Official Title: A Phase II, Randomised, Adaptive, Open-Label Platform Trial to Evaluate Efficacy and Safety of Multiple Combination Therapies in Participants with Chronic Hepatitis B

NCT Number: NCT04225715

Document Date: Protocol Amendment Version 7: 18-July-2022

PROTOCOL

TITLE:	**A PHASE II, RANDOMISED, ADAPTIVE, OPEN-LABEL PLATFORM TRIAL TO EVALUATE EFFICACY AND SAFETY OF MULTIPLE COMBINATION THERAPIES IN PARTICIPANTS WITH CHRONIC HEPATITIS B**
PROTOCOL NUMBER:	WV41073
VERSION:	7.0
EUDRACT NUMBER:	2019-002086-35
IND NUMBER:	141485
TEST PRODUCT:	RO7049389, RO7020531, RO7445482, RO7191863
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	*See electronic signature and date stamp on the final page of this document*
DATE AMENDED:	Version 1: 13 June 2019 Version 2: 25 November 2019 Version 3: 20 July 2020 Version 4: 14 October 2020 Version 5: 25 August 2021 Version 6: 16 December 2021 Version 7: See electronic *signature and* date stamp *on the final page of this document.*

PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE II, RANDOMISED, ADAPTIVE, OPEN-LABEL PLATFORM TRIAL TO EVALUATE EFFICACY AND SAFETY OF MULTIPLE COMBINATION THERAPIES IN PARTICIPANTS WITH CHRONIC HEPATITIS B**
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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 Study Monitor.

PROTOCOL AMENDMENT, VERSION 7
RATIONALE

Protocol WV41073 Version 7 has been amended with the following changes to the global protocol. The key changes in WV41073 protocol along with a rationale for the changes have been summarized below:

- Section 4.1 has been updated to justify additional recruitment of participants in each treatment arm due to significant number of participants with consecutive missing visits as a result of COVID-19 lockdown and restrictions, with potential impact on the evaluation of the primary endpoint due to incomplete data.
- Section 6.8, the nucleoside analogue (NUC) stopping criteria have been amended to take into account participants with very low HBsAg levels at baseline and to prevent participants from stopping NUCs who have not demonstrated more than 1 $\log_{10}$ IU/mL decline in HBsAg after the end of treatment.
- Section 8.3.8.2 was amended to ensure patients who have discontinued NMEs and/or NUC therapy are monitored closely, to enable early detection and prompt management of virological relapse to prevent participants potentially developing liver decompensation. NUC re-starting criteria were amended as a precautionary measure based on feedback received from study Investigators, the publication of a case report from a non-Roche clinical trial in a similar patient population, and feedback received from liver and HBV experts and not based on any safety findings from this study.
- Section 8.3.8.3, for elevated ALT management where twice weekly laboratory tests are recommended, local laboratory tests may be performed in addition to central laboratory for participant's ALT monitoring and management and decision-making may be based on local laboratory results
- Section 9.2 and Section 9.4.2 has been updated accordingly due to the additional recruitment of participant
- Section 4.2.3, 8.7.3 and Section 3, Table 1 and all Appendices tables for Screening and Treatment Periods, footnote 'h' was clarified for HBV genotyping by alternative methodologies.
- Appendix 7-Table 2, Appendix 9-Table 4, Appendix 10-Table 4, Appendix 12-Table 5 and Appendix 13-Table 9, the 24-week primary endpoint follow-up visit window is extended to accommodate individual participants encountering extreme circumstances such as pandemic, natural disasters etc. without compromising the scientific integrity of the analysis.
- Appendix 7-Table 2, Appendix 9-Table 4, Appendix 10-Table 4, Appendix 12-Table 5 and Appendix 13-Table 9, footnote added to the HBV DNA quantitative assessment for close monitoring to enable early detection and prompt management of virological relapse
- Appendix 12-Table 4, Footnote 'x' added to provide further guidance regarding 24 hour pooled urine collection for siRNA PK.

- Appendix 13 has been updated to confirm dose selected and provide dose justification for [redacted], including preliminary pre-clinical AAV-HBV data supporting the rationale for combining PD-L1 LNA and siRNA.
- Appendix 13-Table 7 and Table 8 have been amended to remove PD-L1 LNA dosing regimens that are no longer applicable.
- Appendix 13-Table 7, hematology panel has been added at Week 20, Week 22, and Week 24, and urinalysis at Week 14 and Week 16, which was omitted in error.
- Appendix 13-Table 8 has been amended so that laboratory assessments are performed weekly and not every other week i.e., laboratory assessments performed at Weeks 26, 28, 30, 32, 34, and 36 to be consistent with 24-week treatment arm (Appendix 13-Table 7) and the selection of a weekly dosing regimen. This is not related to any new safety concerns or any new safety data.
- Appendix 13 – Section 13.4 has been amended to address inconsistency and to avoid repetition the text in Section 13.6 has been removed and updated to refer the reader to Appendix 13 - Section 13.4.
- Appendix 13 – Section 13.10.1 has been updated to align discrepant text with the timepoints outlined in Table 7 and Table 8.
- Appendix 13 – Section 13.11.1 has been updated to remove text regarding the collection of exploratory kidney biomarkers which were not included in Table 7 and Table 8.
- Appendix 13-Table 9, added the note regarding frequency of visits for those participants who discontinue NUC therapy later in follow up which was omitted in error.

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
AAV-HBV	Recombinant adeno-associated virus carrying hepatitis B virus genome
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibodies
ANA	Antinuclear antibody
ASGPR	asialoglycoprotein receptor
ASMA	Anti–smooth muscle antibody
ARFI	Acoustic radiation force impulse
AST	Aspartate aminotransferase
a-TPO	Anti-thyroperoxidase antibodies
AUC	Area under the curve
BID	Twice daily
CAP	Controlled attenuation parameter
cccDNA	Covalently closed circular deoxyribonucleic acid
CHB	Chronic hepatitis B
CL	Clearance
CM	Composite measure
C_{max}	Peak concentration
CpAM	Core protein allosteric modulator
CRS	cytokine release syndrome
CSR	Clinical study report
CYP	Cytochrome P450
DAA	Direct-acting antiviral
DDI	Drug-drug interaction
DAIDs	Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIH	Entry-into-human

EOT	End-of-treatment
ETV	Entecavir
EU	European Commission
EV	Extracellular vesicle
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GalNAc	N-acetyl-D-galactosamine
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
HA	Health Authority
HAP	Heteroaryldihydropyrimidine
HAV	Hepatitis A
HBcrAg	Hepatitis B core-related antigen
HBeAg	Hepatitis B early antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HDL	High-density lipoproteins
HEV	Hepatitis E virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HV	Healthy volunteers
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IM	Immunomodulatory agent
IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IP-10	Interferon gamma-induced protein 10
IRB	Institutional Review Board
IR	Injection reaction

ISG	Interferon-stimulated genes
ISR	Injection site reaction
IVRS/IWRS	Interactive Voice/Web Response System
LDL	Low-density lipoproteins
LFT	Liver function test
LLN	Lower limits of normal
LLOQ	Lower limit of quantification
LNA	Locked nucleic acid
LPLV	Last participant, last visit
MDRD	Modification of Diet in Renal Disease
mISR	Modified injection site reaction
MN	Mobile nursing
MR	Magnetic resonance
NIMP	Non-investigational medicinal product
NK	Natural killer
NME	New molecular entity
NPLC	non-parenchymal liver cells
NUC	Nucleos(t)ide
OATP	Organic anion transporter polypeptide
OTC	Over-the-counter
PD	Pharmacodynamic
pDC	Plasmacytoid dendritic cells
PD-L1	Programmed Death Ligand-1
PEG IFN-α	Pegylated interferon-alpha
pgRNA	Pre-genomic ribonucleic acid
PK	Pharmacokinetic
PT	Prothrombin time
QD	Once a day
QOD	Once every other day
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate using the Bazett's correction factor
QTcF	QT corrected for heart rate using the Fridericia's correction factor
QW	Once a week
Q4W	Every 4 weeks

RBC	Red blood cell
RBR	Research biosample repository
RISC	RNA-induced silencing complex
RGT	Response-guided therapy
RNA	Ribonucleic acid
RO7049389	CpAM
RO7020531	TLR7
RO7445482	siRNA
RUO	Research-use only
SAE	Serious adverse event
SAP	*Statistical Analysis Plan*
sc	subcutaneous
siRNA	Short interfering RNA
SoA	Schedule of activities
SOC	Scientific Oversight Committee
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TAF	Tenofovir alafenamide
TBD	To be determined
TDF	Tenofovir disoproxil fumarate
TLR7	Toll-like receptor 7
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE II, RANDOMISED, ADAPTIVE, OPEN-LABEL PLATFORM TRIAL TO EVALUATE EFFICACY AND SAFETY OF MULTIPLE COMBINATION THERAPIES IN PARTICIPANTS WITH CHRONIC HEPATITIS B**
SHORT TITLE	COMBINATION THERAPIES FOR CHB
PROTOCOL NUMBER:	WV41073
VERSION:	7.0
TEST PRODUCT:	RO7049389, RO7020531, RO7445482, RO7191863
PHASE:	II

STUDY RATIONALE

Chronic hepatitis B (CHB) virus infection is a major global healthcare problem, with an estimated prevalence of 257 million people. Current treatments reduce the risk of CHB sequelae but are associated with very low rates of functional cure (hepatitis B surface antigen [HBsAg] loss rates generally not exceeding 3% after one year of therapy).

Multi-drug therapies with compounds targeting different steps in viral replication or combinations with drugs that restore the innate and/or adaptive host immune responses are presumably more likely to be efficacious than monotherapy. New treatment regimens may be more likely to achieve functional cure by a combination of multiple direct antiviral mechanisms or through the augmentation of anti-hepatitis B virus (HBV) immune responses.

The Sponsor intends to identify finite-duration combination therapies including one or more new molecular entities (NMEs), that are associated with high rates of sustained loss of HBsAg ($<$0.05 IU/mL; functional cure) using the present platform Phase 2 study.

Platform studies have the objective to study multiple therapies in the context of a single disease, with therapies allowed to enter or leave the platform based on availability and emerging data. Thus, the Sponsor plans to study combination therapies employing a master protocol, where combination therapies can enter the study in a dynamic manner after obtaining Health Authority (HA)/Ethics Committee (EC) approval of subsequent protocol amendments.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To estimate the effect of NME combination therapies on inducing a functional cure over the control arm.	• % participants with HBsAg loss at 24 weeks post-EOT.
Secondary [a]	
• To characterize the efficacy profile of NME combination therapies.	• % participants with HBsAg loss. • % participants with HBsAg seroconversion. • % participants with HBeAg loss (baseline HBeAg-positive participants). • % participants with HBeAg seroconversion (baseline HBeAg-positive participants). • % participants with HBV DNA < lower limit of quantification (LLOQ), < 200 IU/mL and < 2,000 IU/mL.
• To characterize the PD profile of NME combination therapies.	• Including but not limited to: change from baseline in quantitative HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, HBcrAg, HBV RNA, and HBV DNA levels over time.
• To characterize the plasma PK profiles of NMEs.	• Estimated PK parameters from sparse sampling and population PK models.
• To assess the safety and tolerability of NME combination therapies.	• Incidence, nature, and severity of AEs and laboratory abnormalities.
• To identify presence of PK/PD relationship.	• Analyses of PK/PD data.
• To explore potential effects of ADA on NMEs and/or IMP, as applicable.	• Relationship between ADA status, PK, safety, PD, and efficacy.

Abbreviations: %=percent; AE=adverse event; DNA=deoxyribonucleic acid; EOT=end-of-treatment; HBcrAg=hepatitis B core-related antigen; HBeAg=hepatitis B e antigen; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; LLOQ=lower limit of quantification; NME=new molecular entity; NUC=nucleos(t)ides; PD=pharmacodynamic; PK=pharmacokinetic; RNA=ribonucleic acid.

[a] Efficacy and PD endpoints are assessed at every 12-week time point.

OVERALL DESIGN

STUDY DESIGN

This is a Phase II, randomized, adaptive, open-label, multi-arm, multi-center, international, platform study designed to evaluate safety, tolerability, and efficacy of new combination therapies including one or more NMEs in CHB participants with preserved liver function and without significant fibrosis/cirrhosis. The platform design allows comparison of multiple new combination therapies against a common control, and introduction of additional treatment arms at later study time points.

This study is designed to be adaptive to open additional shorter duration treatment arms or to expand existing treatment arms for NME combination therapies that show promising efficacy outcomes. The platform design also has the flexibility to open new treatment arms to explore different combination regimens or different patient populations pending new submission and HA/EC approval. Based on emerging data and/or company prioritization of assets, treatment arms may be terminated early or not opened for randomization or certain NMEs in the combination treatment arm might be terminated while therapy is maintained with the remaining NMEs. The Sponsor will notify the Investigator and HA/EC if the study or certain treatment arms or certain NMEs are placed on hold, or if the Sponsor decides to discontinue certain treatment arms or certain NMEs.

For the first combination, participants will be randomized on Day 1 to an NME combination arm (N=30) or the control arm (N=30) using an adaptive stratified sampling method, stratified at screening HBsAg level ($<$1,000 IU/mL, $\geq$1000 IU/mL), with a minimum of 12 participants per arm with a screening HBsAg level of $<$1000 IU/mL. For NME combination arms that will be introduced later into the platform study, the allocation ratio of participants to the control arm, will depend on the number of actively enrolling arms with the stipulation that no more than 17% of participants will be randomly allocated to a control arm. Additionally, for subsequent arms the proportion of patients with HBsAg level $<$1000 IU/mL, $\geq$1000 IU/mL within each treatment arm, will be maintained as closely as possible to the first combination treatment arm.

Due to strict lockdowns and restrictions in China in March - May 2022, as of 31 May 2022 approximately 30-53% of participants in each treatment arm have missed study visits and siRNA drug administration at the site. As a result, a number of participants have consecutive visits missed with potential impact on the evaluation of the primary endpoint due to incomplete data. To preserve the viability of the study, if COVID-19 restrictions continue, or any future COVID-19 outbreaks or any force majeure (e.g. natural disasters, supply chain disruption, outbreak of hostilities etc.) impacting participants, will lead to additional participants being recruited to the study to ensure that the number of participants per treatment arm with the full dose as per the randomized dose regimen remains approximately 30. The maximum number of additional participants to be recruited will be approximately 30 for each treatment arm.

The treatment period duration will be a maximum of 48 weeks, after which participants will enter a 48-week follow-up period. Treatment duration may be shortened (12 or 24 weeks) for 48 week NME combination arms, and/or a response-guided therapy (RGT) arm may be added following planned interim analyses; up to four planned interim analyses will be conducted for each treatment arm. Treatment arms that achieve 30% difference, compared to NUC control arm, for HBsAg loss at EOT or follow-up Weeks 12 and 24 (primary endpoint) may be expanded to accrue additional efficacy and safety data and to contribute to Phase 3 design planning as guided by the emerging data, for example, enrichment for HBeAg-positive or HBeAg-negative participant populations. An expansion may also be triggered prior to EOT, for a treatment arm that gives an early indication of efficacy. The decision criteria to trigger an expansion arm in this case, will be documented as an appendix to the IMC/Scientific Oversight Committee (SOC) charter.

LENGTH OF STUDY

The total length of the study, from screening of the first participant to the end-of-study, is expected to be approximately 3 to 5 years, depending on the number and timing of additional treatments arms that are added to the study.

The study duration for each participant will be approximately 2 years divided as follows:

- Screening period: up to 8 weeks.
- Treatment period: up to 48 weeks.
- Safety follow-up period: 48 weeks.

END-OF-STUDY

A participant is considered to have completed the study if he/she has completed all phases of the study including the last study visit. The end-of-study is defined as the date when the last participant completes the last visit (LPLV).

DATA MONITORING COMMITTEE: YES

An Internal Monitoring Committee and a *Scientific Oversite Committee* will be utilized in this study.

PARTICIPANT POPULATION

The study will enroll CHB participants with preserved liver function and without significant fibrosis/cirrhosis.

The initial study population will consist of virologically suppressed CHB participants on established NUC therapy between 18 and 65 years of age, inclusive. Additional participant populations (e.g., treatment naïve CHB participants) may be explored within the study in treatment arms to be added at a later date pending new submission and HA/EC approval.

INCLUSION/EXCLUSION CRITERIA

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

Informed Consent

1. Able and willing to provide written informed consent and to comply with the study protocol according to International Council for Harmonization (ICH) and local regulations.

Age

2. Participants must be between 18 and 65 years of age, inclusive, at the time of signing the informed consent.

Weight

3. Body mass index between 18 and 32 kg/m^2 inclusive.

Type of Participants and Disease Characteristics

4. Participants with CHB infection (HBsAg positive for $\geq$ 6 months) who are on NUC (entecavir or tenofovir alafenamide/disoproxil fumarate) monotherapy for $\geq$12 months, having received the same NUC therapy for $\geq$3 months prior to screening.
5. HBV DNA below the lower LLOQ or < 20 IU/mL for > 6 months prior to screening and confirmed at screening.
6. Alanine transaminase (ALT) $\leq$ 1.5 x upper limit of normal (ULN) for > 6 months prior to screening, and confirmed at screening
7. Screening laboratory values (hematology, chemistry, urinalysis) within normal range, or judged not clinically significant by the Investigator.

Sex

8. Male and female participants:

   The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for 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 fetal/embryonic drug exposure.

   The following contraception requirements must be followed unless otherwise stated in the respective appendix of each treatment arm.

   a) Female Participants:

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

   - Woman of non-childbearing potential (WONCBP).
   - Woman of childbearing potential (WOCBP), who:
     - Agrees to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the final dose of study treatment. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal occlusion, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
     - Has a negative pregnancy test at screening (Day -14 to -7). In addition, WOCBP must be willing to undergo a urine pregnancy test every three months until the end of study.

   b) Male Participants:

   During the treatment period and for at least 6 months after the final dose of study treatment, agree to:

   - Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year, with a partner who is a woman of childbearing potential (WOCBP).
   - With pregnant female partner, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.
   - Refrain from donating sperm.

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

Medical Conditions

1. Pregnant (positive pregnancy test) or lactating women.
2. Co-infection with other pathogens such as hepatitis A (HAV), hepatitis C (HCV), hepatitis D (HDV), hepatitis E (HEV), or human immunodeficiency virus (HIV).
3. History of cirrhosis or current evidence of significant liver fibrosis or cirrhosis (F3 or above on liver biopsy, ≥7.4 kPa on transient elastography, > 1.32 m/s on acoustic radiation force impulse [ARFI] elastography, or > 3.13 kPa on magnetic resonance [MR] elastography), or > 7.1 kPa on 2D-shear wave elastography [2D-SWE]), or decompensated liver disease (e.g., ascites, hepatic encephalopathy). Liver biopsy or transient elastography/ARFI/MR result must be obtained within 6 months prior to randomization.
4. History of or suspicion of hepatocellular carcinoma (HCC) (e.g., elevated α-fetoprotein [AFP] levels, or suggestive lesions on abdominal ultrasound or other imaging, etc.).

5. Thyroid disease poorly controlled on prescribed medications or clinically relevant abnormal thyroid function tests (thyroid-stimulating hormone [TSH], free triiodothyronine [FT3], free thyroxin [FT4]) at screening, as judged by the Investigator.
6. Clinically significant disease other than CHB that, in the opinion of the Investigator, makes the participant unsuitable for the study.
7. Pre-existing cardiac disease that in the opinion of the investigator would increase the risk for the participant to participate in the study.
8. History of alcohol abuse and/or drug abuse within one year of randomization.
9. History of having received (in the last 6 months) or currently receiving any systemic anti-neoplastic (including radiation) or immunosuppressive including biologic immunosuppressors) or immune modulating treatment (including non-biological oral immune modulating drugs e.g., methotrexate > 25 mg per week, azathioprine > 3.0 mg/kg/day or 6-mercaptopurine > 1.5mg/kg/day) for malignant or non-malignant disorders.
10. Currently taking, or have received within 3 months of Day 1, systemic corticosteroids at a high-dose (e.g., 40 mg prednisolone per day for) > 7 days, or a low-dose (e.g., 20 mg prednisolone per day) for > 14 days.

Diagnostic Assessments

11. Electrocardiogram (ECG) with clinically significant abnormalities, including QTcF interval (QT corrected using Fridericia's formula) ≥450 msec for males and ≥470 msec for females at screening.
12. Laboratory parameters at screening:
    a. Hemoglobin < lower limit of normal (LLN); platelets < LLN; international normalized ratio (INR) > 1.1 × ULN.
    b. Albumin < 3 g/dL; total bilirubin > ULN (exception: Gilbert's disease).
    c. Positive results for anti-mitochondrial antibodies (AMA > 1:80), antinuclear antibody (ANA > 1:80), anti–smooth muscle antibody (ASMA > 1:40), or anti-thyroperoxidase antibodies (a-TPO ≥ ULN).
    d. White blood cell count < 2500 cells/mm^3; neutrophil count < 1500 cells/mm^3 (< 1000 cells/mm^3 if considered a physiological variant in a participant of African descent).
    e. Glomerular filtration rate (GFR; using Modification of Diet in Renal Disease [MDRD]) < 60 mL/min.
    f. Positive test for drugs of abuse (including recreational drugs) and/or positive alcohol test at screening. For positive cannabinoids test, the eligibility is at the investigator's discretion.

Prior/Concurrent Clinical Study Experience

13. Previous treatment with an investigational agent for HBV within 6 months prior to screening.
14. Unable to comply with any drugs or nutrients listed in prohibited medications and prohibited food sections in the respective treatment arm appendix.
15. Known hypersensitivity to any excipients of the study drug.

NUMBER OF PARTICIPANTS

Approximately 30 participants will be randomized in each treatment arm. The overall number of participants in this study will depend on the number of treatment arms that are included, which is not known at present.

