monitor and Site Monitor in writing of the participant’s wishes using the RBR Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the study is closed. A participant's withdrawal from Study BP42698 does not, by itself, constitute withdrawal of samples from the RBR. Likewise, a participant’s withdrawal from the RBR does not constitute withdrawal from Study BP42698. Data already generated before time of withdrawal of consent to RBR will still be used.

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, which may include data on germline mutations, 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.

Confidentiality for Research Biosample Repository

Data generated from RBR samples must be available for inspection upon request by representatives of national and local Health Authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Participant medical information associated with RBR samples is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data derived from RBR sample analysis on individual participants will generally not be provided to study Investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with Investigators or participants unless required by law.

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

Monitoring and Oversight Research Biosample Repository

Samples collected for the RBR will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the ICF. The Sponsor’s monitors and auditors will have direct access to appropriate parts of records relating to participant participation in RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

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. Clinical Outcome Assessment Data

2.1.2.1 Electronic Clinical Outcome Assessment Data

An eCOA device will be used to capture COA data. The data will be transmitted to a centralized database at the eCOA vendor and the data may be reviewed by site staff via secure access.

eCOA data will be collected using an electronic device provided by an eCOA vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor’s standard procedures.

In the exceptional situation when the scale is not available to be administered and recorded via a digital device, e.g. setup delays of the electronic devices, the scale can be administered in paper format and transcribed into the digital device retrospectively upon availability of the digital device. In the case that a scale is not available in either paper or digital format e.g., due to licensing or translation delays, the participant may still be enrolled into the study and the scale would not be completed.

2.1.3. 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, participant files, and records kept at pharmacies, laboratories, and medico‑technical departments involved in a clinical study.

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.

2.1.4. 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.

2.1.5. Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

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 or discontinuation of the study, or for the length of time required by relevant national or local Health Authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. 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.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local Health Authorities.

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 competent authorities 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 participants 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. Dissemination of Clinical Study Data

A description of this clinical trial will be available at http://www.ClinicalTrials.gov.

2.3.4. Management of Study Quality

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

2.3.5. 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. ADMINISTRATIVE STRUCTURE

3.3. INTERNAL MONITORING COMMITTEE

A dedicated group of selected Sponsor representatives, which will be independent to the project, will be reviewing the safety and efficacy data of the study, and the interim analyses. The roles, responsibilities, membership, scope of activities, time of meetings,

and communication plan for the IMC will be documented in an appropriate charter, but the IMC's responsibilities will include primary responsibility for the conduct of the interim analyses and recommending, after each, whether or not the study should continue.

4. 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 participant 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).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE unless the relapse is unexpectedly accelerated and not in line with the natural history of the disease. If the “Lack of efficacy” would not require safety reporting such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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 serious adverse event (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 or its delegate. 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 or its delegate.

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 terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a predefined grading criteria [e.g., NCI CTCAE]); the event itself may be of relatively minor medical significance (such as severe 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.

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 1 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
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]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to adverse event[d]

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

Note: Based on the NCI CTCAE (v5.0), 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 (see Section 6 of this Appendix for reporting instructions), per the definition of serious adverse event in Section 2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 6 for reporting instructions), per the definition of serious adverse event in Section 2. Grade 4 laboratory abnormalities would only be reported as SAEs if these meets one or more of the conditions outlined in Section 2 (Definition of Serious Adverse Events) of Appendix 2.

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.
- Course of the event, considering especially the effects of, discontinuation of study treatment, or reintroduction 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 or its delegate 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, only 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 RO7049665/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 RO7049665/placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and 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 through use of the reference safety information in the document listed below:

Study Treatment	Document
RO7049665	RO7049665 Investigator's Brochure

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. INJECTION REACTIONS

Adverse events that occur during or after study treatment administration and are judged to be related to study treatment injection should be captured as a diagnosis (e.g., injection-related reaction or injection-site 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 Injection Reaction eCRF. If a participant experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

1.2. OTHER ADVERSE EVENTS

For adverse events other than injection reactions, 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 upper limit of normal (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 BP), 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 (see Appendix 2) 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 (see Section 8.3.6).

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. This includes death attributed to progression of autoimmune hepatitis.

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. LACK OF EFFICACY OR WORSENING OF AUTOIMMUNE HEPATITIS

Medical occurrences or symptoms of deterioration that are anticipated as part of AIH should be recorded as an adverse event if judged by the Investigator to have

unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of AIH on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated Auto Immune Hepatitis”).

10. 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 (e.g., an optional liver biopsy).
- 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.

11. PATIENT-REPORTED OUTCOME DATA (COA DATA REPORTED DIRECTLY BY PATIENTS)

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data. Roche study team will determine whether any PRO data elements may be indicative of a medically significant adverse event (e.g., suicidal ideation, worsening of depression, worsening of hemoptysis) and could necessitate real time review by the site or Sponsor.

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the central laboratory with the exception of urinalysis, pregnancy testing, urine drug screen, and alcohol test. If the local laboratory results are used, the results must be captured in source documentation and entered into the eCRF.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be captured in source documentation and entered as a comment into the eCRF.