CONCOMITANT MEDICATIONS

In general, the following concomitant medication are prohibited during the study:

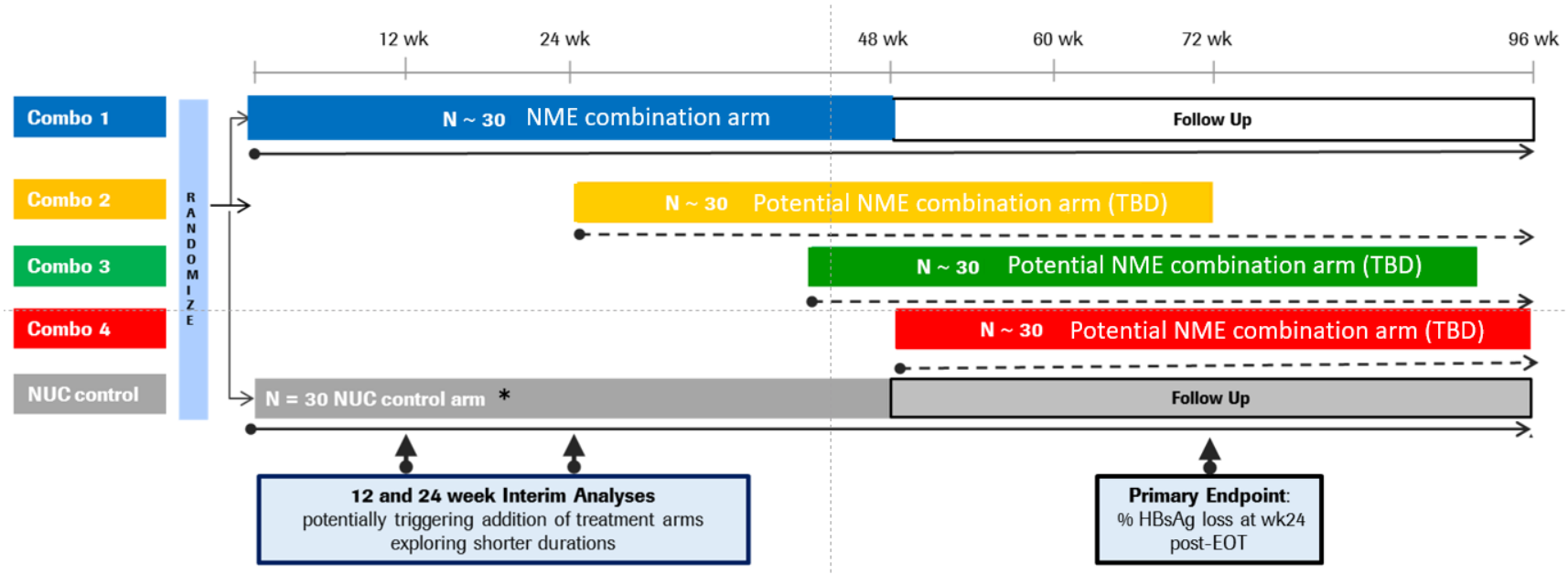
- Systemic immunosuppressive drugs, immunomodulators, cytotoxic or chemotherapeutic agents, radiation therapy.
- Systemic high-dose corticosteroids (e.g., > 40 mg prednisolone per day) > 7 days or low-dose corticosteroids (e.g., > 20 mg prednisolone per day) for > 14 days.

Unless otherwise stated in the respective appendix of each treatment arm, prescribed concomitant medication is not prohibited during the study. Participants should refrain from taking non-prescription medication, unless it is considered necessary by the Investigator.

1.2 SCHEMATIC OF STUDY DESIGN

An overview of the principal elements for the platform study design, including the initial treatment arms, is provided in Figure 1.

Figure 1 Principle Elements of the Planned Platform Study Design



Abbreviations: EOT = end-of-treatment; HBsAg = Hepatitis B surface antigen; NME = new molecular entity; NUC = nucleos(t)ide; TBD = to be determined; wk = week.

*Initially 30 participants. Up to five additional participants per future treatment arm may be randomized to the NUC control arm.

NOTE: This schematic is for illustrative purposes only and demonstrates that treatment duration may be up to 48 weeks, i.e. some arms may have shorter durations of treatment. Treatment duration for each combination arm is detailed in the respective appendix.

1.3 SCHEDULE OF ACTIVITIES

The SoA(s) for each treatment arm is provided in the respective appendix as listed in Appendix 6.

2. INTRODUCTION

2.1 STUDY RATIONALE

Chronic hepatitis B (CHB) virus infection is a major global healthcare problem, with an estimated prevalence of 257 million people (WHO 2018). Nearly 25% of all CHB patients develop serious liver diseases such as cirrhosis and primary hepatocellular carcinoma (HCC). More than 887,000 people die every year due to the consequences of CHB (WHO 2018).

Current treatments reduce the risk of CHB sequelae but are associated with very low rates of functional cure (generally not exceeding 3% after one year of therapy). Due to the therapeutic limitations of the currently available drugs for CHB treatment, there is a need for new treatments of a finite duration that can also yield higher rates of functional cure (Wang and Chen 2014).

Multi-drug therapies with compounds targeting different steps in viral replication or combinations with drugs that restore the innate and/or adaptive host immune responses are presumably more likely to be efficacious than monotherapy. New treatment regimens may be more likely to achieve functional cure by a combination of multiple direct antiviral mechanisms or through the augmentation of anti-hepatitis B virus (HBV) immune responses (Liu et al 2017; Durantel and Zoulim 2016; Lok et al 2017; HBV Forum Nov 15th 2016). Additional strategies to restore anti-HBV T-cell function and further improve the magnitude and durability of the anti-HBV immune response may be required to achieve high rates of functional CHB cure.

The Sponsor intends to identify finite-duration combination therapies including one or more new molecular entities (NMEs) that are associated with high rates of sustained loss of hepatitis B surface antigen (HBsAg < 0.05 IU/mL; functional cure) using the present platform Phase 2 study.

Platform studies have the objective to study multiple therapies in the context of a single disease, with therapies allowed to enter or leave the platform based on availability and emerging data (Woodcock and LaVange 2017). Thus, the Sponsor plans to study combination therapies employing a master protocol, where combination therapies can enter the study in a dynamic manner after obtaining Health Authority (HA)/Ethics Committee (EC) approval of subsequent protocol amendments.

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

2.2 BACKGROUND

2.2.1 Chronic Hepatitis B

Chronic HBV infection (defined as persistent detection of serum HBsAg, the hallmarks of which are high levels of circulating HBV DNA and HBsAg) is a consequence of the presence of a viral reservoir, i.e., episomal covalently closed circular deoxyribonucleic acid (cccDNA) in the nucleus of an infected hepatocyte. Despite advancements in the understanding of HBV disease biology, complete cure, i.e., eradication of cccDNA is not currently possible by available treatments. Nevertheless, the sustained clearance of HBsAg has been shown to protect against disease progression and development of HBV complications including cirrhosis, liver failure, and HCC. Accordingly, functional cure is defined as sustained, undetectable HBsAg in serum and HBV DNA in circulation, with or without seroconversion to anti-HBs, after completion of a finite course of treatment (Lok et al 2017). Partial cure will demonstrate sustained plasma HBV DNA suppression after completion of treatment, but with persistently detectable circulating HBsAg.

Other clinically meaningful endpoints include HBV DNA suppression and alanine aminotransferase (ALT) normalization, which indicate virologic and biochemical responses to therapies, respectively. For hepatitis B e antigen (HBeAg)-positive patients, HBeAg seroconversion is indicative of a better prognosis, including lower rates of cirrhosis and slower disease progression. Sustained suppression of HBV replication, regardless of HBeAg status, is associated with biochemical remission, histological improvement, and reduced risk of disease progression.

2.2.2 Currently Available Therapies

Currently, there are two therapeutic classes available for the treatment of CHB: subcutaneously administered interferon (IFN) preparations (conventional or pegylated interferon-alpha [PEG-IFN-α]) and orally administered nucleos (t)ide analogues (NUCs; tenofovir, entecavir, adefovir, telbivudine, and lamivudine). After 1 year of treatment, both types of treatment can suppress circulating HBV DNA levels (virologic response, 7%-94%), normalize serum liver transaminase enzymes (biochemical response, 32%-83%), and induce HBeAg seroconversion in HBeAg-positive patients (serological response, 10%-32%). Although these treatments reduce the risk of CHB sequelae, they are associated with very low rates of functional cure (HBsAg loss rates generally not exceeding 3% after one year of therapy) (European Association for the Study of the Liver [EASL] 2017).

Furthermore, the existing standard-of-care therapies have important limitations. For example, virologic relapse after treatment discontinuation is a major limitation of currently approved therapies, which rarely result in functional cure. IFN-based therapies have common adverse events of flu-like symptoms and can be associated with treatment-limiting adverse effects (e.g., neutropenia, thrombocytopenia), while NUCs require long-term and possibly lifelong therapy in the majority of treated patients. Given these limitations, there is an unmet need for novel treatments of a finite duration that

yield higher functional cure rates (Liu et al 2017; Durantel and Zoulim 2016; Lok et al 2017; Wang and Chen 2014).

2.3 BENEFIT/RISK ASSESSMENT

This Phase II, platform study is designed to accelerate the development of novel combination regimens by establishing proof-of-concept clinical data in participants with CHB. Enrolment of multiple experimental arms within a single study, rather than one or two experimental arms within multiple studies, will result in an overall reduction in the number of participants receiving control treatment.

The NME combination regimens aim to result in therapeutic benefit for participants, represented by higher functional cure rates than observed with current standard-of-care therapies. For every combination regimen tested, the individual NME has shown acceptable safety/tolerability in Phase I studies, and non-clinical toxicology and safety pharmacology are supportive of its use within a combination regimen. For specific details, refer to the Investigator Brochure of the individual NMEs.

Only participants with preserved liver function and without significant fibrosis/cirrhosis will be enrolled, thus reducing the risk of severe liver-related adverse events. The initial study population will consist of virologically suppressed CHB participants on established NUC therapy. Given NUC therapy is generally administered indefinitely and associated with low rates of functional cure, this population is considered appropriate for studies of novel CHB therapeutic regimens, as highlighted in current guidelines (FDA 2018).

The target and proposed mechanism of action classification for the presently studied investigational medicinal products (IMP) are summarized in Table 2 in Appendix 6. Background information for each treatment arm, including a benefit-risk assessment, is provided in the respective appendix.

3. OBJECTIVES AND ENDPOINTS

This randomized controlled platform study in CHB participants will compare the efficacy and safety of novel combination regimens against a control arm. The primary objective is to compare the functional cure rates assessed at 24 weeks post end-of-treatment (EOT).

The objectives and corresponding endpoints are provided in Table 1.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To estimate the effect of NME combination therapies on inducing a functional cure over the control arm.	• % participants with HBsAg loss at 24 weeks post-EOT.
Secondary [a]	
• To characterize the efficacy profile of NME combination therapies.	• % participants with HBsAg loss • % participants with HBsAg seroconversion. • % participants with HBeAg loss (baseline HBeAg-positive participants). • % participants with HBeAg seroconversion (baseline HBeAg-positive participants). • % participants with HBV DNA < lower limit of quantification (LLOQ), < 200 IU/mL and < 2,000 IU/mL.
• To characterize the PD profile of NME combination therapies.	• Including but not limited to: change from baseline in quantitative HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, HBcrAg, HBV RNA, and HBV DNA levels over time.
• To characterize the plasma PK profiles of NMEs.	• Estimated PK parameters from sparse sampling and population PK models.
• To assess the safety and tolerability of NME combination therapies.	• Incidence, nature, and severity of AEs and laboratory abnormalities.
• To identify presence of PK/PD relationship.	• Analyses of PK/PD data.
• To explore potential effects of ADA on NMEs and/or IMP, as applicable.	• Relationship between ADA status, PK, safety, PD, and efficacy.
Exploratory	
• To characterize the profile of novel viral response markers.	• Profiles and changes from baseline of total HBsAg post-dissociation of HBsAg/HBsAb complexes/components of HBsAg.
• To assess the relationship between baseline disease characteristics and efficacy/safety responses.	• Association between primary and secondary outcomes and HBV genotype (obtained *using* HBV RNA or DNA sequencing *and/or any alternative methodology, and/*or from medical records prior to study entry).
• To assess the association of genetic polymorphisms with the PK profiles of NMEs and/or efficacy/safety primary and secondary endpoints.	• Genetic association with PK parameters and/or primary and secondary endpoints by clinical genotyping.

[a] Efficacy and PD endpoints are assessed at every 12-week time point.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase II, randomized, adaptive, open-label, multi-arm, multi-center, international, platform study (Woodcock et al 2017) designed to evaluate safety, tolerability, and efficacy of new combination therapies including one or more NMEs in CHB participants with preserved liver function and without significant fibrosis/cirrhosis. The platform design allows comparison of multiple new combination therapies against a common control, and introduction of additional treatment arms at later study time points.

This study is designed to be adaptive to open additional shorter duration treatment arms or to expand existing treatment arms for NME combination therapies that show promising efficacy outcomes. The platform design also has the flexibility to open new treatment arms to explore different combination regimens or different participant populations pending new submission and HA/EC approval. Based on emerging data and/or company prioritization of assets, treatment arms may be terminated early or not opened for randomization or certain NMEs in the combination treatment arm might be terminated while therapy is maintained with the remaining NMEs. The Sponsor will notify the Investigator and HA/EC if the study or certain treatment arms or certain NMEs are placed on hold, or if the Sponsor decides to discontinue certain treatment arms or certain NMEs.

Treatment arms may be staggered relative to other treatment arms in order to increase study efficiency with regards to timely interim data readouts or to reduce the complexity of study conduct.

For the first combination, participants will be randomized on Day 1 to an NME combination arm (N=30) or the control arm (N=30) using an adaptive stratified sampling method, stratified at screening HBsAg level ($<$1,000 IU/mL, $\geq$1000 IU/mL), with a minimum of 12 participants per arm with a screening HBsAg level of $<$1000 IU/mL. For NME combination arms that will be introduced later into the platform study, the allocation ratio of participants to the control arm, will depend on the number of actively enrolling arms with the stipulation that no more than 17% of participants will be randomly allocated to a control arm. Additionally, for subsequent arms the proportion of patients with HBsAg level $<$ 1000 IU/mL, $\geq$ 1000 IU/mL within each treatment arm, will be maintained as closely as possible to the first combination treatment arm.

Due to strict lockdowns and restrictions in China in March - May 2022, as of 31 May 2022 approximately 30-53% of participants in each treatment arm have missed study visits and siRNA drug administration at the site. As a result, a number of participants have consecutive visits missed with potential impact on the evaluation of the primary endpoint due to incomplete data. To preserve the viability of the study, if COVID-19 restrictions continue, or any future COVID-19 outbreaks or any force majeure (e.g. natural disasters, supply chain disruption, outbreak of hostilities etc.) impacting participants, will lead to additional participants being recruited to the study to ensure

that the number of participants per treatment arm with the full dose as per the randomized dose regimen remains approximately 30 (see Section 9.2). The maximum number of additional participants to be recruited will be approximately 30 for each treatment arm (see Section 9.2).

Randomization will also take into account arm-specific exclusion criteria of actively enrolling arms. Participants will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (please see arm specific appendix). Details on treatment assignment and randomization are provided in Section 6.4.1

The primary endpoint is the proportion of participants with HBsAg loss at 24 weeks post-EOT as defined in Section 4.4.

The treatment period duration will be a maximum of 48 weeks, after which participants will enter a 48-week follow-up period. Treatment duration may be shortened (12 or 24 weeks) for 48 week NME combination arms, and/or a response-guided therapy (RGT) arm may be added following planned interim analyses; up to four planned interim analyses will be conducted for each treatment arm (see Section 9.5). Treatment arms that achieve 30% difference, compared to NUC control arm, for HBsAg loss at EOT or follow-up Weeks 12 and 24 (primary endpoint) may be expanded to accrue additional efficacy and safety data and to contribute to Phase 3 design planning as guided by the emerging data, for example, enrichment for HBeAg positive or HBeAg negative participant populations. An expansion may also be triggered prior to EOT, for a treatment arm that gives an early indication of efficacy. The decision criteria to trigger an expansion arm in this case, will be documented as an appendix to the IMC/Scientific Oversight Committee (SOC) charter.

An overview of the study design is provided in Section 1.2. Details on the planned treatment arms are provided in Appendix 6.

4.1.1 Length of the Study

The total length of the study, from screening of the first participant to the end-of-study (see Section 4.4), is expected to be approximately 3 to 5 years, depending on the number and timing of additional treatments arms that are added to the study.

The study duration for each participant will be approximately 2 years divided as follows:

- Screening period: up to 8 weeks.
- Treatment period: up to 48 weeks.
- Safety follow-up period: 48 weeks.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study design rationale is provided in Section 4.1.

4.2.1 Rationale for Study Population

The study will enroll CHB participants with preserved liver function and without significant fibrosis/cirrhosis, thus reducing the risk of liver-related adverse events.

The initial participant population consists of virologically suppressed adult CHB participants on established NUC therapy, which current guidelines recommended as an appropriate study population for early phase clinical studies for CHB (FDA 2018).

4.2.2 Rationale for Control Treatment arm

The control arm is considered necessary to generate a within-study comparator dataset in order to evaluate the magnitude of treatment effects within the combination treatment arms.

4.2.3 Rationale for Biomarker Assessments

HBV Dynamic Biomarkers

Functional CHB cure is defined as the sustained, undetectable serum HBsAg (defined as < 0.05 IU/mL) and HBV DNA in plasma, with or without seroconversion to anti-HBs, after completion of a finite course of treatment (Lok et al 2017). Therefore, the main virological endpoint in this study relies on measuring HBsAg and HBV DNA at time points defined in the SoAs (the SoA(s) for each treatment arm is provided in the respective appendix as listed in Appendix 6).

Additional well-established HBV dynamic biomarkers for the assessment of HBV treatment outcomes will include the time course of anti-HBs levels and the evolution of HBeAg and anti-HBe status. In participants that are HBeAg positive at study entry, a validated research-use-only (RUO) semi-quantitative assay may be used to follow the time course of serum HBeAg levels over time. In order to avoid a potential loss of sensitivity of HBsAg detection due to the formation of HBsAg/anti-HBs complexes, an assay is being developed by the Sponsor that may be used in some participants to measure HBsAg independently of the putative formation of complexes, i.e. total HBsAg post-dissociation of HBsAg/HBsAb complexes/components of HBsAg, as appropriate.

Several HBV biomarkers have recently emerged in the field that may further support the demonstration of improved virus control and the achievement of HBV cure. Results from these novel biomarkers will not have an impact on any clinical decisions or other endpoint evaluation.

Among these, pregenomic HBV RNA that bypasses reverse transcription and is released in plasma may provide a direct measure of the transcriptional activity of cccDNA. Consistent with this view, in NUC-treated participants with suppressed HBV DNA, the presence of detectable circulating HBV RNA signals an increased probability of HBV DNA rebound upon NUC cessation (Wang et al 2016; Fan et al 2020; Seto et al 2020; Kaewdech et al 2020). In the course of this study, a validated real-time polymerase

chain reaction-based RUO assay may be used to quantify the ability of NME combinations to affect HBV RNA.

Circulating hepatitis B core-related antigen (HBcrAg) levels provide one additional biomarker that could support demonstration of the achievement of HBV cure. HBcrAg is a composite circulating biomarker comprising HBcAg (core antigen, which is part of HBV virions), HBeAg (which arises from the same open reading frame as HBcAg and is secreted), and p22cr (precore protein). Emerging data correlate HBcrAg measurements with cccDNA levels and activity and HBV treatment outcomes (Mak et al 2018; Chen et al 2017; Inoue and Tanaka 2020; Li et al 2020). In the course of this study, a validated RUO method based on a quantitative enzyme-linked immunosorbent assay may be used to quantify HBcrAg in serum.

Antibodies against HBcAg (anti-HBc) are the first to appear during the acute phase of infection. The IgM anti-HBc levels will gradually disappear and be followed by the production of IgG anti-HBc. Novel assays for the quantification of IgG or total anti-HBc have been developed. The levels of this biomarker have been shown to vary through the different phases of the cHBV infection. They are higher during the immune clearance and reactivation phases than during the immune tolerance and inactive carrier phases. Moreover, high levels of IgG or total anti-HBc correlated with a higher rate of HBeAg seroconversion in HBeAg-positive patients treated with NUCs. In the course of this study, a validated RUO method may be used to quantify total anti-HBc in serum (Jia et al 2014; Yuan et al 2013; Fan et al 2016).

The initial participant population recruited in this study will be established on effective NUC therapy at study entry and will have circulating HBV DNA levels below the assay lower limit of quantification (defined as below 20 IU/mL) for at least 6 months, confirmed at screening. Response to therapy aiming at functional cure could potentially be modulated by HBV genotype. To determine HBV genotype in participants with undetectable HBV DNA, Sanger or deep sequencing may be attempted in some participants using amplified HBV RNA from a plasma sample collected at Day 1 or at any follow-up time point, as appropriate. *The HBV genotype may also be inferred using alternative approaches, such as serovariant determination.*

HBV DNA Monitoring

During the course of the study, participants will be monitored to ensure that HBV DNA suppression is maintained. Participants who experience HBV DNA breakthrough while having NUC therapy, with or without administration of a combination of NMEs, will need to attend a clinic visit for repeat testing. If the HBV DNA level is confirmed to be more than 100 IU/mL or 1-log above nadir, the participants will be assessed for evidence of drug resistance using sequencing and potentially phenotyping. The sample will also be

used to determine the HBV genotype and a pharmacokinetic (PK) sample will be collected.

Finally, participants who have been taken off the combination of NMEs and the NUC therapy will have their HBV DNA monitored every 2 weeks *for the first 3 months and monthly thereafter* until 48 *weeks* post-EOT. If the HBV DNA level rises, participants will be monitored and *managed in case of* virological relapse *as per Section 8.3.8.2* and an unscheduled blood sample will be collected for potential characterization of the HBV genome and where feasible phenotyping (see Sections 8.7.2 and 8.7.3).

4.3 JUSTIFICATION FOR DOSE

Refer to the respective appendix of each treatment arm for details.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the last study visit. The end-of-study is defined as the date when the last participant completes the last visit (LPLV).

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The study will enroll CHB participants with preserved liver function and without significant fibrosis/cirrhosis.

The initial study population will consist of virologically suppressed CHB participants on NUC therapy between 18 and 65 years of age, inclusive, who fulfil all of the study eligibility criteria. Additional participant populations (e.g., treatment naïve CHB participants) may be explored within the study in treatment arms to be added at a later date pending new submission and HA/EC approval.

Prospective approval of protocol deviations from eligibility inclusion/exclusion criteria, also known as protocol waivers or exemptions are not permitted.

Any treatment arm-specific inclusion/exclusion criteria defined in the corresponding appendix (of actively recruiting arms), takes precedence over the inclusion/exclusion criteria defined in Section 5.1 and Section 5.2.

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 Council for Harmonization (ICH) and local regulations.

Age

2. Participants must be between 18 and 65 years of age, inclusive, at the time of signing the informed consent.

Weight

3. Body mass index between 18 and 32 kg/m^2 inclusive.

Type of Participants and Disease Characteristics

4. Participants with CHB infection (HBsAg positive for ≥6 months) who are on NUC (entecavir or tenofovir alafenamide/disoproxil fumarate) monotherapy for ≥12 months, having received the same NUC therapy for ≥ 3 months prior to screening.
5. HBV DNA below the LLOQ or < 20 IU/mL for > 6 months prior to screening and confirmed at screening.
6. Alanine transaminase (ALT) ≤1.5 x upper limit of normal (ULN) for > 6 months prior to screening, and confirmed at screening
7. Screening laboratory values (hematology, chemistry, urinalysis) within normal range, or judged not clinically significant by the Investigator.

Sex

8. Male and female participants:

The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for 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 fetal/embryonic drug exposure.

The following contraception requirements must be followed unless otherwise stated in the respective appendix of each treatment arm.

a) Female Participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- Woman of non-childbearing potential (WONCBP), as defined in Appendix 5.
- Woman of childbearing potential (WOCBP), who:

– Agrees to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the final dose of study treatment. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal occlusion, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices (see Appendix 5).

– Has a negative pregnancy test at screening (Day -14 to -7). In addition, WOCBP must be willing to undergo a urine pregnancy test every 3 months until the end of study.

b) Male Participants:

During the treatment period and for at least 6 months after the final dose of study treatment, agree to:

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

Please refer to the respective appendix of each treatment arm for additional or more stringent treatment-related inclusion criteria that must be checked in all participants before randomization if any arm requiring additional inclusion criteria is open for recruitment. See Table 3 in Appendix 6 for the list of applicable exclusion criteria.