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
Hematology	• Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).
Blood Chemistry	• Sodium, potassium, chloride, CRP, bicarbonate, non-fasting glucose, urea, creatinine, creatine kinase (CK), protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, GGT, IgG, IgA, IgM (IgA and IgM at screening, week 25, every 24 weeks thereafter and at early termination/end of study). Cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.
Coagulation	• Prothrombin time (i.e., INR) and activated thromboplastin time (aPTT).
Viral Testing	• Serology: HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb) • PCR: HCV, EBV and CMV
Hormones	• Free T4, TSH • Follicle-stimulating hormone (FSH) in females
IRR sample	• IgE, tryptase (and includes exploratory safety biomarkers, see Section 8.2.5).
Pregnancy Test	• All women of childbearing potential (including those who have had a tubal occlusion/ligation) will have a blood pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.
Anti-Drug Antibodies	• As specified
Urinalysis	• Specific gravity • Dipstick: pH, glucose, protein, blood. • If there is a clinically significant positive result (confirmed by a positive repeated sample), urine will be sent to the local laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture. • Microscopic examination (red blood cells [RBCs], white blood cells [WBCs], casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal.
Other Screening Tests	• Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, codeine, and benzodiazepines). • Alcohol breath test.

The results of each local test must be entered into the CRF.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study, will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Potential analysis considerations for analyzing laboratory data includes the use of standard reference ranges and potential transformation of data for specific laboratory 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 the analysis described above, 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.
- Only discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

- **Female Participants**

Female participants of childbearing potential are eligible to participate if they agree to use acceptable methods of contraception consistently and correctly as described in Table 1 below (as per CTFG guidance Section 2.3.4).

Per ICH M3(R2), highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly as described in Table 1 below.

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent[a] (Failure rate of < 1% per year when used consistently and correctly)

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Injectable

Highly Effective Methods That Are User-Independent (Failure rate of < 1% per year)
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion/ ligation **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Acceptable Birth Control Methods Which May Not Be Considered As Highly Effective (Failure rate of > 1% per year when used consistently and correctly)

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide [b]
- Cap, diaphragm or sponge with spermicide [b]

a) Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b) A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods. i.e., when the risk of teratogenicity and genotoxicity is unlikely.

3. PREGNANCY TESTING

For WOCBP enrolled in the study, pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.3). If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

4. COLLECTION OF PREGNANCY INFORMATION

- **Female participants who become pregnant**

The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.5 Pregnancy). Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Appendix 2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

5 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.

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female participant 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
Patient-Reported Outcome (PRO) Assessments

For **PROMIS-SF Fatigue 13a** it is better to use the T-score from the scoring manual or it may come directly from the ePRO instead of the raw score. See link to scoring manual: https://www.healthmeasures.net/search-view-measures

EQ-5D-5L comes with 5 questions and a VAS scale. The 5 questions needs to be converted to utility estimates in order to be meaningful and represent the preference of the general population. https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf

SF-12 scores can also be estimated to a normative score (see below).

The **Injection-Site Reaction questionnaire** (see below) is a set of questions to capture self-reported experience of ISRs. The questions cover four symptoms (pain, swelling, redness and itchiness) at a site of study treatment injection. Participants are asked if they experienced any of these symptoms in the past 14 days, with the response options being "Yes", "No" and “Not applicable”. For each symptom reported, participants are asked how bothersome they found the symptom based upon a 5-point Likert scale ranging from “Not at all” to “Very much”.

SF-12v2™ Health Survey

(SF-12 v2 Standard, US Version 2.0)

Identification Number	
Event	

To be completed by the PATIENT

Directions: *This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. If you need to change an answer, completely erase the incorrect mark and fill in the correct circle. If you are unsure about how to answer a question, please give the best answer you can.*

Today's Date (MM/DD/YY)

__ __ / __ __ / __ __

Shade circles like this: ● **Not like this:** ⊗ ✓

Mark only one answer for each question. Please do not mark outside the circles or make stray marks on the questionnaire.

	Excellent	Very Good	Good	Fair	Poor
01. In general, would you say your health is:	○	○	○	○	○
The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
02. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○		
03. Climbing several flights of stairs	○	○	○		
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
04. Accomplished less than you would like	○	○	○	○	○
05. Were limited in the kind of work or other activities	○	○	○	○	○
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
06. Accomplished less than you would like	○	○	○	○	○
07. Did work or activities less carefully than usual	○	○	○	○	○
08. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	A little bit	Moderately	Quite a bit	Extremely
	○	○	○	○	○
These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...	All of the time	Most of the time	Some of the time	A little of the time	None of the time
09. Have you felt calm and peaceful	○	○	○	○	○
10. Did you have a lot of energy	○	○	○	○	○
11. Have you felt downhearted and depressed	○	○	○	○	○
12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	○	○	○	○	○

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Injection-Site Reaction Questionnaire (shortened version)

In the last 14 days, did you have any

	Yes	**No**	**Not applicable**
PAIN at a site of drug injection?	☐	☐	☐
SWELLING at a site of drug injection?	☐	☐	☐
REDNESS at a site of drug injection?	☐	☐	☐
ITCHINESS at a site of drug injection?	☐	☐	☐

Questions in the table below are conditional upon the response from the participant to the question in the table above.

How much did the

	Not at all	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
PAIN at a site of drug injection bother you?	☐	☐	☐	☐	☐
SWELLING at a site of drug injection bother you?	☐	☐	☐	☐	☐
REDNESS at a site of drug injection bother you?	☐	☐	☐	☐	☐
ITCHINESS at a site of drug injection bother you?	☐	☐	☐	☐	☐