5.2 EXCLUSION CRITERIA

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

Medical Conditions

1. Pregnant (positive pregnancy test) or lactating women.
2. Co-infection with other pathogens such as hepatitis A (HAV), hepatitis C (HCV), hepatitis D (HDV), hepatitis E (HEV), or human immunodeficiency virus (HIV).
3. History of cirrhosis or current evidence of significant liver fibrosis or cirrhosis (F3 or above on liver biopsy, ≥ 7.4 kPa on transient elastography, > 1.32 m/s on acoustic radiation force impulse [ARFI] elastography, or > 3.13 kPa on magnetic resonance [MR] elastography or > 7.1 kPa on 2D-shear wave elastography [2D-SWE]), or decompensated liver disease (e.g., ascites, hepatic encephalopathy). Liver biopsy or transient elastography/ARFI/MR result must be obtained within 6 months prior to randomization.

4. History of or suspicion of hepatocellular carcinoma (HCC) (e.g., elevated α-fetoprotein [AFP] levels, suggestive lesions on abdominal ultrasound or other imaging, etc.).
5. Thyroid disease poorly controlled on prescribed medications or clinically relevant abnormal thyroid function tests (thyroid-stimulating hormone [TSH], free triiodothyronine [FT3], free thyroxin [FT4]) at screening, as judged by the Investigator.
6. Clinically significant disease other than CHB that, in the opinion of the Investigator, makes the participant unsuitable for the study.
7. Pre-existing cardiac disease that in the opinion of the investigator would increase the risk for the patient to participate to the study.
8. History of alcohol abuse and/or drug abuse within one year of randomization.
9. History of having received (in the last 6 months) or currently receiving any systemic anti-neoplastic (including radiation) or immunosuppressive (including biologic immunosuppressors) or immune modulating treatment (including non-biological oral immune modulating drugs; e.g., methotrexate > 25 mg per week, azathioprine > 3.0 mg/kg/day or 6-mercaptopurine > 1.5 mg/kg/day) for malignant or non-malignant disorders.
10. Currently taking, or have received within 3 months of Day 1, systemic corticosteroids at a high-dose (e.g., 40 mg prednisolone per day for) > 7 days, or a low-dose (e.g., 20 mg prednisolone per day) for > 14 days.

Diagnostic Assessments

11. Electrocardiogram (ECG) with clinically significant abnormalities, including QTcF interval (QT corrected using Fridericia's formula) ≥450 msec for males and ≥470 msec for females at screening.
12. Laboratory parameters at screening:
    a) Hemoglobin < lower limit of normal (LLN); platelets < LLN; international normalized ratio (INR) > 1.1 × ULN.
    b) Albumin < 3 g/dL; total bilirubin > ULN (exception: Gilbert's disease).
    c) Positive results for anti-mitochondrial antibodies (AMA > 1:80), antinuclear antibody (ANA > 1:80), anti–smooth muscle antibody (ASMA > 1:40), or anti-thyroperoxidase antibodies (a-TPO ≥ ULN).
    d) White blood cell count < 2500 cells/mm^3; neutrophil count < 1500 cells/mm^3 (< 1000 cells/mm^3 if considered a physiological variant in a participant of African descent).
    e) Glomerular filtration rate (GFR; using Modification of Diet in Renal Disease [MDRD]) < 60 mL/min.
    f) Positive test for drugs of abuse (including recreational drugs) and/or positive alcohol test at screening. For positive cannabinoids test, the eligibility is at the Investigator's discretion.

Prior/Concurrent Clinical Study Experience

13. Previous treatment with an investigational agent for HBV within 6 months prior to screening.
14. Unable to comply with any drugs or nutrients listed in prohibited medications and prohibited food sections in the respective treatment arm appendix.
15. Known hypersensitivity to any excipients of the study drug.

Please refer to Table 3 in Appendix 6 for the list of applicable inclusion/exclusion criteria and check the respective appendix of each treatment arm for additional treatment-related inclusion/exclusion criteria that must be checked in all participants before randomization if any arm requiring additional exclusion criteria is open for recruitment.

All eligibility decisions are made by the Investigator. The Medical Monitor is available to the Investigator to answer any medical questions.

5.3 LIFESTYLE CONSIDERATIONS

Alcohol intake should be strongly discouraged, but limited intake is allowed, when in agreement with the Investigator. Refer to the respective appendix of each treatment arm for treatment-related details.

5.4 SCREEN FAILURES

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

If a subject fails an inclusion/exclusion criterion due to a transient and non-clinically significant condition at screening, the Investigator may repeat the relevant assessment(s) within the screening period. If the subject fails a second time, they will be classified as a screen failure.

Re-screening is allowed for participants who were screened in the study and met all study inclusion/exclusion criteria within both screening visits (Day -56 to -7 and Day -14 to -7) but failed to be subsequently randomized within the screening period. In order to re-screen such a subject, all inclusion and exclusion criteria should be re-evaluated and all applicable screening assessments repeated. With the exception of the eye examination if randomization will occur within 6 months from the last examination.

In some instances, participants who did not meet the inclusion/exclusion criteria during the screening period (including those following re-testing) and were registered as screen failures in the IxRS system, can be re-screened and will be treated as new participants provided the new screening informed consent form (ICF) signature date is at least 6 months after the previous screen failure date. In order to re-screen such a subject, all

inclusion and exclusion criteria should be re-evaluated and all applicable screening assessments repeated.

Re-screened participants are required to sign a new ICF and will be assigned a new screening number.

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

6. STUDY TREATMENTS

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

All IMPs required for completion of this study will be provided by the Sponsor. All non-investigational medicinal products (NIMPs) required for completion of this study will be either provided or reimbursed by the Sponsor.

6.1 TREATMENTS ADMINISTERED

Refer to the respective appendix of each treatment arm for details.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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

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

The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and contents. Any damaged shipments will be replaced.

Upon arrival of the IMPs at the site, site personnel will complete the following:

- Check the IMPs for damage.
- Verify proper identity, quantity, integrity of seals, and temperature conditions.
- Report any deviations or product complaints to the Study Monitor upon discovery.

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

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored

in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

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

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

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.4 TREATMENT COMPLIANCE

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

Each participant will be provided with a paper and/or an electronic medication diary. It is mandatory that each treatment which is self-administered is recorded in the diary, including any modified/missed doses and their reason. Participants must bring completed drug diaries to each visit during the treatment period to be reviewed by the investigator. Each modified/missed dose must be recorded on the eCRF.

6.4.1 Method of Treatment Assignment

This is an open-label study; however, the specific treatment to be taken by a participant will be assigned using an Interactive Voice/Web Response System (IVRS/IWRS). Potential selection bias due to the open-label status of this study will be reduced by the use of central randomization. The site will contact the IVRS/IWRS prior to the start of study treatment administration for each participant. The site will record the treatment assignment on the applicable electronic case report form (eCRF), if required.

This study will use an adaptive stratified sampling method, minimization, for randomization. The first participant will be allocated a treatment at random; the treatment allocated to the next participant will be dependent on the characteristics of those

participants already enrolled with the aim of minimizing the imbalance within each stratification level (screening HBsAg level $<$ 1000 IU/mL vs. $\geq$ 1000 IU/mL). A minimum of 12 participants per arm with a screening HBsAg level of $<$ 1000 IU/mL is required.

For treatment arms starting at later study time points, the ongoing central randomization to the control arm ensures any potential selection bias is minimized, specifically, if there is only one treatment arm recruiting. The subsequent randomization ratio will depend on the number of experimental treatment arms that are open for recruitment with the condition that no more than 1/6th (0%-17%) of the participants will be randomly allocated to the control arm at a given time. Additionally, for subsequent arms the proportion of HBsAg level $<$ 1000 IU/mL or $\geq$ 1000 IU/mL within each treatment arm will be maintained as closely as possible to the first combination treatment arm.

Randomization will also take into account arm-specific exclusion criteria of actively enrolling arms. Participants will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (please see arm specific appendix). The arm-specific exclusion criteria will specifically relate to safety due to the molecule's Mechanism of Action (MOA); therefore, it is not expected to introduce any bias in the efficacy outcome. However, a flexible cap will be added to the other recruiting arm(s) to control the number of participants being randomized to these arms, in order to maintain the element of randomization to the end of the randomization period.

Expansion arm/s (of a treatment arm that shows promising efficacy outcomes): If only one expansion arm is open at the time, eligible participants will be enrolled in that arm. If two or more expansion arms are enrolling at one time, a fixed permuted block randomization will be used to allocate participants to arms.

As an additional step to minimize bias, on-treatment and off-treatment virology data (HBV DNA excluded) will not be routinely available to sites, and they will be stored in a restricted data repository for access by the IMC Biometricians. During study conduct, aggregated summaries of data will only be available to the IMC and SOC. However, other members of the Sponsor may have access to aggregated summaries/virology data to assist with decision making, as considered necessary by the IMC.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) and any non-medication interventions (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, rehabilitative therapy) used by a participant from 30 days prior to screening until the follow-up visit must be recorded in eCRF along with reason for use, dates of administration (including start and end dates), and dosage information (including dose and frequency).

The Medical Monitor should be contacted for advice if there are any questions regarding concomitant or prior therapy. All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF. All therapy and/or medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

6.5.1 Permitted Therapy

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Paracetamol/acetaminophen, at doses of up to 2 g/day, is permitted for use any time during the study.

6.5.2 Administrative Structure

For information on the Internal Monitoring Committee (IMC) and *Scientific Oversite Committee* (SOC), please refer to Appendix 1.

6.5.3 Prohibited Therapy

In general, the following concomitant medication are prohibited during the study:

- Systemic immunosuppressive drugs, immunomodulators, cytotoxic or chemotherapeutic agents, radiation therapy.
- Systemic high-dose corticosteroids (e.g., > 40 mg prednisolone per day) > 7 days or low-dose corticosteroids (e.g., > 20 mg prednisolone per day) for > 14 days.

Unless otherwise stated in the respective appendix of each treatment arm, prescribed concomitant medication is not prohibited during the study. Participants should refrain from taking non-prescription medication, unless it is considered necessary by the Investigator.

6.6 DOSE MODIFICATION

Please refer to the respective appendix for each treatment arm for dose modification or interruption guidelines.

6.7 TREATMENT AFTER THE END OF THE STUDY

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

6.8 CRITERIA FOR STOPPING NUCLEOSIDE ANALOGUE

Participants who complete the treatment period will stop NUC *therapy* if laboratory results on samples taken at end-of-treatment or at any of the follow-up visits show:

- ALT $<1.25\times$ baseline values, AND
- HBV DNA < LLOQ or <20 IU/mL, AND
- negative HBeAg, AND
- HBsAg <100 IU/mL *and* $\geq 1\ log_{10}$ *IU/mL decline from baseline or HBsAg loss*.

These criteria for stopping NUCs do not apply to any patients who have discontinued study drug prematurely for any reason.

7. DISCONTINUATION OF STUDY TREATMENT, PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY AND LOST TO FOLLOW-UP

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

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.

7.1 DISCONTINUATION/INTERRUPTION OF STUDY TREATMENT

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

- Participant withdrawal of consent at any time
- Participant non-compliance with study requirements
- Any medical condition or AE/laboratory abnormalities 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

- CHB disease progression (e.g., development of liver cirrhosis or liver decompensation)
- Confirmed virological breakthrough

For management of virological breakthrough see Section 8.3.8.1; for ALT elevations see Section 8.3.8.3, and for NME-related adverse events refer to the respective appendix of each treatment arm for details.

Before permanently discontinuing study treatment (regardless of whether initiated by the participant, the Investigator, or the Sponsor), an interruption should be considered. Unless otherwise stated in the respective appendix of each treatment arm, participants who have temporarily interrupted study treatment should be considered to restart as soon as medically justified in the opinion of the Investigator. The Medical Monitor is available to the Investigator to answer any medical questions.

Table 2 below serves as a reference guide for the reasons of study treatment discontinuation/interruption which may occur in the study.

Table 2 All Combination Arms: General Criteria for Dose Interruptions/Discontinuations for All New Molecular Entities

Laboratory/Clinical Parameters	Recommendation	Reference
Liver transaminases and liver function test		
ALT elevation >10 × ULN (with preserved hepatic function)	**Interrupt** NMEs, continue NUC. Resume NMEs when ALT <3 × ULN (case-by-case basis)	Section 8.3.8.3
ALT >3 × ULN accompanied by declining liver function (total bilirubin >2 × ULN, or INR >1.5 or albumin <3.0 g/dL), or other signs of hepatic impairment	**Discontinue** NMEs, continue NUC. Investigate the etiology and including potential DILI	
Virological breakthrough		
Confirmed virological breakthrough	**Discontinue** NMEs and continue treatment according to local standards	Section 8.3.8.1
Others (excluding consent withdrawal and non-compliance)		
Any clinically-significant AEs or laboratory abnormalities that in the opinion of Investigator may be related to NME(s)	**Interrupt** NME(s) until AEs/laboratory abnormalities are resolved. Re-introduce NME(s) (on a case-by case basis, which may be at a modified dose if deemed necessary)	Section 7.1
Any medical condition or AE/laboratory abnormalities that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study	**Discontinue** NMEs, continue NUC	
Sponsor or Investigator determination that treatment discontinuation is the best interest for the participant		
Pregnancy		
CHB disease progression		

Every effort should be made to obtain information on participants who withdraw from the treatment but have not withdrawn from the study. Participants who permanently discontinue study treatment will be asked to return to the clinic for an unscheduled/early

termination visit and will undergo follow-up assessments. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF.

Participants, who permanently discontinue study treatment as part of an early termination of a treatment arm due to Sponsor's decision, will undergo safety follow-up assessments as described in Appendix 6. For participants who are in treatment arms NOT terminated by the sponsor, will proceed as planned and undergo follow up as per the SOA of the respective treatment arm.

Participants who discontinue study treatment due to non-safety reasons may be replaced.

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 the 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).

See the SoA (the SoA for each treatment arm is provided in the respective appendix as listed in Appendix 6) for data to be collected at the time of study discontinuation, at safety and follow-up visits, and for any further evaluations that need to be completed.

7.3 LOST TO FOLLOW-UP

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

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

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

Discontinuation of sites or of study as a whole is described in Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time points are summarized in the SoA (the SoA(s) for each treatment arm is provided in the respective appendix as listed in Appendix 6). Protocol waivers or exemptions are not allowed.

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

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.

Mobile nursing (MN) services (e.g., home visits, study drug administration, vital signs, laboratory sample collection, etc.) may be offered to sites and patients who express interest in these services and which may benefit the study conduct, as per local regulations. The Sponsor will select a healthcare company that will be responsible for providing MN services for the participating sites (MN vendor), and details regarding the services provided will be described in the MN Manual. Patient participation with MN services will be optional and will require signing of an additional MN ICF that will detail the specifics of these mobile services.

All residual laboratory samples (e.g., safety laboratory, PK, PK/PD, biomarker, immunogenicity, etc.) may be used to repeat laboratory tests in the event of a problem with the original sample as outlined in the SoA. Additionally, the residual samples may be used for HBV biomarker analyses to further understand disease biology and treatment impact, where country regulations allow it. This may include, but is not limited

to, analysis of viral and host response factors (DNA and/or non-DNA) to infection and treatment, development/validation of HBV assays, and immunogenicity analyses.

Unless otherwise specified below, all residual samples (including blood, slides, extracts, etc.) will be destroyed within 5 years after the date of final CSR. For participants who provide additional consent to the optional RBR, and where country regulations allow it, leftover samples will be transferred to RBR (see Section 8.9).

8.1 EFFICACY ASSESSMENTS

Efficacy assessment endpoints are measured through markers of antiviral activity in the study. Blood samples will be taken at defined time points (the SoA[s] for each treatment arm is provided in the respective appendix as listed in Appendix 6) to monitor viral markers and study their correlation with administered doses and PK data.

The primary efficacy parameter is the incidence of HBsAg loss (i.e., defined as HBsAg < 0.05 IU/mL) at 24 weeks post-EOT. Additional parameters include the change in HBsAg and anti-HBs over time, incidence, and timing of HBsAg and anti-HBs seroconversion, changes in HBeAg and anti-HBe status in the course of the study. Other efficacy biomarkers including changes in HBV DNA, HBcrAg, anti-HBc, total HBsAg (post-dissociation of HBsAg/HBsAb complexes/components of HBsAg), and HBV RNA levels may be measured, as appropriate.

The efficacy assessments will include all participants in the efficacy analysis population analyzed according to the treatment arm and dose schedule to which they are randomized (see Section 9.3).

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (the SoA[s] for each treatment arm is provided in the respective appendix as listed in Appendix 6).

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest; 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.

Refer to arm-specific appendices for combination specific safety assessments.

8.2.1 Physical Examinations

A complete physical examination will be conducted at screening and at the end-of-treatment period, and will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological, neurological, and musculoskeletal systems.

Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF.

At other visits, limited, symptom-directed physical examinations should be performed when clinically indicated. Changes from baseline abnormalities should be recorded in participants' notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Height will be recorded at screening. Weight will be recorded at screening, Day 1, and every 12 weeks thereafter during the treatment period *(or as outlined in the treatment arm specific appendix).*

8.2.2 Vital Signs

Vital signs (temperature, pulse rate, respiratory rate, and blood pressure) will be assessed after the participant has been resting in a supine or sitting position for a period of at least 5 minutes prior to a blood draw or at least 10 minutes following a blood draw. Blood pressure (systolic and diastolic), pulse rate, respiratory rate and body temperature (oral or tympanic) will be recorded at the time points specified in the SoA tables within the respective appendix of each treatment arm.

Blood pressure and pulse measurements will be assessed with a well-calibrated automatic instrument with a digital readout in triplicate. The mean of the triplicate recordings will be used for the time point result. Manual techniques will be used only if an automated device is not available. When measuring blood pressure, the participant's arm should be unconstrained by clothing or other material and the individual should be comfortably seated, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum). The ideal cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1).

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (the SoA[s] for each treatment arm is provided in the respective appendix as listed in Appendix 6) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. To minimize variability, it is important that participants be in a resting position for at least 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 case of an absolute QTc of > 500 msec, and/or an increase from baseline QTc > 60 msec, a triplicate ECG must be recorded within the next 5 minutes. It may be appropriate to

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

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

ECG characteristics, including heart rate, QRS duration, and PR, and QT intervals, will be recorded on the eCRF. QTcF (Fridericia's correction) and RR will be calculated/recorded on the eCRF. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented. 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 Liver Imaging Assessments

Abdominal hepatic ultrasound will be conducted at screening and during the study as outlined in the SoA (the SoA(s) for each treatment arm is provided in the respective appendix as listed in Appendix 6) for HCC surveillance, as participants with CHB are at risk of disease progression to liver cirrhosis and/or developing HCC.

Staging of liver fibrosis will be conducted at screening in order to exclude participants with significant fibrosis/cirrhosis (Metavir F3/F4). Liver biopsy or transient elastography/ARFI/MR results obtained within 6 months prior to randomization are also acceptable. Acceptable non-invasive assessments for staging degree of fibrosis for this study includes transient elastography (Fibroscan) (Li et al 2018), acoustic radiation force impulse (ARFI) elastography (Dong et al 2015), and magnetic resonance (MR) elastography (Huwart et al 2008).

Of the above, liver stiffness measurement using transient elastography has been widely accepted in the assessment and staging of liver fibrosis. Transient elastography should be performed on a participant lying supine with the right arm elevated to facilitate access to the right liver lobe. A participant has to be in fasted state. At each assessment, at least 10 valid measurements should be taken and the following results recorded:

- No. of readings taken & reading success rate (n, %)
- Median stiffness (kPa)
- Interquartile range / IQR (kPa)
- Controlled attenuation parameter (CAP), if available

The final result of a transient electrography assessment can be regarded as valid if the number of valid readings is ≥10, the success rate (ratio of valid readings to total number

of readings) is > 60%, and the IQR (reflecting variability of measurements) is less than 30% of the median liver stiffness measurements (EASL-ALEH 2015).

8.2.5 Clinical Safety Laboratory Assessments

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 (the SoA(s) for each treatment arm is provided in the respective appendix as listed in Appendix 6). Normal ranges for the laboratory parameters must be supplied to the Sponsor if local laboratory is used.

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 that 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 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.

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

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

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

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

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

8.2.6 Medical History and Demographic Data

Medical history includes clinically significant diseases (e.g., cancer), history of surgery, reproductive status, smoking habits, use of alcohol and drugs of abuse, and all prescribed or OTC medications used by the participant within 30 days prior to the screening visit.

For all participants, the detailed HBV history will be documented including date of HBV diagnosis, any previous assessment of liver fibrosis (including date and outcome of any liver biopsy), HBV genotype (if documented), and all previous HBV treatment and outcomes of treatment including occurrence of any NUC resistance.

Demographic data will include age, sex, and self‑reported race/ethnicity. The information about race/ethnicity of CHB participants is important because host genetics may modulate responses to study treatments. In addition, the information can be used to infer the likely HBV genotype where genotype information has not been obtained in routine clinical care, which is a common circumstance. There are different HBV variants with geographical distribution (Tanwar et al 2012; Sunbul et al 2014) that show different transmission modalities (e.g., vertical, in childhood, in adulthood), disease course, and response to treatment. The relevance of HBV genotypes is that HBV genotypes have a distinct geographical distribution and are known to influence clinical and virological parameters to treatment responses to IFNα (Rajoriya et al 2017).

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

The Investigator and any qualified designees are responsible for ensuring that all adverse events (including assessment of seriousness, severity and causality (see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2. Procedures used for recording adverse events are provided in Appendix 3.

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

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

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

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

After initiation of study treatment, all adverse events, regardless of relationship to study treatment, will be reported until the last follow-up visit.

Post-study adverse events and serious adverse events: The Investigator is not required to actively monitor participants for adverse events after their last follow-up visit.

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

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

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

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

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

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

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

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

8.3.3.2 Sponsor Follow-Up

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

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE is essential (i.e., no more than 24 hours after learning of the event) so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

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

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

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

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

8.3.4.1 Emergency Medical Contacts

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

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study.

Male participants will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 6 months 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, and ectopic pregnancy) are considered SAEs (Appendix 5).

8.3.6 Adverse Events of Special Interest

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

Adverse events of special interest for this study include the following:

- Cases of elevated ALT or AST (> 3 × ULN and > 3 × baseline) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice (Potential Hy's law)
- ALT or aspartate aminotransferase (AST) elevations ≥ 10 × ULN
- 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.
- Grade ≥3 hematology lab abnormalities (e.g., lymphopenia, neutropenia, leukopenia)
- Severe/serious injection site reactions and/or injection reactions

8.3.7 Disease-Related Events Not Qualifying as Adverse Events

The following disease-related events (DREs) can be observed in participants with CHB:

- ALT or AST increase < 10 × ULN with preserved hepatic function

Because these events may be associated with the disease under study, they should not be reported according to the standard process for AEs. ALT increase > 3 × ULN should be managed according to Section 8.3.8.3.

8.3.8 Management of Specific Adverse Events

8.3.8.1 Management of Virological Breakthrough

Participants with suspected virological breakthrough (HBV DNA > 100 IU/mL or > 1-log increase from nadir) during treatment will attend a study visit (scheduled or unscheduled) within 2 weeks for:

- a confirmatory test of HBV DNA and plasma drug levels
- thorough evaluation of adherence and factors that may be affecting treatment compliance

If virological breakthrough is confirmed:

- the sample will be further tested for HBV genome characterization through HBV DNA sequencing and where feasible phenotyping
- NMEs will be discontinued
- The investigator will manage the CHB participant's NUC treatment, according to current guidelines and local regulations (guided by participant's treatment history, assessment of adherence, HBV DNA levels, and any available result of drug resistance testing).

8.3.8.2 Management of Virological Relapse

Participants who have discontinued all study treatments (NME combinations) including NUC therapy should be followed up every 2 weeks for first 12 weeks, thereafter monthly up to week 48 of the follow up period to enable early detection of HBV DNA rebound and appropriate management of virological relapse.

In addition, participants with HBV DNA > 20 IU/mL but < 2,000 IU/mL in follow-up, should undergo monitoring every two weeks.

Participants who discontinue all study treatment (NME combination and NUC therapy *for the treatment arms or NUC therapy for the NUC control arm*) and subsequently experience virological relapse (HBV DNA > 2,000 IU/mL) during the follow-up period will undergo weekly monitoring: an unscheduled blood sample will be collected for potential HBV genome characterization and where feasible phenotyping.

NUC therapy *should* be restarted *in the following scenarios:*

- *HBV DNA > 20,000 IU/mL (regardless of other biochemical parameters or ALT values)*
- *HBV DNA > 2,000 IU/mL and ALT >1.5 x ULN*
- *HBV DNA > 2,000 IU/mL and ALT ≤ 1.5 x ULN and if the retest (central or local laboratory) of HBV DNA performed within 1 week after availability of the initial results from the central laboratory confirms HBV DNA > 2,000 IU/mL (regardless of ALT values or other biochemical parameters)*
- *Immediately restart treatment in participants with clinically significant signs of decreasing liver function based on laboratory findings (e.g., INR, direct bilirubin) or clinical assessments (e.g., ascites, hepatic encephalopathy) regardless of HBV DNA or ALT levels.*

For these additional unscheduled monitoring visits, the following laboratory assessments should be performed using the unscheduled lab kit: hematology, chemistry, coagulation, GLDH, urinalysis, HBV serology, HBV DNA quantitative, Total HBsAg, HBcrAg, and HBV RNA quantitative.

Note: The guidance for the management of virological relapse (frequency of monitoring, laboratory assessments, NUC restarting rules) described in this section should be followed in conjunction with the guidance for the management of elevated ALT levels described in Section 8.3.8.3.

8.3.8.3 Management of Elevated Alanine Aminotransferase (ALT) Levels

The initial study population consists of CHB participants who are virally suppressed following > 12 months of NUC treatment. The majority of these participants (90%) have normal ALT levels, while approximately 10% have ALT levels within 1–2 × ULN at baseline (Marcellin et al 2019).

For this study, close monitoring will be initiated if ALT elevations exceed > 3 × ULN.

ALT elevations during treatment

- ALT elevation with preserved hepatic function (e.g., no significant changes in bilirubin, International Normalized Ratio [INR]/prothrombin time [PT], albumin, and/or alkaline phosphatase [ALP]):
  - ALT 3–10 × ULN: *Repeat ALT, LFTs (including total bilirubin, direct bilirubin, AST, ALP, albumin), coagulation (INR, PT), and PD parameters (HBV DNA, HBsAg, quantitative HBeAg) every week until ALT< 3 × ULN.
  - ALT > 10 × ULN: Immediately interrupt NMEs and continue NUC treatment. *Repeat ALT, LFTs, coagulation, and PD parameters #twice weekly until ALT level < 10 × ULN, then weekly until ALT < 3 × ULN. Consider re-introducing NME therapy on a case-by-case basis based on subsequent lab results. The Medical Monitor is available to the Investigator to answer any medical questions.
- ALT elevation accompanied by declining liver synthetic and excretory functions (total bilirubin > 2 × ULN, or albumin < 3.0 g/dL, or INR > 1.5) or other signs of hepatic impairment (severe fatigue, vomiting):
  - Immediately discontinue NMEs and continue NUC treatment.
  - *Repeat ALT, LFTs, Coagulation, and PD parameters #twice weekly until levels return towards baseline levels or normal range
    - Investigate the participant for potential etiologies of the laboratory changes.
    - If alternative reasons/diagnoses cannot explain the laboratory changes, potential drug-induced liver injury (DILI) will be considered.

*Frequency of monitoring may need to be adjusted based upon clinical scenario and severity of injury. # *As the central laboratory results generation and reporting will take time, for*

participant safety monitoring an additional local laboratory tests may be performed at the same time as the central laboratory test, and decision-making may be based on local laboratory results.

For marked and/or persistent ALT elevations, collect a spare serum sample (to allow retrospective evaluation of potential etiologies) and consider liver biopsy on a case-by-case basis (if deemed clinically relevant).

If ALT elevations are associated with increased HBV DNA levels, virological breakthrough will be suspected and managed as described in Section 8.3.8.3.

ALT elevations during follow-up

- ALT elevation with preserved hepatic function:
  - ALT 3–10 × ULN: *Repeat ALT, LFTs, Coagulation (INR, PT) and PD parameters every week until ALT< 3 × ULN.
  - ALT > 10 × ULN: *Repeat ALT, LFTs, Coagulation (INR, PT) and PD parameters #twice weekly until ALT< 10 × ULN; then weekly until ALT < 3 × ULN.
- ALT elevation accompanied by declining liver synthetic and excretory functions or other signs of hepatic impairment:
  - Continue/restart NUC treatment.
  - *Repeat ALT, LFTs, Coagulation, and PD parameters #twice weekly until levels return towards baseline levels or normal range.
  - Investigate the participant for potential etiologies of the laboratory changes.
  - If alternative reasons/diagnoses cannot explain the laboratory changes, potential drug-induced liver injury (DILI) will be considered.
  - Further management according to local standard clinical practice.

*Frequency of monitoring may need to be adjusted based upon clinical scenario and severity of injury. # *As the central laboratory results generation and reporting will take time, for participant safety monitoring an additional local laboratory tests may be performed at the same time as the central laboratory test, and decision-making may be based on local laboratory results.*

For marked and/or persistent ALT elevations, collect a spare serum sample (to allow retrospective evaluation of potential etiologies) and consider liver biopsy on a case-by-case basis (if deemed clinically relevant).

In participants who have discontinued NUC therapy, NUC treatment *should* be restarted *if the criteria outlined in* Section 8.3.8.2 are met. *Note: The guidance for the management of ALT elevations (frequency of monitoring, laboratory assessments, NUC restarting rules) described in this section should be followed in conjunction with the guidance for the management of virological relapse described in Section 8.3.8.2*.

In participants who have not discontinued NUC therapy (e.g., NUC control arm), if ALT elevations are associated with increased HBV DNA levels, virological breakthrough will be suspected and managed as described in Section 8.3.8.1.

8.3.8.4 Management of NME-Related AEs

Refer to the respective appendix of each treatment arm for details.

8.4 TREATMENT OF OVERDOSE

Any dose above that planned will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose. Refer to the local prescribing information or NME Investigator Brochure's for more details.

8.5 PHARMACOKINETICS

Pharmacokinetic analyses that are specific to a treatment arm are stated in each respective appendix. Pharmacokinetic that are applicable to all treatment arms are described below.

Blood and/or urine samples to evaluate concentrations of the standard-of-care drugs, the NMEs, and their metabolites when applicable will be collected as outlined specifically in the SoA tables in the respective appendix of each treatment arm.

In general, PK sampling will be represented by sparse sampling throughout the duration of the study. During the course of the study, PK sampling time points may be modified based on emerging data, to ensure the PK of all standards-of-care and NMEs can be adequately characterized. Additional PK samples may be taken at the time of treatment discontinuation, if the participant experiences an unexpected adverse event or if the participant experiences an adverse event leading to dose-reduction or delayed treatment administration. The date and time of each sample collection will be recorded on the eCRF. All treatment drug levels and their metabolites as appropriate will be analyzed using validated assays. NUC control participants will not be analyzed in the first instance, but retained for subsequent analysis if appropriate. Details on sampling procedures, sample storage and shipment are given in the sample documentation.

8.6 IMMUNOGENICITY ASSESSMENTS

NMEs or IMPs included in combination therapies in this study that are human antibodies, oligopeptides, or oligonucleotides can present a risk that anti-drug antibodies (ADAs) against them could develop, potentially reducing their efficacy and/or potentially resulting in symptomatic hypersensitivity reactions, including immune-complex reactions.

When a particular combination will include such type of molecules (human antibodies, oligopeptides, or oligonucleotides), antibodies against them may be evaluated in blood samples collected from all participants according to their corresponding SoA.

Validated screening, confirmatory, and titer assays will be employed to detect ADAs against these molecules. The date and time of each sample will be recorded in the eCRF.

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

8.7 PHARMACODYNAMICS AND BIOMARKERS ASSESSMENTS

Pharmacodynamic and biomarker analyses that are specific to a treatment arm are stated in each respective appendix. Pharmacodynamic and biomarker analyses that are applicable to all treatment arms are described below.

8.7.1 HBV Dynamic Biomarker Assessments

The following well-established HBV laboratory tests will be measured using serum samples: quantitative and qualitative HBsAg, quantitative anti-HBs, qualitative HBeAg, semi-quantitative HBeAg (calculated), and qualitative anti-HBe.

Additional HBV dynamic biomarkers may be measured in all or some participants, as appropriate. This may include, but not be limited to, quantitative HBV RNA, quantitative HBcrAg, quantitative total anti-HBc, and quantitative total HBsAg (post-dissociation of HBsAg/HBsAb complexes/components of HBsAg) using plasma or serum samples.

8.7.2 HBV DNA Monitoring

The emergence of a virological breakthrough while on NUC therapy, or the emergence of a virological relapse in participants taken off NME combination and NUC therapy during the follow-up period, will be monitored through the quantification of HBV DNA in plasma. In the event that the HBV DNA level is above the defined thresholds for potential virological breakthrough (HBV DNA > 100 IU/mL or 1-log above nadir during treatment) or relapse (> 2,000 IU/mL for participants off NUC therapy) (as defined in Section 8.3.8), a plasma sample will be collected for a confirmatory quantification of HBV DNA at an unscheduled visit or at the next visit of the participant.

8.7.3 HBV Genome Sequencing

In some participants, HBV genome (DNA and/or RNA) sequencing may be done as appropriate.

HBV RNA sequencing: HBV RNA will be extracted and amplified using the plasma sample collected at Day 1. If this sample is missed, it can be collected at any other scheduled visit. If the amplification yields enough HBV RNA material, RNA-based sequencing will be attempted to determine the HBV genotype. *The HBV genotype may also be inferred using alternative approaches, such as serovariant determination.*

HBV DNA sequencing: In the event of a confirmed HBV DNA breakthrough, as defined in Section 8.3.8.1, HBV DNA will be extracted and amplified using the plasma sample

collected for the confirmatory HBV DNA quantification. If the amplification yields enough HBV DNA material, DNA sequencing of either the whole HBV genome or selected regions of interest will be attempted to determine genotype and mutations with potential to be associated with drug resistance and where feasible phenotyping. If this process fails, extraction, amplification, and sequencing may be attempted at a later time point.

In the event of an HBV DNA virological relapse, as defined in Section 8.3.8.2, the plasma sample collected for the confirmatory HBV DNA quantification will be stored for potential HBV genome characterization and where feasible phenotyping.

8.7.4 Genetic and Genomic Analyses

8.7.4.1 Clinical Genotyping

A whole blood sample for germline DNA analysis will be taken once, at baseline or before study treatment administration (the SoA(s) for each treatment arm is provided in the respective appendix as listed in Appendix 6). If this sample is missed, it can be collected at any other scheduled visit. DNA will be used to determine if alleles at genes associated with transport, metabolism, and/or mode of action of NMEs, tested in combination in this study, affect the PK, pharmacodynamic (PD), activity, or safety of the study treatment. Known candidate genes of interest specific to NME combinations are listed in the respective appendices. These assessments may be performed if safety or activity rationales develop and if considered appropriate by local regulations.

8.7.4.2 Transcriptome Analysis

RNA extraction and subsequent gene expression profiling may be performed from leftover samples to identify biomarker signatures predictive or associated with treatment response/safety. These assessments may be performed in some of the participants if safety or activity rationales develop, pending approval from country health authorities and local ethic committees as appropriate.

Given the complexity and nature of these analyses, genetic and genomic data and analyses will not be shared with investigators or study participants unless required by law. Participants will not be identified by name or any other personally identifying information. Data arising from all biosamples including samples for analyses of inherited DNA will be subject to the confidentiality standards described in the sample documentation.

8.8 PHARMACODYNAMICS AND BIOMARKER SAMPLES

Samples should be collected as specified in the SoA (the SoA(s) for each treatment arm is provided in the respective appendix as listed in Appendix 6).

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 or for measuring the primary outcome may be only tested in some of the participants and/or some of the scheduled visits.

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

8.8.1 Mandatory Samples

Unless otherwise stated, the following samples for pharmacodynamics and biomarker research are required and will be collected from all participants in this study:

8.8.1.1 Blood Sampling

Mandatory whole blood samples will be collected according to the SoA (the SoA(s) for each treatment arm is provided in the respective appendix as listed in Appendix 6) for quantitative and/or qualitative measurement of the HBV dynamic markers, the HBV DNA monitoring, and the HBV genome sequencing (see Section 8.7.1, Section 8.7.2, and Section 8.7.3).

A mandatory whole blood sample will also be taken for germline 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 (see Section 8.7.4.1). The sample for clinical genotyping will be destroyed immediately after the analysis is performed and the results are checked for accuracy.

8.8.1.2 Urine Sampling

Urine samples will be collected according to the SoA (the SoA(s) for each treatment arm is provided in the respective appendix as listed in Appendix 6) for renal standard safety biomarkers (see Appendix 4).

8.9 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

8.9.1 Overview of the Research Biosample Repository

The Roche Research Biosample Repository (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 participants in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional Research Biosample Repository, in countries where regulations allow this collection. 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 adverse events or can lead to improved adverse event 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

Leftover plasma, serum, urine, *solid tissues,* and blood samples collected through the duration of the study will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to the NMEs administered in combinations in this study, CHB, or drug safety.

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 will 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 they are exhausted or no longer needed. The RBR storage period will be in accordance with the IRB/EC-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 HEALTH ECONOMICS

Health Economics parameters are not evaluated in this study.

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 56 days prior to Day 1, unless otherwise specified.

8.11.2 Assessments during Treatment

All assessments must be performed according to the SoA (the SoA(s) for each treatment arm is provided in the respective appendix as listed in Appendix 6). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment. The following sequence should be followed unless otherwise specified in the SoA.

- Urine collection
- ECG recordings
- Vital signs
- PK, viral dynamic, safety blood sampling
- Study drug administration

8.11.3 Assessments at Study Completion

Participants who prematurely discontinue study treatment but remain in the study, should continue to attend the follow-up visits including the 48 weeks, after the EOT visit.

Participants who prematurely discontinue the study should attend an early termination visit.

8.11.4 Follow-up Assessments

After the study completion, adverse events should be followed as outlined in Section 8.3.1 and Section 8.3.3.

8.11.5 Assessments at Unscheduled Visits/Early termination Visit

Please see the SoA(s) for each treatment arm as provided in the respective appendix as listed in Appendix 6 for activities that are required to be performed in case of an unscheduled visit/early termination visit.

9. STATISTICAL CONSIDERATIONS

For each treatment arm, the analysis of complete data will be performed when all participants have either completed the follow-up period or have discontinued early from the arm, all data from the arm are in the database and have been cleaned and verified, and the database is locked.

The final analysis for safety efficacy and pharmacodynamic endpoints for each treatment arm will be based on participant data collected for that arm. No adjustment for multiplicity will be made as each investigational treatment arm will be compared separately to NUC control and is therefore independent. The study is not powered to compare investigational treatment arms against each other.

Continuous variables will be summarized using descriptive statistics including means, standard deviations, medians, and minimum and maximum values. Categorical variables will be summarized through use of counts and percentages. Listings will be used in place of tables in the event of small sample sizes.

Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP).

9.1 STATISTICAL HYPOTHESES

As this is an exploratory study, no formal hypothesis testing will be performed.

9.2 SAMPLE SIZE DETERMINATION

Approximately 30 participants will be randomized in each treatment arm. Approximately five participants per arm may be replaced if participants have a dose regimen change or discontinue due to non-safety reasons, this is to ensure that the number of participants per arm of the randomized dose regimen remains close to 30. Participants may be replaced at the Sponsor's discretion. *In the event of COVID-19 or force majeure events that significantly impact compliance with the randomized dosing regimen, up to 30 additional participants may be enrolled per treatment arm to ensure that the randomized dose regimen remains close to 30. Criteria and the decision to enroll additional participants will be at the Sponsor's discretion.* Please refer to specific combo arms in the appendix for additional information about participants. The overall number of participants in this study will depend on the number of treatment arms that are included, which is not known at present.

The primary endpoint is the proportion of participants with HBsAg loss at 24 weeks post-EOT. Assuming a 3% NUC response rate (EASL 2017), a sample size of 30 participants per arm provides 78% power to detect a pairwise 30% difference between a combination treatment arm and the NUC control arm. This is based on two-treatment arm continuity corrected, two-sided, chi-squared test of equal proportions at a significance level of 5 %.

The sample size of combination treatment arms that achieve 30% delta for HBsAg loss at Week 48 (EOT) or follow-up Week 12 or 24 may be expanded up to approximately 100 participants. An expansion may also be triggered prior to EOT, for a treatment arm that gives an early indication of efficacy. The decision criteria to trigger an expansion arm in this case, will be documented as an appendix to the IMC/SOC charter. The expansion arm may be utilized to increase the precision of the efficacy treatment

estimates; exploration of participant subgroups (e.g., baseline HBeAg status) and/or gain more additional safety data prior to Phase 3 clinical trials.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 3.

Table *3* Analysis Populations

Population	Description
Safety	All participants randomized to a treatment regimen who received at least one dose of any drug for their assigned treatment regimen, whether prematurely withdrawn from the study or not, will be included in the safety analysis.
Modified ITT	All participants who were randomized and received at least one dose of each drug for their assigned treatment regimen. Participants will be analyzed according to the treatment arm to which they were randomized.
Pharmacokinetic	Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.
Immunogenicity (when applicable)	Participants who had at least one pre-dose (baseline) or at least one post-dose ADA assessment will be included and analyzed according to the treatment they actually received or were allocated to receive.

9.4 STATISTICAL ANALYSES

9.4.1 Demographics and Baseline Characteristics

Descriptive statistics will be generated for demographic and baseline disease characteristics including sex, race, ethnicity, origin (for Asian participants only), age, weight, height, body mass index, HBV DNA and HBsAg levels, and HBV history including but not limited to duration of HBV disease, likely route of transmission, HBV genotype, HBeAg status, previous HBV treatments, and length of time on NUCs.

9.4.2 Efficacy Analyses

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

For the treatment arms where additional patients have been recruited to proactively mitigate any impact of COVID-19 or force majeure events, the primary analysis will be performed when approximately 30 patients considered evaluable for the primary analysis reach the primary endpoint of Week 24 post EOT. The criteria to assess evaluability will be described in the SAP. If the primary analysis is positive for an experimental treatment arm, any additional patients that have been recruited to that treatment arm, will continue and be included in the final CSR.

Any sensitivity analyses including patients considered 'unevaluable' for the primary analysis will be specified in the SAP.

For the primary endpoint (% participants with HBsAg loss at 24 weeks post-EOT), the estimated treatment difference adjusted for baseline HBsAg level, along with the associated 95% Confidence Interval in the proportion of participants with HBsAg loss at 24 weeks post-EOT between the experimental and the associated control arm will be provided.

Confidence Intervals will be estimated using Cochran-Mantel-Haenszel (CMH) weighting method with continuity correction (Lu 2008). Participants with missing or no response assessments will be classified as non-responders.

Summary statistics will be produced by treatment arm for each of the endpoints defined Table 4. In addition, graphical displays will be produced of mean and individual participant data as appropriate.

Table *4* Efficacy Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary	Treatment effect with associated binomial CI
Secondary	Descriptive statistics

9.4.3 Safety Analyses

All safety analyses will be based on the safety analysis population grouped according to the treatment assigned at randomization.

All safety analyses will be based on the entire safety analysis population (Table 5). The safety data, including AEs, reasons for withdrawal from study, laboratory data, ECGs, concomitant medications, vital signs, and physical examination results will be listed and summarized descriptively. Marked abnormalities will be flagged for laboratory data. As appropriate, listings, summary tables and graphs (participant plot and/or mean plots) will be provided for safety and tolerability assessments.

Table 5 Safety Statistical Analysis Methods

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

9.4.4 Pharmacokinetic Analyses

Analyses will be carried out on the PK analysis population (see Table 3).

Plasma concentrations of the NMEs and/or their metabolites when applicable, and standard-of-care drugs (where applicable) will be plotted and reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm, over time when appropriate and as data allow. PK parameters including volume of distribution [V_d], clearance [CL]) may be estimated using population PK models developed for each asset from the literature or from the Phase 1 studies conducted with each NME. Based on these models secondary PK parameters including area under the curve (AUC) and peak concentration (C_{max}) may be estimated.

9.4.5 Immunogenicity Analyses

The analyses will be carried out on the immunogenicity analysis population, irrespective of whether or not a participant receives any treatment (Shankar et al 2014, see Table 3).

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

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

9.4.6 Pharmacodynamic Analyses

Analyses will be carried out on the efficacy analysis population (see Table 3).

All pharmacodynamic parameters will be presented by listings and descriptive summary statistics separately by treatment arm or treatment arms.

9.4.7 Pharmacokinetic/ Pharmacodynamic Relationships

Relationship between study drug(s) and/or metabolites exposure and any PD parameters and/or outcome (e.g., safety-related marker, adverse events, safety biomarkers, viral dynamic markers, and viral response) may be presented by graphical analysis and used for further development of a model.

9.5 INTERIM ANALYSES

There will be up to four planned interim analyses for each treatment arm. The exact number of planned interim analyses will depend on the overall duration of the treatment arm as well as the sequencing of the drugs in the treatment arm.

The first three interim analyses will occur, depending on the overall duration of the treatment arm as well as the sequencing of the drugs in the treatment arm, once all participants within a treatment arm have been randomized and have reached 12 weeks, 24 weeks, and EOT respectively after the start of therapy (or have discontinued from the study). The fourth interim analyses will be performed when all participants within a

treatment arm have completed the follow-up Week 12 visit (or have discontinued from the study).

Additional design considerations are provided. The below timing of planned interim analyses and RGT are illustrated based on a 48-week treatment duration arm; for arms with shorter treatment duration, the number of the interim analyses as well as the RGT early treatment discontinuations will be adjusted accordingly.

- First interim analysis at 12 weeks for a treatment arm: if the observed on-treatment HBsAg loss rate of a combination is at least 30% greater than that of control, the Sponsor will take into consideration the available safety and pharmacodynamic data and may commence a new treatment arm of sample size of approximately 30 participants with 12-weeks' treatment duration. In addition, the Sponsor may start a new arm of sample size of approximately 30 participants with a RGT, whereby participants will discontinue treatment early at Weeks 12, 24, or 36 if HBsAg loss is observed.
- Second interim analysis at 24 weeks for a treatment arm: if the observed on-treatment HBsAg loss rate of a combination is at least 30% greater than that of control, the Sponsor will take into consideration the available safety and pharmacodynamic data and may commence a new treatment arm of sample size of approximately 30 participants with 24-weeks treatment duration. In addition, the Sponsor may start a new arm of sample size of approximately 30 participants with a RGT approach, whereby participants will discontinue treatment early at Week 12, 24, or 36 if HBsAg loss is observed.
- Third and fourth interim analyses at Week 48 and follow-up Week 12: for safety and internal decision-making purposes (e.g., front-loading Ph3 activities), and if the observed HBsAg loss rate of a combination is at least 30% greater than that of control, the Sponsor may decide to expand the treatment arm up to approximately 100 participants. An expansion may also be triggered prior to EOT, for a treatment arm that gives an early indication of efficacy. The decision criteria to trigger an expansion arm in this case, will be documented as an appendix to the IMC/SOC charter.

Above pre-specified study adaptations allow for NME combination therapies that show promising efficacy outcomes to be further evaluated promptly, based on emerging data, without delays that would be otherwise incurred through protocol amendments. These decision criteria assume that the on-treatment HBsAg loss rate is predictive of the 24-week post-EOT HBsAg loss rate.

The Statistical Analysis Plan will describe the planned interim analyses in detail.

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim analyses not specified above. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the

Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

9.6 SUMMARIES OF CONDUCT OF STUDY

The number of participants who were randomized, discontinued treatment, completed treatment, discontinued study and completed the study (including follow-up period) will be summarized. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by each treatment arm.

For safety-evaluable participants, study drug administration data will be tabulated or listed by treatment arm within each stage, and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose and dose intensity for each study drug. Reasons for discontinuation of study drugs will also be tabulated.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes standard appendices such as Appendix 1 (For regulatory, ethical, and study oversight considerations), Appendix 2 (For AE definitions and reporting) and Appendix 3 (Procedures of recording), Appendix 4 (Clinical laboratory tests), Appendix 5 (Contraceptive guidance and collection of pregnancy information).

Additional study-related appendices, in order of appearance in the protocol, are listed below.

Appendix 6 Planned Treatment Arms

Appendix 7 Study Details Specific to NUC Control Arm

Appendix 8 Study Details Specific to CpAM (RO7049389) + TLR7 (RO7020531) + NUC Arm

Appendix 9 Study Details Specific to siRNA (RO7445482) + NUC Arm

Appendix 10 Study Details Specific to siRNA (RO7445482) + PEG-IFN + NUC Arm

Appendix 11 Study Details Specific to siRNA (RO7445482) + CpAM (RO7049389) + NUC Arm

Appendix 12 Study Details Specific to siRNA (RO7445482) + TLR7 (RO7020531) + NUC Arm

Appendix 13 Study Details Specific to siRNA (RO7445482) + PD-L1 LNA (RO7191863) + NUC Arm

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 European Commission/European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

1.3. INFORMED CONSENT

The Sponsor's Master Informed Consent Form (and ancillary sample ICFs such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants or their

legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant’s legally authorized representative.

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

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

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

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

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

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research, as appropriate. A separate signature will be required to document a participant's agreement to allow any remaining samples to be used for exploratory research.

Consent to Participate in the Research Biosample Repository

The Informed Consent Form 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.

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

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 Informed Consent Form by each site's Institutional Review Board or Ethics Committee (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 WV41073 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

WV41073. 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 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 Informed Consent Form (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 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 Roche, 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 Informed Consent Form. Roche 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 Roche. 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.

In addition, the Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring subject safety and data integrity. Prior to first subject entry into the study, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for the control and review of these risks. Risk control includes the selection of risk-based parameters and establishing associated quality tolerance limits. Detection of deviations from defined quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the management and review of quality tolerance limits will be provided in a separate Quality Tolerance Limit plan.

2.1.2. CLINICAL OUTCOME ASSESSMENT DATA

Not applicable.

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, 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 study-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.

2.2. RETENTION OF RECORDS

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

2.3. STUDY RECORDS

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

Roche shall also submit an Annual Safety Report once a year to the IEC and regulatory 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 study 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 study initiation, the Sponsor will identify and evaluate potential risks associated with critical trial processes and data and will implement controls for the communication, review and reporting of these risks. Details regarding the applied approach for the study will be provided in the integrated Risk Based Quality Management Plan.

Risk control includes the selection of risk-based parameters and establishing associated quality tolerance limits. Detection of deviations from defined quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the management and

review of quality tolerance limits will be provided in a separate Quality Tolerance Limit 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

Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC)

The IMC will perform periodic safety data review to ensure that continuation of the study does not pose a health hazard to participants, and review the results from the interim analyses to make decision about initiating new treatment arms.

IMC meetings will be scheduled following each of the planned interim analyses. Additional review meetings may be scheduled as determined by the IMC. Membership of the IMC will include representatives from Clinical Science (Translational Medicine), Clinical Safety, Biostatistics. If required, additional functional representatives may attend an IMC meeting.

A SOC will act as a consultative body to the Sponsor, providing external expert opinions on the safety data collected during the study. This committee will consist of an external group of at least two CHB therapeutic area experts who will advise the Sponsor on the interpretation of study data.

Data being evaluated by the SOC will include demographic, adverse event, serious adverse event, and relevant laboratory data. SOC may review efficacy data if safety concerns necessitate benefit-risk assessments. The Sponsor will retain all decision-making authority for this study.

Further details on the IMC and SOC, including membership, roles and responsibilities, are provided in the IMC and SOC Charter.

4. STUDY ARM, STUDY, AND SITE CLOSURE

The Sponsor (or designee) has the right to close a study site, terminate this study, study arms or certain NMEs in combination at any time. Reasons for terminating the study,

study sites, study treatment arms or certain NMEs 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.
- Emerging data and/or prioritization of assets.

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 or terminate study arms or terminate certain NMEs in combination.

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 subject 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 pre-existing 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 progression 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 pre-existing 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 pre-existing 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

  - elevated ALT or AST (> 3 × ULN and > 3x baseline) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia (Potential Hy's law).
  - 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 Medical Monitor. 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 Medical Monitor.

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 (according to pre-defined Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [DAIDS] criteria); 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 DAIDS (v2.1) will be used for assessing severity for adverse events (see Appendix 2-Table 1).

Appendix 2-Table 1 DAIDS Adverse Event Severity Grading Scale

Grade	Description
1	Mild; symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
2	Moderate; symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
3	Severe; symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
4	Potentially life-threatening; symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
5	Death

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see above). DAIDS v2.1 grading scale is available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Pyrexia will be graded by using the following DAIDS V2.1 (see Appendix 2-Table 2).

Appendix 2-Table 2 DAIDS Pyrexia Severity Grading Scale

Grade	Temperature
1 (mild)	38.0 to < 38.6°C (100.4 to < 101.5°F)
2 (moderate)	≥ 38.6°C to < 39.3 (≥ 101.5 to < 102.7°F)
3 (severe)	≥ 39.3 to < 40°C (≥ 102.7 to < 104°F)
4 (life threatening)	≥ 40°C or ≥ 104°F

If the treatment regimen will include NME(s) that may trigger immune activation (and potentially CRS (cytokine release syndrome), additional AEs and the associated clinical management will be specifically reported into the eCRF by the Investigator: flu-like

symptom specific eCRF page for capturing each of the symptoms experienced, presence of hypotension (requiring fluid or use of vasopressors), and presence of hypoxia (requiring medical intervention). Data from eCRF pages on pyrexia and flu-like symptoms in combination with the data on eCRF pages on hypoxia and hypotension will allow the Sponsor to evaluate the severity of AEs associated with immune activation following specific CRS consensus grading (ASTCT Consensus Grading for Cytokine Release Syndrome. Biol Blood Marrow Transplant, 25; (2019) 625-38).

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 dose-reduction, 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 Medical Monitor 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 study. 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
- Adverse events of special interest (AESI)
- Pregnancies (see Section 8.3.5)
- Accidental overdose or medication errors (see Appendix 2, Section 5.2)

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 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 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, OVERDOSE, MEDICATION ERROR, DRUG ABUSE, OR DRUG MISUSE

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse} (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
- Intentional overdose: intentional 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.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm}
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse. In cases where drug is to be self-administered by the

participant, drug misuse could involve the drug being administered to someone other than the participant.

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 study treatments, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.}

In addition, all special situations associated with the study treatments, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2, Section 5.1). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse"
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

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 AESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

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

- IMPs Investigator's Brochure
- NUC prescribing information in required territories

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

For adverse events, 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.

1.1. INJECTION-SITE REACTIONS/INJECTION REACTIONS

Adverse events that occur during or after study drug administration and are judged to be local and related to the SC study drug injection should be captured as a diagnosis (e.g., “injection site reaction)" on the Adverse Event eCRF and if judged to be systemic should be captured as a diagnosis ‘’injection reaction (IR)’’. If possible, avoid ambiguous terms such as "systemic reaction"). Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF.

Injection Site Reactions (ISR) are usually immunological with delayed onset. The SAP will include analyses of ISR using a modified (mISR) definition of ISR of onset of 4 or more hours post-dose.

Grading of pre-defined ISR signs and symptoms (pain, erythema swelling and pruritus) should be based on DAIDS (Appendix 2, Section 3.1). If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated signs and symptoms eCRF for Systemic Injection Reaction and ISR.

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., dose 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., dose modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator’s judgment.

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

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

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

6. ABNORMAL LIVER FUNCTION TESTS

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

- Treatment-emergent ALT/AST $>3\times$ULN and $>3\times$ baseline, in combination with total bilirubin $>2\times$ULN.
- Treatment-emergent ALT or AST $>3\times$ULN and $>3\times$ baseline, in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) as a AESI (Section 8.3.6) and serious adverse event, if the SAE definition criteria is met.

7. DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Appendix 2, Section 5), 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 CHB.

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. WORSENING OF CHRONIC HEPATITIS B

Lack of efficacy in terms of changes in HBsAg does not qualify for adverse event in this study.

Medical occurrences or symptoms of deterioration in the course of chronic hepatitis B 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 Chronic Hepatitis B on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., Progression of Chronic Hepatitis B).

Hepatitis B virological breakthrough, hepatitis B virological relapse, and abnormal liver function tests (see Section 8.3.8) should be reported as adverse events.

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., for study treatment administration or insertion of access device for study treatment administration)
- For administrative reasons (e.g., participant lives far away and is kept in the clinic/hospital for participant and/or site convenience)
- Hospitalization for a preexisting condition (not CHB), provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
    - The participant has not suffered an adverse event.

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

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

Appendix 4
Clinical Laboratory Tests

The tests detailed in Appendix 4-Table 1 below will be performed by the central laboratory, with the exception of urinalysis, alcohol and drugs of abuse screen, which will be performed locally.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration (including for the randomization/dosing day) and/or a 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 a 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.

Appendix 4-Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and glycated hemoglobin (HbA1c).
Clinical Chemistry	• Sodium, potassium, chloride, bicarbonate, phosphorus, calcium, magnesium, urea, uric acid, blood urea nitrogen (BUN), creatinine and cystatin C, estimated glomerular filtration rate (eGFR), glucose, total protein, albumin, total and direct bilirubin, alkaline phosphatase (ALP), ALT, AST, gamma-glutamyl transferase (GGT), alpha fetoprotein, glutamate dehydrogenase (GLDH), lipase, creatine kinase/creatine phosphokinase (CK/CPK), LDH and amylase.
Lipids	• Total cholesterol, low-density lipoproteins (LDL) cholesterol, high-density lipoproteins (HDL) cholesterol, triglycerides.
Thyroid Function Tests	• TSH, free T3 and free T4.
Coagulation	• INR, activated partial thromboplastin time, PT.
Viral Serology	• HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis A virus (HAV IgM antibody), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, hepatitis D virus (HDV) antibody, hepatitis E virus (HEV) antibody.
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 subsequent visits according to SOAs. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.
Urinalysis	• Specific gravity. • Dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrites, leukocytes. If there is a clinically significant positive result (e.g., 2+ or greater for blood, protein or leukocytes) confirmed by a positive repeated sample, urine will be sent to the central laboratory for microscopy and culture. In addition, if there is clinically significant proteinuria (2+ or greater for protein), central laboratory will measure the urine protein: creatinine ratio. 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 (sediment, red blood cells [RBCs], WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal.
Other Screening Tests	• Alcohol and drug screen according to local procedure to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines. • Auto-antibodies (ANA, AMA, ASMA, a-TPO).

Investigators must document their review of each laboratory safety report.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Potential analysis considerations for analyzing laboratory data includes the use of standard reference ranges and potential transformation of data for specific lab tests.

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

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

- Definition of Laboratory Abnormalities

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

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

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

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

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

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

a) Pre-menarchal

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

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

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

c) Post-menopausal female

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

2. CONTRACEPTION GUIDANCE

- **Female Participants**

Unless otherwise stated in the respective appendix of each treatment arm, female participants of childbearing potential are eligible to participate if they agree to use highly

effective method of contraception consistently and correctly as described in Appendix 5-Table 1 below.

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 Appendix 5-Table 1 below.

Appendix 5-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 **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.

Appendix 5-Table 1 Highly Effective Contraceptive Methods (cont.)

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, blood sample and urine pregnancy tests will be performed according to respective treatment arm specific Schedule of Activities table. 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

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

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

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and

child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- **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 Appendix 2, Section 5).

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 Appendix 2, Section 5).

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, or female partner of a male participant exposed to study treatment, should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Appendix 6
Planned, Ongoing, and Terminated Treatment Arms And Terminated Arm Safety Follow Up

An overview of the planned, ongoing, and terminated treatment arms is shown in Appendix 6-Table 1.

Arms depicted in Appendix 6-Table 1 as 2 and 6, were terminated due to Sponsor's decision to discontinue the development of CpAM (RO7049389) in the NUC-suppressed CHB participant population. At the time this decision was taken the CpAM+TLR7+NUC arm was fully recruited and the siRNA+CpAM+NUC arm was partially recruited. As a result of this decision, no further participants were enrolled in the siRNA+CpAM+NUC arm and the participants who were already randomized to both treatment arms were asked to attend an early termination visit to discontinue both study drugs, maintain NUC therapy, and enter the safety follow-up period.

Appendix 6-Table 1 Planned, Ongoing, and Terminated Treatment Arms

Arm	Treatment Arm	Arm Status	Number of Participants	Link to Appendix
1	NUC control	Ongoing	30[b]	Appendix 7
2	CpAM (600 mg) (RO7049389) + TLR7 (150 mg) (RO7020531) + NUC	Terminated[c]	~30	Appendix 8
3	siRNA (100 mg) (RO7445482) + NUC	Ongoing	~30	Appendix 9
4	siRNA (200 mg) (RO7445482) + NUC	Ongoing	~30	Appendix 9
5	siRNA (200 mg) (RO7445482) + PEG-IFN (180 µg)+ NUC	Ongoing	~30	Appendix 10
6	siRNA (200 mg) (RO7445482) + CpAM (600 mg) (RO7049389) + NUC	Terminated[c]	~30	Appendix 11
7	siRNA (200 mg) (RO7445482) + TLR7 (150 mg) (RO7020531) + NUC	Ongoing	~30	Appendix 12
8	siRNA (200 mg) (RO7445482) + PD-L1 LNA [redacted] (RO7191863) + NUC – 24 week treatment	Planned	~30	Appendix 13
9	siRNA (200 mg) (RO7445482) + PD-L1 LNA [redacted] (RO7191863) + NUC – 36 week treatment	Planned	~30	Appendix 13
TBD[a]	TBD		TBD	TBD

Abbreviations: NUC=nucleos(t)ide; TBD=to be determined.

[a] Additional treatment arms may be added to the study.

[b] Additional participants will be added as additional treatment arms are added to the study.

[c] Treatment arms terminated; patients performed early termination visit and entered in the safety follow-up period.

Appendix 6-Table 2 Mechanism of Action Classification for Investigational Medicinal Products

IMP	Target	Mechanism of Action
CpAM (RO7049389)	HBV core protein	DAA: Core protein allosteric modulator (class I)
TLR7 (RO7020531)	Human toll-like receptor 7	IM: Toll-like receptor 7 agonist
siRNA (RO7445482)	HBV RNA transcripts	DAA: HBV gene expression inhibitor
PD-L1 LNA (RO7191863)	PD-1/PD-L1 checkpoint inhibitory pathway	IM: PD-L1 inhibitor

Appendix 6-Table 3 Applicable Inclusion/Exclusion Criteria

Treatment arm	Applicable Exclusion Criteria
NUC Control Arm	Section 5.2
CpAM (RO7049389) + TLR7 (RO7020531) + NUC	Section 5.2 and Section A8.4 in Appendix 8
siRNA (100 mg) (RO7445482) + NUC	Section 5.2 and Section A9.4 in Appendix 9
siRNA (200 mg) (RO7445482) + NUC	Section 5.2 and Section A9.4 in Appendix 9
siRNA + PEG-IFN + NUC	Section 5.2 and Section A10.4 in Appendix 10
siRNA (RO7445482) + CpAM (RO7049389) + NUC	Section 5.2 and Section A11.4 in Appendix 11
siRNA (RO7445482) + TLR7 (RO7020531) + NUC	Section 5.2 and Section A12.4 in Appendix 12
siRNA (RO7445482) + PD-L1 LNA (RO7191863) + NUC	Section 5.2 and Section A13.4 in Appendix 13

SAFETY FOLLOW UP FOR PARTICIPANTS FROM EARLY TERMINATED STUDY TREATMENT ARM BY THE SPONSOR

Participants, who permanently discontinue study treatment as part of an early termination of a treatment arm due to Sponsor's decision, will undergo safety follow-up assessments as described in Appendix 6-Table 4 and participants will remain on their NUC therapy.

All participants will be followed up for 24 weeks according to the following Schedule of Assessments.

Appendix 6-Table 4 Schedule of Activities of Safety Follow-up Period for Early Terminated Study Treatment Arms

	Follow-up Period[a]			
Week	**4**	**8**	**12**	**24**
Day	**28 (±3)**	**56 (±3)**	**84 (±7)**	**168 (±7)**
Physical examination, vital signs [b, c]				x
ECG				x
Abdominal ultrasound				x
Alfa-fetoprotein				x
Pregnancy test [d]	x	x	x	x
Thyroid function tests				x
Hematology	x	x	x	x
Chemistry	x	x	x	x
Coagulation	x	x	x	x
GLDH	x	x	x	x
Urinalysis	x	x	x	x
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x	x	x	x
HBV DNA quantitative	x	x	x	x
HBV RNA quantitative	x	x	x	x
NME ADA[e]			x	x
Diary review	x	x	x	x
Adverse events & concomitant medications	x	x	x	x

DNA = deoxyribonucleic acid; ECG = electrocardiogram; GLDH = glutamate dehydrogenase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; RNA = ribonucleic acid.

[a] Safety follow-up is mandatory for 24 weeks for all participants. Additional unscheduled visits may be performed if deemed clinically relevant.

[b] Limited symptom-directed physical exam and as clinically indicated.

[c] Blood pressure, pulse rate, respiratory rate and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

[d] Pregnancy testing for females of childbearing potential only to be conducted monthly at the visit or at home using pregnancy kits supplied by sponsor or obtained locally; If urine test is positive, it must be confirmed by a serum test.

[e] As applicable according to impacted study arm.

Note, for participants who are in treatment arms NOT terminated by the sponsor, the above safety follow-up is not applicable. The follow up period for these patients is as per the SoA of the respective treatment arm.

Appendix 7
Study Details Specific to NUC Control Arm

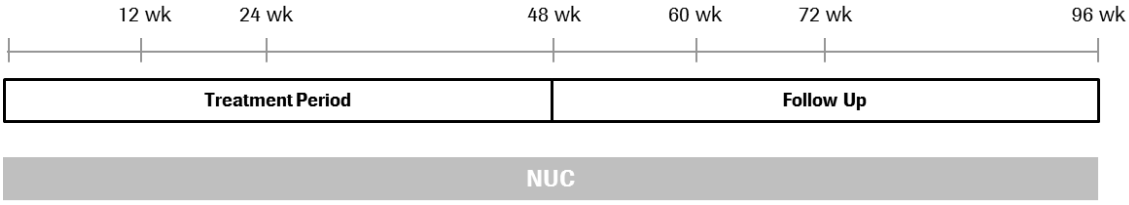
An overview of the nucleos(t)ide (NUC) control treatment arm is shown in Appendix 7-Figure 1.

Participants will continue their background NUC therapy for the 48-week treatment period. At the end of the treatment period, in line with current CHB treatment guidelines, participants will continue NUC treatment during the follow-up unless the NUC discontinuation criteria have been met (see Section 6.8).

Initially, 30 participants will be randomized to the NUC control arm. The subsequent randomization ratio will depend on the number of actively enrolling NME treatment arms, with the stipulation that no more than 17% of participants will be randomly allocated to the NUC control arm.

Participants in the NUC control arm who complete the follow-up Week 48 visit, and continue to meet the study eligibility criteria, may be offered to participate in an expansion cohort of a combination regimen within this study. This will allow access for NUC control participants to an investigational combination regimen that has shown a positive benefit/risk profile, as this is a pre-requisite for an expansion cohort to commence.

Appendix 7-Figure 1 NUC Control Treatment Arm



A7.1 BACKGROUND SPECIFIC TO NUC CONTROL ARM

Not applicable.

A7.2 BENEFIT/RISK ASSESSMENT SPECIFIC TO NUC CONTROL ARM

Although participants randomized to the control arm are not expected to receive additional benefit within this arm beyond that attained with their current treatment, the control arm is important to increase the robustness of the study in terms of the clinical data generated, and in identifying efficacious combination regimens. In turn, their participation will guide further clinical development and thereby benefit the overall CHB population.

Furthermore, after completing the follow-up Week 48 visit, participants who meet the study eligibility criteria may be offered to participate in an expansion cohort of a combination regimen within this study. The expansion cohort may result in additional therapeutic benefit for the participants.

A7.3 JUSTIFICATION FOR DOSE SPECIFIC TO NUC CONTROL ARM

Not applicable.

A7.4 LIFESTYLE CONSIDERATIONS SPECIFIC TO NUC CONTROL ARM

NUCs will be given according to the local prescribing information.

A7.5 TREATMENT ADMINISTERED SPECIFIC TO NUC CONTROL ARM

Appendix 7-Table 1 summarizes the treatments administered.

Appendix 7-Table 1 Summary of Treatments Administered for NUC Control Treatment Arm

Study Treatment Name	NUC
IMP and NIMP	NIMP*
Dose Formulation	Film-coated tablet
Unit Dose Strength(s)/Dosage Level(s)	Refer to local prescription information
Dose	ETV: 0.5 mg TDF: 300 mg TAF: 25 mg
Route of Administration	oral
Sourcing	Provided centrally by the Sponsor or locally by the study site
Packaging and Labeling	Study treatment will be packaged and labeled as required per local regulation.

*NUC are considered IMP in the UK only.

For guidelines for dosage modification, please refer to the NUC local prescribing information.

For more details, refer to the NUC local prescribing information and the Pharmacy Manual.

A7.6 PHARMACODYNAMICS AND BIOMARKERS ANALYSES SPECIFIC TO NUC CONTROL ARM

A7.6.1 CLINICAL GENOTYPING

If safety or activity rationales develop, clinical genotyping will be performed (see Sections 8.7.4.1 and 8.8.1.1). Known candidate genes of interest that are stated in appendices for NME combination arms will be queried in the NUC control arm as well.

A7.7 SCHEDULE OF ACTIVITIES (NUC CONTROL ARM)

An overview of the schedule of the activities is provided in Appendix 7-Table 2.

Appendix 7-Table 2 Schedule of Activities for NUC Control Arm

	Screening		Treatment Period						Follow-up Period											VB/VR	UV(Flu like/ ET) [p]
Week			1	4	12	24	36	48 [n]	2 [o]	4 [o]	6 [o]	8 [o]	10 [o]	12	16 [o]	20 [o]	24[q]	36	48		-
Day	-56 to -7	-14 to -7	1	28 (± 3)	84 (± 3)	168 (± 7)	252 (± 7)	336 (± 7)	14 (±3)	28 (±3)	42 (±3)	56 (±3)	70 (±3)	84 (±7)	112 (±7)	140 (±7)	168 (±7)	252 (±7)	336 (±7)		
Informed consent	x																				
Demography, medical history	x																				
Physical examination, vital signs [a, b]	x		x	x	x	x	x	x									x		x	x	x
Randomization			x																		
ECG	x		x		x	x	x	x									x		x		
Transient elastography/ARFI/MR [c]	x																				
Abdominal ultrasound	x					x		x									x		x		
Alfa-fetoprotein	x					x		x									x		x		
HAV, HCV, HDV, HEV, HIV	x																				
Autoantibodies [d]	x																				
Alcohol and drugs of abuse screen [e]		x						x													x
Pregnancy test [f]		x			x	x	x	x						x			x	x	x		
Thyroid function tests	x				x	x		x									x		x		
Hematology (include HbA1c [g])	x		x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry		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
GLDH	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	x	x

Appendix 7-Table 2 Schedule of Activities for NUC Control Arm (cont.)

	Screening		Treatment Period						Follow-up Period											VB/VR	UV(Flu like/ ET) [p]
Week			1	4	12	24	36	48 [n]	2 [o]	4 [o]	6 [o]	8 [o]	10 [o]	12	16 [o]	20 [o]	24[q]	36	48		-
Day	-56 to -7	-14 to -7	1	28 (± 3)	84 (± 3)	168 (± 7)	252 (± 7)	336 (± 7)	14 (±3)	28 (±3)	42 (±3)	56 (±3)	70 (±3)	84 (±7)	112 (±7)	140 (±7)	168 (±7)	252 (±7)	336 (±7)		
Clinical genotyping [h]			x																		
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
HBV DNA quantitative[r]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Total HBsAg [i]			x	x	x	x	x	x		x		x		x			x		x	x	
HBcrAg			x	x	x	x	x	x		x		x		x			x		x	x	
Total anti-HBc quantitative			x		x	x	x	x						x			x		x		
HBV RNA quantitative			x	x	x	x	x	x		x		x		x			x		x	x	
HBV RNA sequencing [h]			x																		
HBV DNA sequencing [j]																				x	
Plasma PK (NUC) [k]			x		x	x	x	x												x	
RBR [l]			x			x	x	x												x	
Study treatment administration &/or diary review			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events & concomitant medications [m]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ARFI = acoustic radiation force impulse; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET= early termination; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics; RBR = Research Biosample Repository; RNA = ribonucleic acid; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV= unscheduled visit.

[a] Full physical exam at screening and Week 48. Limited symptom-directed physical exam at other visits and as clinically indicated. Height at screening only. Weight at screening, Day 1, and Week 12, 24, 36, 48.

Appendix 7-Table 2 Schedule of Activities for NUC Control Arm (cont.)

[b] Blood pressure, pulse rate, respiratory rate and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

[c] Historical liver biopsy or transient elastography/ARFI/MR/2D- shear wave elastography [2D-SWE] results obtained within 6 months prior to randomization are also acceptable. During screening transient elastography/ARFI/MR/2D-SWE are acceptable.

[d] Autoantibodies refer to ANA, AMA, ASMA, and a-TPO.

[e] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[f] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine pregnancy test is positive, the pregnancy must be confirmed by a serum test.

[g] HbA1c should be assessed only at screening.

[h] If not collected at Day 1, samples for clinical genotyping and HBV RNA sequencing can be collected at any subsequent time point. *The sample for HBV RNA sequencing aims at determining the HBV genotype. The HBV genotype may also be inferred using alternative approaches, such as serovariant determination.*

[i] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb complexes/components of HBsAg.

[j] HBV DNA sequencing will be collected in case of virological breakthrough/relapse, blood sample to be collected up to 6 times.

[k] Plasma PK samples for NUC to be collected at pre-dose. During the PK assessments for VB/VR visits, only one predose sample is required for collection, no other additional time points should be collected.

[l] RBR samples collected only from RBR-consenting participants.

[m] Pre-treatment, only serious adverse events should be reported.

[n] Participants who achieve HBsAg loss during treatment or during follow-up will discontinue NUC.

[o] Additional post-treatment visits for participants who discontinued NUC at Week 48. If participants discontinue NUC later in the follow-up additional visits *should* be scheduled with a frequency of every 2 weeks for the first three months and every 4 weeks up to week 48 of follow-up period.

[p] Participants who permanently discontinue study treatment will need to attend an unscheduled/early termination visit.

[q] Visit window may be extended to +6 weeks in extreme circumstances such as pandemic, natural disasters, supply chain disruption, outbreak of hostilities.

[r] Participants with HBV DNA > 2,000 IU/mL during the follow-up period will undergo weekly monitoring. Participants with HBV DNA >20 IU/mL but < 2,000 IU/mL, should undergo monitoring every two weeks. Participants, who have discontinued NUC therapy at EOT, should have monthly visits from follow-up Week 24 to Week 48, instead of the 3 monthly follow-up visits shown in SoA, to enable early detection and appropriate management of HBV DNA rebound. At these additional unscheduled monitoring visits, the following laboratory assessments should be performed using the unscheduled lab kit: hematology, chemistry, coagulation, GLDH, urinalysis, HBV serology, HBV DNA quantitative, total HBsAg, HBcrAg, and HBV RNA quantitative.

Note: Additional assessments may be conducted before randomization if required by other arms that are currently recruiting as described in Section 5.2.

Appendix 8
Study Details Specific to CpAM (RO7049389) + TLR7 (RO7020531) + NUC Arm

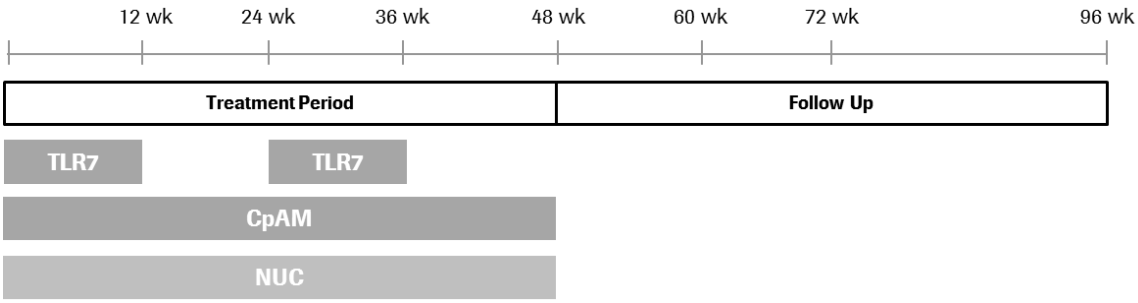
An overview of CpAM + TLR7 + NUC treatment arm is shown in Appendix 8-Figure 1.

Participants will receive RO7049389 (600 mg QD) in addition to their background NUC therapy for the 48-week treatment period. RO7020531 (150 mg once every other day [QOD]) will be administered during Weeks 1-12 and Weeks 25-36 (i.e., 2 treatment cycles of 12 weeks' duration each and 42 doses of RO7020531 for each cycle). At the end of the treatment period, participants will continue NUC treatment during the follow-up unless the NUC discontinuation criteria have been met (see Section 6.8).

Approximately 30 participants will be randomized to this treatment arm.

If a 30% delta for HBsAg loss is observed at Week 48 (EOT) or follow-up Week 12 or 24 (primary endpoint) the treatment arm may be expanded to accrue additional efficacy and safety data, and to contribute to Phase 3 design planning. If a successful interim analysis is observed at Weeks 12 or 24, shorter treatment duration arms (12 and 24 weeks' duration) and/or a response-guided therapy (RGT) arm may be added.

Appendix 8-Figure 1 CpAM + TLR7 + NUC Treatment Arm



A8.1 BACKGROUND SPECIFIC TO CpAM + TLR7 + NUC ARM

A8.1.1 BACKGROUND ON RO7049389

RO7049389 is a core protein allosteric modulator (CpAM) and belongs to the well-studied class of heteroaryldihydropyrimidine (HAP) compounds. This class of compounds induces formation of abnormal HBV core protein aggregates, which are subsequently recognized and depleted. Depleting functional core protein results in interruption of viral assembly and inhibition of HBV replication.

The HBV core protein is involved in multiple steps of the viral life cycle such as encapsulation of pre-genomic ribonucleic acid (pgRNA), subsequent initiation of reverse

transcription, and is an important component of covalently closed circular DNA (cccDNA) mini-chromosome. Furthermore, literature suggests that the HBV core protein may play a role in suppressing host innate immune responses (Twu et al 1988; Fernandez et al 2003; Gruffaz et al 2013). Depletion of functional core protein may therefore facilitate host immune restoration. RO7049389 can therefore potentially provide anti-HBV benefits by both direct inhibition of viral replication and augmentation of host immune responses against the virus.

RO7049389 has shown potent antiviral activity through the induction of HBV core protein misassembly and subsequent degradation, and has a high degree of selectivity against HBV. RO7049389 demonstrated activity against most prevalent HBV genotypes (A, B, C, D) and against a panel of nucleos(t)ide analogue-resistant HBV variants tested in vitro.

To date, clinical experience with RO7049389 includes three Phase 1 clinical studies: an entry-into-human (EIH) study in healthy volunteers (HV) and patients (YP39364), a study in HVs of Chinese descent (YP39406), and a drug-drug interaction (DDI) study in HVs (YP40218).

A8.1.2 BACKGROUND ON RO7020531

RO7020531 is an oral double prodrug of the toll-like receptor 7 (TLR7)-specific agonist RO7011785. A prodrug approach was chosen for oral delivery of the TLR7 agonist RO7011785 in order to improve bioavailability and limit TLR7 activation in the gastrointestinal (GI) tract, which may be associated with GI intolerability.

TLRs are a family of pathogen-recognition receptors that activate the innate immune response. The stimulation of TLR7 mediates an endogenous type I IFN response, which is critical in development of a broad, effective, and protective immunity against hepatitis viruses (Horscroft et al 2012, Funk et al 2014). Compared to pegylated interferon-alpha (PEG-IFN-α) therapy, treatment with a TLR7 agonist induces broader immunomodulatory effects that are likely to lead to more effective control and functional cure of chronic HBV infection (Strader et al 2004, Isogawa et al 2005). TLR7 agonists induce the production of multiple isotypes of IFN from plasmacytoid dendritic cells (pDCs) which have been shown in vitro to possess additive or synergistic antiviral effects compared to exogenous PEG-IFN.

Non-clinical studies with RO7020531 suggest that it is rapidly converted to the active metabolite RO7011785 and data from in vivo studies with RO7020531 and in vitro studies with RO7011785 support immune activation as the mechanism of action.

To date, clinical experience with RO7020531 includes two Phase 1 clinical studies: an EIH study in HVs and CHB patients (NP39305) and a study in HVs of Chinese descent (YP39553).

A8.2 BENEFIT/RISK ASSESSMENT SPECIFIC TO CpAM + TLR7 + NUC ARM

The 48-week treatment with RO7049389 and RO7020531 treatment in combination with NUC aims to result in therapeutic benefit for participants, including possibly higher functional cure rates than observed currently with standard-of-care therapies (monotherapy with NUC or PEG-IFN). The concurrent RO7049389 and RO7020531 administrations in the initial 12 weeks aim to test the scientific hypothesis whether early concurrent direct-acting antiviral and immunomodulatory agent combination therapy maximizes the efficacy outcomes.

This concept is supported by in vivo non-clinical data, whereby in a recombinant adeno-associated virus carrying HBV genome (AAV-HBV) mouse model the combination of RO7049389 (a direct antiviral agent that works as a core protein allosteric modulator) and toll-like receptor 7 (TLR7)-agonist, RO7020531 (an immune modulator) resulted in significantly greater HBV DNA and hepatitis B surface antigen (HBsAg) reductions post treatment (Day 84) than either agent as monotherapy (Appendix 8-Table 1). HBsAg loss (< lower limit of quantification [LLOQ]) was observed in 5 of 7 mice by the end of the 6-week combination treatment and sustained in the 6-week off-treatment period but in none of the monotherapy groups, suggesting a transformational efficacy impact with the combination treatment of RO7049389 and RO7020531.

Appendix 8-Table 1 Summary of Viral Marker Reductions (AAV-HBV Mouse Model)

Treatment	HBV DNA Reduction (Log)			HBsAg Reduction (Log)		
	Day 14	Day 42	Day 84	Day 14	Day 42	Day 84
RO7020531: 100 mg/kg QOD	1.2±0.2	1.9±0.4	0.2±0.1	0.6±0.4	1.6±0.5	0.4±0.2
RO7049389: 20 mg/kg QD	3.5±0.1	3.8±0.1	1.5±0.2	0.0±0.1	1.5±0.2	1.9±0.3
Combination therapy	3.8±0.1	4.1±0.1	3.4±0.5	0.9±0.5	3.1±0.3	3.1±0.3
Vehicle	0.0±0.1	0.0±0.1	0.0±0.1	0.0±0.1	0.0±0.2	0.0±0.2

Notes: Day 84 is 42 days post-treatment. Data presented as mean ± SEM (7 mice per group).

Non-clinical chronic toxicology in rats and non-human primates has provided data supporting the QOD dosing regimen for RO7020531 over 12 week intervals for evaluation in CHB participants.

RO7049389 and RO7020531 separately, have shown acceptable safety/tolerability in Phase 1 studies involving healthy volunteers and CHB participants, and non-clinical toxicology and safety pharmacology studies support the proposed 48-week combination regimen.

For details, refer to the RO7049389 and RO7020531 Investigator's Brochures.

A8.3 JUSTIFICATION FOR DOSE SPECIFIC TO CpAM + TLR7 + NUC ARM

For RO7049389, a dose of 600 mg QD has been selected for this Phase 2 study. This dose is within the predicted therapeutic dose-range in humans and is expected to be safe and well tolerated. A summary of the key data supporting the selected dose is provided below:

- RO7049389 doses up to 1000 mg QD (for 28 days), 800 mg BID (for 6 days) and 2500 mg (single dose) have been observed to be safe and well tolerated in three Phase 1 studies involving healthy volunteers and CHB participants.
- Although 200 mg to 600 mg QD doses resulted in robust pharmacodynamic effects (HBV DNA decline 2.66 – 3.2 $\log_{10}$ IU/mL) in the Phase 1 studies, a trend of increased HBV DNA decline was observed with higher doses. In addition, disease-modelling utilizing non-clinical and clinical PK/PD data predicts an increased PD effect with the 600 mg QD dose.
- The non-clinical chronic toxicology studies provide acceptable safety margins for the 600 mg QD dose.

For RO7020531, a dose of 150 mg QOD has been selected for this Phase 2 study, to be administered continuously over two 12-week cycles separated by a 12-week dosing holiday (for RO7020531 only). This dose and regimen is within the predicted therapeutic dose-range in humans and is expected to be safe and well tolerated. A summary of the key data supporting the selected dose is provided below:

- RO7020531 doses up to 170 mg QOD and 150 mg QOD (both for 6 weeks) have been observed to be safe and with acceptable tolerability in two Phase 1 studies involving healthy volunteers and CHB participants.
- Pharmacodynamic effects consistent with TLR7 activation was observed in the 100-170 mg QOD dose-range, with increasing magnitude of response associated with higher doses.

Further details are provided in the RO7049389 and RO7020531 Investigator's Brochures.

A8.4 INCLUSION/EXCLUSION CRITERIA SPECIFIC TO CpAM + TLR7 + NUC ARM

Participants must meet the following criterion for inclusion in the CpAM + TLR7 + NUC treatment arm;

Sex

1. Female participants:

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

   - Woman of non-childbearing potential (WONCBP).
   - Woman of childbearing potential (WOCBP), who:
     - Agrees to remain abstinent (refrain from heterosexual intercourse) or use two acceptable contraceptive methods of which at least one is considered highly effective (result in a failure rate of < 1% per year) during the treatment period and for at least 6 months after the final dose of study treatment (see A8.7 and Appendix 5).
     - Has a negative pregnancy test at screening (Day -14 to -7). In addition, willing to undergo a urine pregnancy test at Day 1 and every month during treatment and up to 6 months follow-up, thereafter every 3 months until end of follow-up. Where the subsequent visit is greater than 4 weeks, pregnancy test will be done at home using kits supplied by the sponsor.

Participants are excluded from the CpAM + TLR7 + NUC arm if any of the following criteria apply:

Weight

1. Body mass index < 21 and weight at screening: $<$55 kg for men or < 45 kg for women

Medical Conditions

2. Current symptoms of depression or history of depression requiring treatment.
3. History of autoimmune hepatitis or other autoimmune disorders.
4. Diabetes that is not well controlled (HbA1c$\geq$7% at screening)
5. Pre-existing ophthalmologic disorders (known history or as assessed by eye examination at screening), which in the opinion of the investigator would increase the likelihood of clinical significance of potential drug-induced retinopathy (e.g., diabetic or hypertensive retinopathy, glaucoma, dense cataract, visual field abnormalities, severe retinopathy).

6. History of pulmonary disorders including interstitial pneumonitis, bronchiolitis obliterans, pulmonary hypertension, and sarcoidosis.
7. History of pancreatitis.
8. Participants with history or present evidence of orthostatic hypotension.

A8.5 SAFETY ASSESSMENTS SPECIFIC TO CPAM + TLR7 + NUC ARM

Physical Examinations

Eye examination will be performed at screening, preferably by an ophthalmologist, and will include funduscopic examination with dilation, visual acuity, assessment, visual field testing, and color visual testing.

Vital signs

Assessment of orthostatic hypotension will be done at screening. To assess the presence of orthostatic hypotension, blood pressure will be measured both while the participant is sitting and while standing. Participants will be excluded if a drop of 20 millimeters of mercury (mm Hg) in systolic blood pressure or a drop of 10 mm Hg in diastolic blood pressure within two to five minutes of standing up, or if standing causes signs and symptoms of hypotension.

A8.6 LIFESTYLE CONSIDERATIONS SPECIFIC TO CpAM + TLR7 + NUC ARM

Both RO7049389 and RO7020531 will be given in fasted state (at least 2 hours after a meal or 2 hours before the next meal). NUCs will be given according to the local prescribing information.

For RO7049389, any nutrients known to modulate activity of CYP enzymes (e.g., grapefruit-, or Seville orange-containing products) will be prohibited within 3 days before Day -1 through to the last dose of RO7049389.

For RO7020531, consumption of green tea beverages should be minimized during the treatment period, as these may inhibit aldehyde oxidase activity (Tayama et al 2011).

For CHB participants who routinely take herbal medicines that in Investigator's opinion may have immune-modulatory effects, herbal medicines should strongly be discouraged.

A8.7 CONTRACEPTIVE REQUIREMENTS SPECIFIC TO CpAM + TLR7 + NUC ARM

For WOCBP: agreement to remain abstinent (refrain from heterosexual intercourse) or use two acceptable contraceptive methods of which at least one is considered highly

effective (see Appendix 5), during the study and for at least 6 months after the last dose of study drug.

- Examples of acceptable highly effective contraceptive methods (< 1% failure rate per year) include combined or progesterone-only hormonal contraception, intrauterine device, and vasectomized partner.

- Examples of acceptable not as highly effective contraceptive methods (> 1% failure rate per year) include progesterone only hormonal contraception (where inhibition of ovulation is not the primary mode of action) and male or female condoms with or without spermicide.

For men: agreement to remain abstinent (refrain from heterosexual intercourse) or agree to use contraceptive measures, and agree to refrain from donating sperm, as defined below:

- Men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of study drug to avoid exposing the embryo.

- Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial 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 contraception.

A8.8 TREATMENT ADMINISTERED SPECIFIC TO CpAM + TLR7 + NUC ARM

Appendix 8-Table 2 summarizes the treatments administered.
Paracetamol/acetaminophen are considered non investigational medicinal products (NIMPs).

Appendix 8-Table 2 Summary of Treatments Administered for CpAM + TLR7 + NUC Treatment Arm

Study Treatment Name	CpAM (RO7049389)	TLR7 (RO7020531)	NUC
IMP and NIMP	IMP	IMP	NIMP*
Dose Formulation	film-coated tablet	film-coated tablet	film-coated tablet
Unit Dose Strength(s)/Dosage Level(s)	200 mg	150 mg 100 mg	Refer to local prescription information
Dose:	600 mg	150 mg QOD 100 mg QOD 100 mg QW	ETV: 0.5 mg TDF: 300 mg TAF: 25 mg
Route of Administration	Oral	oral	oral
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor or locally by the study site
Packaging and Labeling	Study treatment will be packaged and labeled as required per local regulation.	Study treatment will be packaged and labeled as required per local regulation.	Study treatment will be packaged and labeled as required per local regulation.

*NUC are considered IMP in the UK only.

Guidelines for dosage modification and treatment interruption/discontinuation are in Section *A8.* (in this Appendix).

For more details, refer to the RO7049389 and RO7020531 Investigator's Brochures, NUC local prescribing information, and the Pharmacy Manual.

A8.9 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non serious AESIs 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 documents listed below:

Drug	Document
RO7020531	RO7020531 Investigator's Brochure
RO7049389	RO7049389 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.

A8.10 CONCOMITANT THERAPY SPECIFIC TO CpAM + TLR7 + NUC ARM

The following concomitant medications are prohibited:

- Inducers of CYP3A enzyme: e.g., efavirenz, nevirapine, pioglitazone, rifampin, rifabutin, troglitazone, phenobarbital, phenytoin, carbamazepine, and St. John's wort within 14 days or 5 half-lives (whichever is longer) before the first administration of RO7049389 and while on study treatment with RO7049389.
- Inhibitors of CYP3A enzyme: e.g., indinavir, nelfinavir, clarithromycin, itraconazole, ketoconazole, nefazodone, ketoconazole, verapamil, suboxone, diltiazem, cimetidine, amiodarone, fluvoxamine, troleandomycin, and voriconazole within 7 days or 5 half-lives (whichever is longer) before the first administration of RO7049389 and while on study treatment with RO7049389.
- Strong inducers of UDP-glucuronosyltransferase (UGT) 1A3 enzymes: e.g., carbamazepine and nicotine within 14 days, or 5 half-lives (whichever is longer) before the first administration of RO7049389 and while on study treatment with RO7049389.
- Strong inhibitors of UGT1A3/1A1 enzymes: e.g., indinavir, atazanavir, gemfibrozil, indinavir, and ketoconazole within 7 days, or 5 half-lives (whichever is longer) before the first administration of RO7049389 and while on study treatment with RO7049389.
- Inhibitors of OATP1B transporters: e.g., cyclosporine, rifampicin, eltrombopag, lapatinib, lopinavir, ritonavir within 7 days, or 5 half-lives (whichever is longer) before the first administration of RO7049389 and while on study treatment with RO7049389.
- Inhibitors of Organic Anion Transporter 1 and 3 (OAT 1 and OAT 3): e.g., p-aminohippuric acid (PAH), probenecid, and teriflunomide, within 7 days, or 5 half-lives (whichever is longer) before the first administration of RO7020531 and while on study treatment with RO7020531.
- Inhibitors of P-gp transporters: e.g., amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine,

ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil within 7 days, or 5 half-lives (whichever is longer) before the first administration of RO7020531 and while on study treatment with RO7020531.

The following concomitant medications are to be used with caution and the Sponsor should be informed before these drugs are administered. When co-administered with study drugs, the recommendation is to use the lowest necessary dose of the substrate, titrate the dose carefully, and monitor closely for substrate-associated adverse reactions.

- Substrates of OATP1B: e.g., atrasentan, bosentan, ezetimibe, irinotecan, statins (e.g., atorvastatin, rosuvastatin, simvastatin, pitavastatin, pravastatin), repaglinide, rifampin, valsartan, and olmesartan.
- CYP3A4 substrates with a narrow therapeutic range.
- Drugs metabolized by aldehyde oxidase including famciclovir and/or inhibiting this enzyme including tamoxifen, raloxifen, cimetidine, promethazine, clozapine, and chlorpromazine, which could decrease the formation of RO7011785.
- Drugs that reduce renal function or compete for active tubular secretion that may increase serum concentrations of RO7011785 study drug.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication when determining whether a certain medication inhibits or induces above mentioned enzymes or transporters or renal function. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications that are not listed above.

A8.11 MANAGEMENT OF ADVERSE EVENTS SPECIFIC TO CpAM + TLR7 + NUC ARM

TLR-RELATED AES

TLR7 agonist activates innate and adaptive immune responses, and these mechanisms include induction of type I interferon (IFNα). Safety data from the ongoing Phase 1 studies showed IFN-related flu-like symptoms (headache, pyrexia, chills, myalgia, nausea), mostly of mild intensity; and in some participants, hematological abnormalities (e.g., neutropenia, lymphopenia). During the two clinical studies with RO7020531 (NP39305 and YP39553), all hematological abnormalities were asymptomatic and in most cases reversible within 24 to 48 hours.

TLR7 agonists as a class may have the potential, in a dose-dependent manner, to lead to hypotension and distributive shock due to excessive cytokine release (cytokine release syndrome [CRS])—e.g., IL-1, IL-6,IL-10, IFN-γ, TNF-α etc.—by immune activation. CRS can present with a variety of symptoms, from mild symptoms overlapping with mild flu-like symptoms to severe or life-threatening manifestations. Mild

symptoms of CRS include fever, fatigue, headache, rash, arthralgia, and myalgia. More severe cases are characterized by hypotension that requires vasopressor treatment and/or hypoxia that requires medical intervention. They can progress to an uncontrolled systemic inflammatory response with circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi–organ-system failure. Flu-like symptoms were observed during the two clinical studies with RO7020531 (NP39305 and YP39553) at 140 mg to 170 mg single or multiple QOD doses up to 6 weeks. These symptoms overlap with and are not distinguishable from mild cases of CRS.

A8.12 ENHANCED SAFETY MONITORING DURING COMBINATION TREATMENT WITH CpAM + TLR7 + NUC

Based on the emerging data from Phase 1 studies NP39305 (HV and patient cohorts) and YP39553 (single– and multiple–ascending-dose clinical study in Chinese HVs), it became evident that in all cases of flu-like symptoms, the initial onsets emerged within the initial 3 doses of RO7020531. For this reason, pre-dose laboratory analyses and optional extended in-hospital stay with frequent vital sign monitoring (every 2 to 4 hours) and ECGs (pre-dosing and 6 to 8 hours after dosing at each visit) are scheduled for the initial 3 doses of each combination cycle and guided by emerging AEs as follows:

- on Day 1 and/or Day 169 (first day of the second cycle of TLR7 dosing), participants will stay in the clinical unit for 12 hours with an option to stay in the clinic for up to 24 hours (at the Investigator's discretion) in case pyrexia and additional flu-like symptom(s) emerge and do not respond to symptomatic treatment (paracetamol/acetaminophen up to 2 g/day) during the first 12 hours post-combination dosing. For those participants who stay up to 24 hours, an additional 24 hours post-dose laboratory assessment will be done on Day 2 and Day 170, respectively.
- on Day 3 and Day 171 (third day of the second cycle of TLR7 dosing), participants will stay in the clinical unit for 8 hours with an option to stay in the clinic for up to 12 hours (at the Investigator's discretion) in case pyrexia and additional flu-like symptom(s) emerged and would not respond to symptomatic treatment (paracetamol/acetaminophen up to 2 g/day) during the first 8 hours post-combination dosing.
- on Day 5 and Day 173 (fifth day of the second cycle of TLR7 dosing), participants will stay in the clinical unit for 8 hours with an option to stay in the clinic for up to 12 hours (at the Investigator's discretion) in case pyrexia and additional flu-like symptom(s) emerged during the first 8 hours and would not respond to symptomatic treatment (paracetamol/acetaminophen up to 2 g/day) during the first 8 hours post-combination dosing.

The Sponsor will promptly communicate to the Investigator any change to the proposed enhanced monitoring plan based on emerging data and interim safety evaluations. In

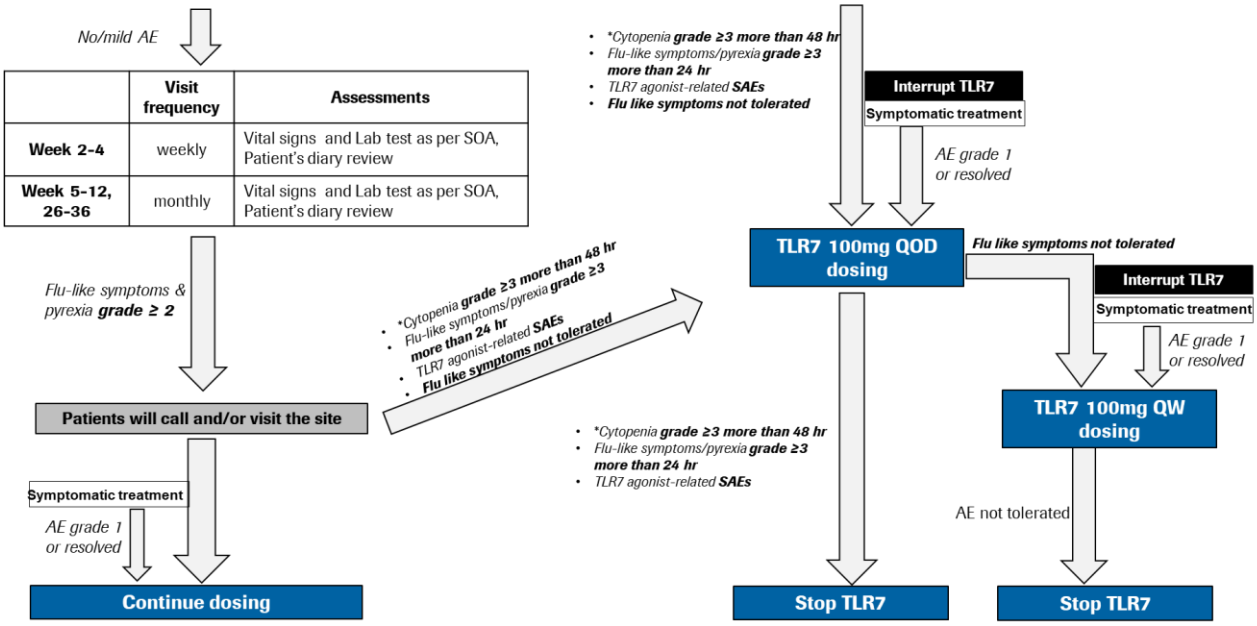
case the prolonged hospital stay is not required but participants live far away and may need to be back on the following day, the investigator may decide to allow them to stay at a hotel nearby.

The Sponsor will provide participants a thermometer to use for temperature self-monitoring in case flu-like symptoms and pyrexia emerge. If at any time during the combination cycles (CpAM + TLR7 + NUC) participants experience flu-like symptoms with pyrexia (Grade 2 or above), it will be recommended to call the site and the PI or the medical personnel on site:

- may recommend participants visit the clinic for an unscheduled visit according to the SOA in Appendix 8.
- may recommend symptomatic treatment with paracetamol/ acetaminophen up to 2 g/day.

Appendix 8-Figure 2. Safety monitoring and RO7020531 dosing interruption for flu-like symptoms and cytopenia during combination treatment with CpAM + TLR7 + NUC

Combination treatment week(s)	Day	Clinic stay duration	Assessments
Week 1 (or week 25 if the second cycle)	1 (or169 if second cycle)	12- to up to 24-hr[a] post dose	*Lab test (pre-dose), vital signs, ECG[c]
	3 (or171 if second cycle)	8- to up to12-hr[b] post dose	
	5 (or173 if second cycle)	8- to up to12-hr[b] post dose	
	[a] 24 hr if pyrexia and flu-like symptoms emerged and do not respond to symptomatic treatment within the first 12 hr [b] 12 hr if pyrexia and flu-like symptoms emerged and do not respond to symptomatic treatment within the first 8 hr [c] 24 hr post dose lab analyses if patients will stay in the clinic due to pyrexia and flu-like symptoms during day 1 (or 169)		



*Based either on central laboratory (as per the SoA in this appendix) and/or local laboratory if performed for participant management and/or decision-making. In such a scenario, if local laboratory tests are performed, an additional sample will be sent to the central laboratory, but decisions will be based on local laboratory results.

A8.13 DOSE MODIFICATION

Dose reduction to 100 mg QOD with RO7020531 for intolerability associated with adverse events should be considered following discussion with the Medical Monitor (if possible) during the treatment phase in the following situations:

- Grade 3 (severe) TLR7 agonist-related AEs of flu-like symptoms that persist > 24 hours despite prophylactic and/or symptomatic treatment with acetaminophen (paracetamol)
- Grade 3 (severe) hematological (e.g., cytopenia) laboratory abnormalities that persist for > 48 hours

- TLR7 agonist-related SAE
- Flu-like symptoms that are not tolerated

In the above situations, RO702053 150 mg QOD dosing should be interrupted until AEs, laboratory abnormalities, or SAEs improve to Grade 1 or less, before initiating a dose reduction to RO7020531 100 mg QOD.

For repetitive/recurrent flu-like symptoms/pyrexia (either responsive or unresponsive despite symptomatic treatment with acetaminophen or poorly manageable despite prophylactic treatment with acetaminophen) or other TLR7 agonist-related AEs (including repetitive AEs) which are not well manageable, the Investigator in discussion with the participant should consider a RO7020531 dose reduction to 100 mg QOD. The Medical Monitor is available to the Investigator to answer any medical questions.

Following the RO7020531 dose reduction to 100 mg QOD, the Investigator should interrupt RO7020531 dosing if any of the following situations occur:

- Grade 3 (severe) TLR7 agonist-related AEs of flu-like symptoms that persist for > 24 hours despite prophylactic and/or symptomatic treatment with acetaminophen (paracetamol)
- Grade 3 (severe) hematological (e.g., cytopenia) laboratory abnormalities that persist for > 48 hours
- TLR7 agonist-related SAE

Following the RO7020531 dose reduction to 100 mg QOD, if flu-like symptoms are still not tolerated by the participants, a reduction of the dosing frequency of RO7020531 to 100 mg QW (once a week) should be considered.

Appendix 8-Table 3 summarizes possible reasons for dose modification, interruption /discontinuation guidelines of study treatment (or withdrawal from the study) for the CpAM+TLR7+NUC arm.

Appendix 8-Table 3 Dose Interruption/Modification/Discontinuation Guidelines for CpAM+TLR7+NUC Combination Arm

Laboratory/Clinical Parameters	Recommendation	Reference
TLR7-related AEs		
Grade 3 flu-like symptoms >24 hr despite prophylactic and/or symptomatic treatment, or, repetitive flu-like symptoms that are poorly tolerated	**Interrupt** RO7020531 dosing (150 mg QOD). **Reduce** RO7020531 to **100 mg QOD** when AEs improved to Grade 1 or SAE resolved. Following dose reduction (100 mg QOD), if similar Grade 3 AEs or laboratory abnormalities occur, interrupt RO7020531. In general, consider **switching to 100 mg QW** (at least 5 days after the last dose) prior to drug discontinuation (case-by-case basis).	Appendix 8 (Section A8.12)
Grade 3 hematological abnormalities that persist >48 hr		
TLR7 agonist-related SAE		
CpAM-related AEs		
No laboratory or clinical parameters have been identified yet	No dose modification recommendations for CpAM	N/A
General criteria for dose interruptions/discontinuations for all NMEs		
Liver transaminases and liver function test	See Section 7.1	Section 8.3.8.3
Confirmed virological breakthrough	**Discontinue** NMEs and continue treatment according to local standards	Section 8.3.8.1
Others	See Section 7.1	

In general, when addressing tolerability issues with RO7020531, prior to the investigator making a decision to discontinue study treatment or participant withdrawal of consent from study treatment, a dose reduction should be discussed and evaluated if considered in the participant's best interest. The Medical Monitor is available to the Investigator to answer any medical questions.

The first dose of RO7020531 100 mg QOD should be administered in the clinic, and participants should be monitored for at least 8 hours as per SoA (with pre-dose safety laboratory assessment, every 2 to 4 hours for vital signs, and ECG assessment at pre-dose and 6 to 8 hours post-dose). This first visit should be synchronized with the participant's current RO7020531 QOD dosing schedule.

In case participants are changed to 100 mg QW dosing, at least 5 days should have elapsed since the last dose. If Grade 2 flu-like symptoms occur, the Investigator may recommend symptomatic treatment with paracetamol/ acetaminophen. If symptoms respond to symptomatic treatment and the treatment is tolerable, participants will continue QW dosing. If there is poor tolerability, participants will permanently discontinue further RO7020531 dosing. Participants changed to the QW dosing will follow the same SOA of participants in the QOD dosage, with two 12-week combination treatment cycles (Weeks 1 to 12 and 25 to 36) and a 12-week holiday period (Weeks 13-24).

Participants who change to 100 mg QW dosing or discontinue because of non-safety reasons may be replaced at the sponsor's discretion. This is to ensure the number per arm of the randomized QOD dose regimen remains close to the planned 30 participants.

Participants on RO7020531 100 mg QOD will follow the SoA as included in Appendix 8. In case of RO7020531 100 mg QW dosing, participants will follow the SoA as included in Appendix 8, but QW dosing administration will be aligned with SoA visits.

For ALT elevations, refer to Section 8.3.8.3.

A8.14 PHARMACODYNAMICS AND BIOMARKERS ANALYSES SPECIFIC TO CpAM + TLR7 + NUC ARM

A8.14.1 TLR7 ACTIVITY BIOMARKERS

TLR7 is expressed on human pDC and B-cells, and its activation induces both humoral and cellular changes (Iwasaki and Medzhitov 2004, Lester and Li 2014). These changes include the production of cytokines and chemokines such as IFN- α, IL-6, TNF-α, IL-10, IL-12p40, IP-10, and changes in the expression of ISGs, e.g., *MX1* and myxovirus resistance 1 gene (*MX1*) and of the TLR7 gene itself (Fidock et al 2011), as well as changes in markers of immune stimulation such as neopterin.

To characterize TLR7 PD biomarkers (secondary objective), blood samples will be collected at time points according to the SoA (see Appendix 8-Table 4 and Appendix 8-Table 5) to measure cytokines including INF-α and IP-10, IL-6, TNF-α as well as a panel of transcriptional response of Interferon Stimulated Genes (*ISG15, OAS1, MX1, and TLR7*) if appropriate. Following review of these PD biomarkers and the AEs, further cytokines may be tested using a separate aliquot collected at the same time points including IL-1, IL-10, and IFN-γ.

A8.14.2 CLINICAL GENOTYPING

If safety or activity rationales develop, clinical genotyping will be performed (see Sections 8.7.4.1 and 8.8.1.1) if appropriate. This exploratory objective will aim at evaluating the association of genetic polymorphisms in known candidate genes with the PK profiles of the two NMEs and with primary and secondary endpoints. Known candidate genes of interest that are specific to TLR7 and/or CpAM include *AOX1*, *TLR7*, *UGT1A1*, *PGP*, *OATP1B1*, *OATP1B3*, *CYP3A4*, and *UGT1A3*. Further genes may be queried from the data based on progressing knowledge on these NMEs and their targets.

A8.15 SCHEDULE OF ACTIVITIES CpAM + TLR7 + NUC ARM

An overview of the schedule of the activities is provided in Appendix 8-Table 4 and Appendix 8-Table 5.

Appendix 8-Table 4 Schedule of Activities for CpAM + TLR7 + NUC Treatment Arm (Screening and Treatment Periods)

	Screening		Treatment Period																	100 mg QOD [u]	VB/VR	UV (Flu-like/ET) [v]
Week			**1**			**2**	**3**	**4**	**8**	**12** [o, q]	**18**	**25** [p, q]			**28**	**32**	**36**	**42**	**48**		**-**	**-**
Day	**-56 to -7**	**-14 to -7**	**1**	**3** [s]	**5** [s]	**14 (±2)**	**21 (±2)**	**28 (±2)**	**56 (±3)**	**83 (-2** [r]**)**	**126 (±3)**	**169 (±3)**	**+2** [s]	**+2** [s]	**196 (±6)**	**224 (±6)**	**251 (-5/+3** [r]**)**	**294 (±3)**	**336 (-3** [q]**)**			
Informed consent	x																					
Demography, medical history	x																					
Physical examination, vital signs [a, b]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization			x																			
ECG	x		x [t]	x [t]	x [t]	x	x	x	x	x		x [t]	x [t]	x [t]	x	x	x		x	x [t]		
Transient elastography/ARFI/MR [c]	x																					
Abdominal ultrasound	x											x							x			
Alfa-fetoprotein	x											x							x			
HAV, HCV, HDV, HEV, HIV	x																					
Autoantibodies [d]	x																					
Alcohol and drugs of abuse screen [e]		x																	x			x
Pregnancy test [f]		x	x					x	x	x	x	x			x	x	x	x	x			x
Thyroid function tests	x									x		x							x			

Appendix 8-Table 4 Schedule of Activities for CpAM + TLR7 + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

	Screening		Treatment Period																	100 mg QOD [u]	VB/VR	UV (Flu-like/ET) [v]
Week			1			2	3	4	8	12 [o, q]	18	25 [p, q]			28	32	36	42	48		-	-
Day	-56 to -7	-14 to -7	1	3 [s]	5 [s]	14 (±2)	21 (±2)	28 (±2)	56 (±3)	83 (-2 [r])	126 (±3)	169 (±3)	+2 [s]	+2 [s]	196 (±6)	224 (±6)	251 (-5/+3 [r])	294 (±3)	336 (-3 [q])			
Hematology (include HbA1c [g])	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry		x	x	x	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	x	x	x
GLDH	x		x	x	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	x	x	x	x	x
Clinical genotyping [h]			x																			
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x		x			x	x	x	x	x	x	x			x	x	x	x	x		x	x
HBV DNA quantitative	x		x			x	x	x	x	x	x	x			x	x	x	x	x		x	x
Total HBsAg [i]			x					x		x		x				x	x		x		x	
HBcrAg			x					x		x		x				x	x		x		x	
Total anti-HBc quantitative			x							x		x					x		x			
HBV RNA quantitative			x					x		x		x				x	x		x		x	
HBV RNA sequencing [h]			x																			
HBV DNA sequencing [j]																					x	

Appendix 8-Table 4 Schedule of Activities for CpAM + TLR7 + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

	Screening		Treatment Period																	100 mg QOD [u]	VB/VR	UV (Flu-like/ET) [v]
Week			1			2	3	4	8	12 [o, q]	18	25 [p, q]			28	32	36	42	48		-	-
Day	-56 to -7	-14 to -7	1	3 [s]	5 [s]	14 (±2)	21 (±2)	28 (±2)	56 (±3)	83 (-2 [r])	126 (±3)	169 (±3)	+2 [s]	+2 [s]	196 (±6)	224 (±6)	251 (-5/+3 [r])	294 (±3)	336 (-3 [q])			
Plasma PK (TLR7) [k]			x	x	x					x		x	x	x			x			x	x	
Plasma PK (CpAM) [k]			x							x		x					x		x		x	
Plasma PK (NUC) [k]			x							x		x					x		x		x	
Cytokine panel [l]			x	x	x					x		x	x	x			x			x		x
ISG panel [l]			x	x	x					x		x	x	x			x			x		x
RBR [m]			x									x					x		x		x	
Study treatment administration and diary review			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events & concomitant medications [n]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ARFI = acoustic radiation force impulse; CpAM = Core protein allosteric modulator; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IFN- α+ interferon alpha; IP-10 = interferon gamma-induced protein 10; ISG = interferon-stimulated genes; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics; QW = first day of RO7020531 dosing after switching to QW regimen; RBR = Research Biosample Repository; RNA = ribonucleic acid; TLR = toll-like receptor; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

Appendix 8-Table 4 Schedule of Activities for CpAM + TLR7 + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

[a] Full physical exam at screening and at the end-of-treatment. Limited symptom-directed physical exam at other visits and as clinically indicated. Height at screening only. Weight at screening, Day 1, and Week 12, 25, 36, 48. Eye examination (including fundoscopy) only at screening.

[b] Blood pressure, pulse rate, respiratory rate and body temperature obtained at least 5 minutes after participant has been in supine/sitting position. Orthostatic hypotension test only at screening. Vital signs assessments on Days 1 and 169: predose, 2-4 hrs, 4-6 hrs, 6-8 hrs and 8-12 hrs; Vital signs assessments on Days 3 (second dose), 5 (third dose) of the first RO7020531 cycle, on the first day of those switching to QW dosing and on the days of the second and third RO7020531 dose in the second cycle: predose, 2-4hrs, 4-6hrs, 6-8hrs (and 8-12 hours optional in case of extended in-clinic stay).

[c] Historical liver biopsy or transient elastography/ARFI/MR/2D- shear wave elastography [2D-SWE] results obtained within 6 months prior to randomization are also acceptable. During screening transient elastography/ARFI/MR/2D-SWE are acceptable.

[d] Autoantibodies refer to ANA, AMA, ASMA, and a-TPO.

[e] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[f] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. Where the subsequent visit is greater than 4 weeks duration, pregnancy test will be done at home. If urine test is positive, it must be confirmed by a serum test.

[g] HbA1c should be included in hematology, and is required only at screening.

[h] If not collected at Day 1, samples for clinical genotyping and HBV RNA sequencing can be collected at any subsequent time point. *The sample for HBV RNA sequencing aims at determining the HBV genotype. The HBV genotype may also be inferred using alternative approaches, such as serovariant determination.*

[i] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb complexes/components of HBsAg.

[j] HBV DNA sequencing will be collected in case of virological breakthrough/relapse, blood sample to be collected up to 6 times.

[k] Plasma PK samples for CpAM and TLR7 to be collected at pre-dose, 1-3 and 4-6 hours post-dose. Plasma PK samples for NUC to be collected at pre-dose. During the PK assessments for VB/VR visits, only one pre-dose sample is required for collection, no other points required.

[l] Cytokine panel (INF-α, IP-10, IL-1, IL-6, IL-10, IFN-γ, and TNF-α) and ISG panel to be collected at pre-dose and 6 hours post-dose of TLR7. At an unscheduled visit or early termination visit, preferably a pre-dose, otherwise, just a sample for cytokine and ISG panels should be collected if the visit is linked to a TLR7 related adverse reaction (e.g., influenza-like symptoms). No samples are required, for unscheduled visit or early termination visit not linked to TLR7 related adverse reaction (e.g., influenza-like symptoms).

[m] RBR samples collected only from RBR-consenting participants.

[n] Pre-treatment, only serious adverse events should be reported.

[o] End-of-treatment visit for participants in the 12-week finite treatment arm (if commenced after an interim analysis).

[p] End-of-treatment visit for participants in the 24-week finite treatment arm (if commenced after an interim analysis).

Appendix 8-Table 4 Schedule of Activities for CpAM + TLR7 + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

[q] End-of-treatment visit for participants with HBsAg loss in the 48-week response-guided therapy arm (if commenced after an interim analysis).

[r] visit will be on dosing days for PK and PD sampling: -7 if the participant is on QW dosing.

[s] Not applicable to participants who switched to QW RO7020531 dosing.

[t] ECGs to be assessed predose and 6-8hrs post-dose on the first 3 doses of each 12-week RO7020531 cycle and on first dose if 100 mg QOD dosing is started.

[u] For participants who move from 150 mg QOD to 100 mg QOD, this first dose of 100 mg QOD should be administered in the clinic and should be synchronized with the participants' current RO7020531 QOD dosing schedule e.g., if the next current QOD dosing falls over the weekend, then it would be acceptable to miss doses for the first dose visit to take place outside the weekend.

[v] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

Appendix 8-Table 5 Schedule of Activities for CpAM + TLR7 + NUC Treatment Arm (Follow-up period)

	Follow-up period											VB/VR	UV (Flu like/ET)[i]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Physical examination, vital signs [a, b]									x		x	x	x
ECG									x		x		
Abdominal ultrasound									x		x		
Alfa-fetoprotein									x		x		
Alcohol and drugs of abuse screen [c]													x
Pregnancy test [d]		x		x		x	x	x	x	x	x		
Thyroid function tests									x		x		
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry	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
GLDH	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
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x	x	x	x	x	x	x	x	x	x	x	x	x
HBV DNA quantitative	x	x	x	x	x	x	x	x	x	x	x	x	x
Total HBsAg [e]		x		x		x		x	x		x	x	
HBcrAg		x		x		x		x	x		x	x	
Total anti-HBc quantitative						x			x		x		
HBV RNA quantitative		x		x		x		x	x		x	x	
HBV DNA sequencing												x	
Plasma PK (TLR7)													
Plasma PK (CpAM)													

Appendix 8-Table 5 Schedule of Activities for CpAM + TLR7 + NUC Treatment Arm (Follow-up period) (cont.)

	Follow-up period											VB/VR	UV (Flu like/ET)[i]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Plasma PK (NUC)[f]												x	
RBR[g]												x	
Diary review	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events & concomitant medications[h]	x	x	x	x	x	x	x	x	x	x	x	x	x

ARFI = acoustic radiation force impulse; CpAM = Core protein allosteric modulator; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IP-10 = interferon gamma-induced protein 10; ISG = interferon-stimulated genes; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics; RBR = Research Biosample Repository; RNA = ribonucleic acid; TLR = toll-like receptor; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

Note: If participants discontinue NUC later in the follow-up, additional visits can be scheduled with a frequency of every 2 weeks for the first three months and every 4-12 weeks up to week 48 of follow-up period, similarly to the monitoring proposed for those who will discontinue NUC and CpAM at week 48 at the end-of-treatment period.

Appendix 8-Table 5 Schedule of Activities for CpAM + TLR7 + NUC Treatment Arm (Follow-up period) (cont.)

[a] Full physical exam at screening and at the end-of-treatment. Limited symptom-directed physical exam at other visits and as clinically indicated. Height at screening only. Weight at screening, Day 1, and Week 12, 25, 36, 48.

[b] Blood pressure, pulse rate, respiratory rate and body temperature obtained at least 5 minutes after participant has been in supine/sitting position. Orthostatic hypotension test only at screening. Eye examination (fundoscopy) only at screening.

[c] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[d] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[e] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb complexes/components of HBsAg.

[f] During the PK assessments for VB/VR visits only one sample is required, pre-dose sample if on NUC therapy, no other additional time points should be collected.

[g] RBR samples collected only from RBR-consenting participants.

[h] Pre-treatment, only serious adverse events should be reported.

[i] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

Appendix 9
Study Details Specific to siRNA (RO7445482) + NUC Arms

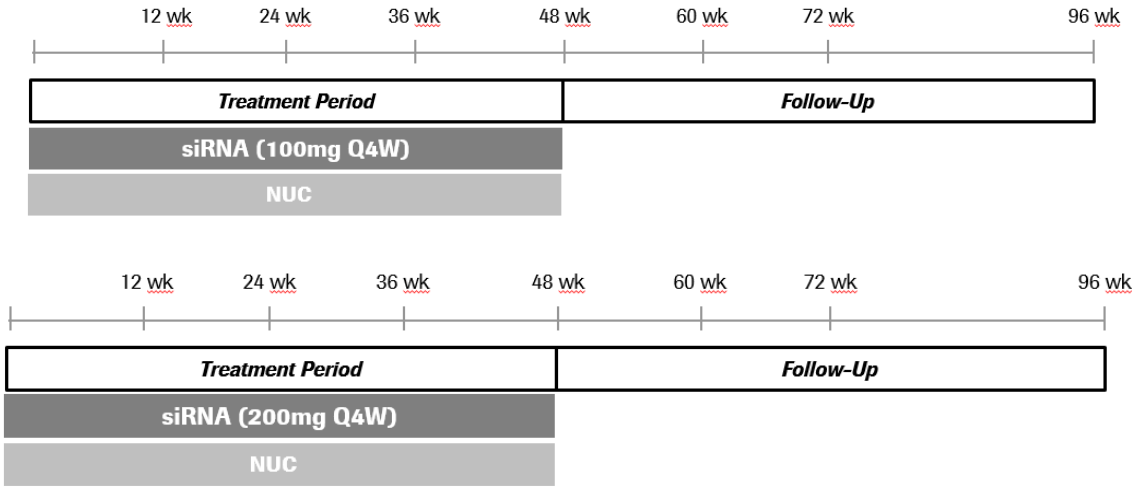
An overview of short interfering RNA (siRNA) + nucleos(t)ide (NUC) treatment arms is shown in Appendix 9-Figure 1.

Participants will receive RO7445482 (also known as DCR-HBVS; 100 mg or 200 mg every 4 weeks [Q4W]) in addition to their background NUC therapy for the 48-week treatment period. At the end of the treatment period, participants will continue NUC treatment during the follow-up unless the NUC discontinuation criteria have been met (see Section 6.8).

Approximately 30 participants will be randomized to this treatment arm.

If a 30% delta for hepatitis B surface antigen (HBsAg) loss is observed at Week 48 (end-of-treatment [EOT]) or follow-up Weeks 12 or 24 (primary endpoint), the treatment arm may be expanded to accrue additional efficacy and safety data and to contribute to Phase 3 design planning. If a successful interim analysis is observed at Weeks 12 or 24, shorter treatment duration arms (12 and 24 weeks' duration) and/or a response-guided therapy (RGT) arm may be added.

Appendix 9-Figure 1 siRNA + NUC Treatment Arms



A9.1 BACKGROUND SPECIFIC TO siRNA + NUC ARM

A9.1.1 BACKGROUND ON RO7445482 (DCR-HBVS)

RO7445482 (DCR-HBVS) is an siRNA conjugated to N-acetyl-D-galactosamine (GalNAc), which enables liver targeting through binding to the asialoglycoprotein receptor (ASGPR) that is highly expressed in the liver. After forming the RNA-induced silencing complex (RISC), the RO7445482 antisense strand targets HBV RNA for degradation by triggering RNAi-mediated cleavage within the HBsAg coding sequence, thereby inhibiting HBV gene expression.

Literature indicates that HBV antigens suppress the host immune response through several pathways, including the direct effects of long-term exposure to high concentration of viral antigens resulting in T-cell immune tolerance and T-cell exhaustion (Hai-Jun et al 2015). Depletion of viral antigens through inhibition of hepatitis B virus (HBV) gene expression may therefore facilitate the restoration of the host immune response.

Non-clinical studies with RO7445482 have shown potent antiviral activity. HBsAg reductions of up to 3.5 $\log_{10}$ for more than 7 weeks, as well as significant reductions in HBcAg, were observed after a single translationally relevant dose in mice, demonstrating duration of action suitable for infrequent dosing.

To date, clinical experience with RO7445482 is based on a Phase I clinical study (DCR-HBVS-101) involving healthy volunteers and participants with CHB.

A9.2 BENEFIT/RISK ASSESSMENT SPECIFIC TO siRNA + NUC ARM

The 48-week treatment with RO7445482 in combination with NUC aims to result in therapeutic benefit for participants, including possibly higher functional cure rates than observed currently with standard-of-care therapies (monotherapy with NUC or PEG-IFN). The concurrent RO7445482 and NUC administrations aims to test the hypothesis whether prolonged reduction in HBV antigens, including but not limited to HBsAg, will result in immune-restoration and potentially functional cure.

Interim Phase 1 data have shown significant and durable antiviral activity with 4 monthly doses of RO7445482 in NUC-suppressed participants with chronic hepatitis B (CHB). At Day 112, mean HBsAg $\log_{10}$ IU/mL reduction from baseline were 1.39, 1.80, and 1.84 for participants who received 1.5 mg/kg, 3.0 mg/kg or 6 mg/kg, respectively. Approximately 80% of participants achieved > 1.5 $\log_{10}$ IU/mL reduction (irrespective of hepatitis B early antigen [HBeAg]-status), 60% had HBsAg levels < 100 IU/mL, and durability of response was demonstrated up to Day 392.

Based on the interim Phase 1 data, RO7445482 was safe and well tolerated in healthy volunteers (HV) and CHB patients. The safety profile appears to be similar between HVs and patient participants, and there were no safety signals or dose related trends

identified. No severe or serious treatment-emergent adverse events (TEAEs) or TEAEs leading to treatment discontinuation, apart from generally mild injection site reactions (ISRs), there was absence of other potential oligonucleotide class effects.

RO7445482 has shown acceptable safety/tolerability in the Phase 1 study involving healthy volunteers and CHB participants, and non-clinical toxicology and safety pharmacology studies support the proposed 48-week combination regimen.

For details, refer to the RO7445482 Investigator's Brochure.

A9.3 JUSTIFICATION FOR DOSE SPECIFIC TO siRNA + NUC ARM

For RO7445482, fixed dose of 200 mg Q4W (equivalent to 3 mg/kg monthly) has been selected for Phase 2 study in combination with other IMPs/NMEs. This dose is within the anticipated therapeutic dose-range in humans and is expected to be safe and well tolerated. A summary of the key data supporting the selected dose is provided below:

- The dose-response trend in the HBsAg declines, together with PK/PD modeling of interim Phase 1 data, supports the proposed 200 mg Q4W dosing regimen. Preliminary PK/PD modeling predicts that the proportion of participants who will achieve > 1.5 and > 2 $\log_{10}$ IU/mL reductions in HBsAg, following Q4W doses up to Week 12, will be higher with a 200mg Q4W regimen (97% and 56%, respectively) compared to a 100 mg Q4W regimen (89% and 6%, respectively).

- The non-clinical chronic toxicology studies provide acceptable safety margins for the 200 mg Q4W fixed dose (3 mg/kg equivalent) for treatment period of 48 weeks.

- PK/PD modelling supports use of fixed (200 mg) instead of weight-based (3 mg/kg) RO7445482 dosing.

An additional RO7445482 fixed dose of 100 mg Q4W (equivalent to 1.5 mg/kg) is included for the evaluation of dose-response over the 48-week treatment period. This dose is within the anticipated therapeutic dose-range in humans and is expected to be safe and well tolerated.

Further details are provided in the RO7445482 Investigator's Brochure.

A9.4 INCLUSION/EXCLUSION CRITERIA SPECIFIC TO siRNA + NUC ARM

Participants must meet the following criterion for inclusion in the siRNA+ NUC treatment arm:

Sex

1. Female participants:

   A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

   - Woman of non-childbearing potential (WONCBP).
   - Woman of childbearing potential (WOCBP), who:
     - Agrees to remain abstinent (refrain from heterosexual intercourse) or use 2 acceptable contraceptive methods, of which at least 1 is considered highly effective (result in a failure rate of < 1% per year) during the treatment period and for at least 6 months after the final dose of study treatment (see A9.6 and Appendix 5).
     - Has a negative pregnancy test at screening (Day -14 to -7). In addition, willing to undergo a urine pregnancy test at Day 1 and every month during treatment and up to 6 months follow-up, thereafter every 3 months until end of follow-up.

A9.5 LIFESTYLE CONSIDERATIONS SPECIFIC TO siRNA + NUC ARM

NUCs will be given according to the local prescribing information.

For CHB participants who routinely take herbal medicines that, in the Investigator's opinion, may have immune-modulatory effects, herbal medicines should strongly be discouraged.

A9.6 CONTRACEPTIVE REQUIREMENTS SPECIFIC TO siRNA + NUC ARM

For WOCBP: agreement to remain abstinent (refrain from heterosexual intercourse) or use 2 acceptable contraceptive methods of which at least one is considered highly effective (see Appendix 5) during the study and for at least 6 months after the last dose of study drug.

- Examples of acceptable highly effective contraceptive methods (< 1% failure rate per year) include combined or progesterone-only hormonal contraception, intrauterine device, and vasectomized partner.

- Examples of acceptable not as highly effective contraceptive methods (> 1% failure rate per year) include progesterone-only hormonal contraception (where inhibition of ovulation is not the primary mode of action) and male or female condoms with or without spermicide.

For men: agreement to remain abstinent (refrain from heterosexual intercourse) or agree to use contraceptive measures, and agree to refrain from donating sperm, as defined below:

- Men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of study drug to avoid exposing the embryo.
- Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial 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 contraception.

A9.7 TREATMENT ADMINISTERED SPECIFIC TO siRNA + NUC ARM

Appendix 9-Table 1 summarizes the treatments administered.

Appendix 9-Table 1 Summary of Treatments Administered for siRNA + NUC Treatment Arm

Study Treatment Name	**siRNA (RO7445482)**	**NUC**
IMP and NIMP	IMP	NIMP*
Dose Formulation	Sterile colorless to yellow solution of drug substance RO7445482 in water for injection	film-coated tablet
Unit Dose Strength(s)/Dosage Level(s)	120 mg/mL, 2 mL filled in a 6 mL vial	Refer to local prescription information
Dose:	Fixed dose 100 or 200 mg Q4W	ETV: 0.5 mg OD TDF: 300 mg OD TAF: 25 mg OD
Route of Administration	SC	oral
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor or locally by the study site
Packaging and Labeling	Study treatment will be provided in vials, packaged, and labeled as required per local regulation.	Study treatment will be packaged and labeled as required per local regulation.

*NUC are considered IMP in the UK only.

RO7445482 administrations will be via the subcutaneous (SC) route utilizing sterile technique. RO7445482 doses will be administered at the study clinic preferably in the morning by investigational staff.

The SC administration site (e.g., left abdomen, right abdomen, etc.) should be rotated between visits.

Guidelines for dosage modification and treatment interruption/discontinuation are in Section A9.8 (in this Appendix).

For more details, refer to the RO7445482 Investigator's Brochure, NUC local prescribing information, and the Pharmacy Manuals.

A9.8. EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non serious AESIs 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 documents listed below:

Drug	Document
RO7445482	RO7445482 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.

A9.9 DOSE MODIFICATIONS

Appendix 9-Table 2 summarizes the dose interruption/discontinuation guidelines for the siRNA+NUC combination arm.

Appendix 9-Table 2 Dose Interruption/Discontinuation Guidelines for siRNA+NUC Combination Arm

Laboratory/Clinical Parameters	Recommendation	Reference
siRNA-related AEs		
No laboratory or clinical parameters have been identified yet	No dose modification recommedations for siRNA	N/A
General criteria for dose interruptions/discontinuations for all NMEs		
Liver transaminases and liver function test	See Section 7.1	Section 8.3.8.3
Confirmed virological breakthrough	**Discontinue** NMEs and continue treatment according to local standards	Section 8.3.8.1
Others	See Section 7.1	

A9.10 PHARMACOKINETICS ANALYSES SPECIFIC TO siRNA + NUC ARM

A9.10.1 OPTIONAL LIVER BIOPSY SUB-STUDY

At one or more selected sites with established expertise, participants may be offered to participate in a liver biopsy sub-study, which will involve collection of paired liver biopsy samples. This procedure will be performed during the treatment period (Days 169 or 337) and the follow-up period (Day 168). Liver biopsy tissue will be used to measure intra-hepatic RO7445482 exposure levels (including metabolites, if applicable). Participation in the liver biopsy sub-study will require a separate consent and will involve a select number of participants.

For further details, refer to the study operations manual.

A9.11 PHARMACODYNAMICS AND BIOMARKERS ANALYSES SPECIFIC TO siRNA + NUC ARM

A9.11.1 CLINICAL GENOTYPING

If safety or activity rationales develop, clinical genotyping will be performed (see Sections 8.7.4.1 and 8.8.1.1) if appropriate. This exploratory objective will aim at evaluating the association of genetic polymorphisms in known candidate genes with the PK profiles of the NME and with primary and secondary endpoints. Known candidate genes of interest that are specific to siRNA includes ASGR1. Further genes may be queried from the data based on progressing knowledge on these NMEs and their targets.

A9.11.2 OPTIONAL LIVER BIOPSY SUB-STUDY

At one or more selected sites with established expertise, participants may be offered to participate in a liver biopsy sub-study, which will involve collection of paired liver biopsy samples. This procedure will be performed during the treatment period (Days 169 or 337) and the follow-up period (Day 168). Liver biopsy tissue will be used to measure

intra-hepatic viral parameters including but not limited to HBsAg, HBV DNA, HBcrAg, HBV RNA, cccDNA. Where feasible, residual tissue samples may be used to measure immunological parameters (e.g., HBV specific T-cells) and/or routine histopathology. Participation in the liver biopsy sub-study will require a separate consent and will involve a select number of participants.

For further details, refer to the study operations manual.

A9.12 SCHEDULE OF ACTIVITIES siRNA + NUC ARM

An overview of the schedule of the activities is provided in Appendix 9-Table 3 and Appendix 9-Table 4.

Appendix 9-Table 3 Schedule of Activities for siRNA (100 mg or 200mg) + NUC Treatment Arm (Screening and Treatment Periods)

	Screening		Treatment Period														VB/VR	ET/UV[q]
Week			**1**	**3**	**5**	**9**	**13[n, p]**	**17**	**21**	**25[o,p]**	**29**	**33**	**37**	**41**	**45**	**49[p]**		
Day	**-56 to -7**	**-14 to -7**	**1**	**15 (±2)**	**29 (±3)**	**57 (±3)**	**85 (±3)**	**113 (±3)**	**141 (±3)**	**169 (±3)**	**197 (±3)**	**225 (±3)**	**253 (±3)**	**281 (±3)**	**309 (±3)**	**337 (±3)**		
Informed consent	x																	
Demography, medical history	x																	
Physical examination, vital signs [a, b]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization			x															
ECG	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Transient elastography/ARFI/MR [c]	x																	
Abdominal ultrasound	x									x						x		
Alfa-fetoprotein	x									x						x		
HAV, HCV, HDV, HEV, HIV	x																	
Autoantibodies [d]	x																	
Alcohol and drugs of abuse screen [e]		x														x		x
Pregnancy test [f]		x	x		x	x	x	x	x	x	x	x	x	x	x	x		x
Thyroid function tests	x						x			x			x			x		
Hematology (includes HbA1c[g])	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry		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
GLDH	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	x
Clinical genotyping [h]			x															
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 9-Table 3 Schedule of Activities for siRNA (100 mg or 200 mg) + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

	Screening		Treatment Period														VB/VR	ET/UV[q]
Week			**1**	**3**	**5**	**9**	**13[n, p]**	**17**	**21**	**25[o,p]**	**29**	**33**	**37**	**41**	**45**	**49[p]**		
Day	**-56 to -7**	**-14 to -7**	**1**	**15 (±2)**	**29 (±3)**	**57 (±3)**	**85 (±3)**	**113 (±3)**	**141 (±3)**	**169 (±3)**	**197 (±3)**	**225 (±3)**	**253 (±3)**	**281 (±3)**	**309 (±3)**	**337 (±3)**		
HBV DNA quantitative	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Total HBsAg [i]			x		x		x			x			x			x	x	
HBcrAg			x		x		x			x			x			x	x	
Total anti-HBc quantitative			x				x			x			x			x		
HBV RNA quantitative			x		x		x			x			x			x	x	
HBV RNA sequencing [h]			x															
HBV DNA sequencing [j]																	x	
Plasma PK (siRNA) [k]			x				x			x			x			x	x	
Plasma PK (NUC) [k]			x				x			x			x			x	x	
Plasma ADA (siRNA) [s]			x				x			x			x			x	x	x
Liver Biopsy [r]										x						x		
RBR[l]			x							x			x			x	x	
Clinic siRNA 100 mg or 200 mg sc Q4W treatment administration			x		x	x	x	x	x	x	x	x	x	x	x	x		
NUC treatment administration OD			x															
Adverse events, concomitant medications, and diary review [m]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 9-Table 3 Schedule of Activities for siRNA (100 mg or 200 mg) + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

ADA = anti-drug antibodies; ARFI = acoustic radiation force impulse; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics; RBR = Research Biosample Repository; RNA = ribonucleic acid; siRNA= short interfering ribonucleic acid; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

[a] Full physical examination at screening and at the end-of-treatment. Limited symptom-directed physical examination at other visits and as clinically indicated. Height at screening only. Weight at screening, Day 1, and Weeks 13, 25, 37, and 49.

[b] Blood pressure, pulse rate, respiratory rate, and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

[c] Historical liver biopsy or transient elastography/ARFI/MR/2D- shear wave elastography [2D-SWE] results obtained within 6 months prior to randomization are also acceptable. During screening transient elastography/ARFI/MR /2D-SWE are acceptable.

[d] Autoantibodies refer to ANA, AMA, ASMA, and a-TPO.

[e] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[f] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[g] HbA1c should be included in hematology and is required only at screening.

[h] If not collected at Day 1, samples for clinical genotyping and HBV RNA sequencing can be collected at any subsequent time point. *The sample for HBV RNA sequencing aims at determining the HBV genotype. The HBV genotype may also be inferred using alternative approaches, such as serovariant determination.*

[i] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb complexes/components of HBsAg.

[j] HBV DNA sequencing will be collected in case of virological breakthrough/relapse; blood sample to be collected up to 6 times.

[k] Plasma PK samples for siRNA to be collected at pre-dose, 1-3 and 4-6 hours post-dose. Plasma PK samples for NUC to be collected at pre-dose. During the PK assessments for VB/VR visits, only one pre-dose sample is required for collection, no other points required.

[l] RBR samples collected only from RBR-consenting participants.

[m] Pre-treatment, only serious adverse events should be reported.

[n] End-of-treatment visit for participants in the 12-week finite treatment arm (if commenced after an interim analysis).

[0] End-of-treatment visit for participants in the 24-week finite treatment arm (if commenced after an interim analysis).

[p] End-of-treatment visit for participants with HBsAg loss in the 48-week response-guided therapy arm (if commenced after an interim analysis).

Appendix 9-Table 3 Schedule of Activities for siRNA (100 mg or 200 mg) + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

[q] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

[r] Only for participants in the liver biopsy sub-study. Liver biopsy sample will be collected during the treatment period on Day 169 or 337. Participation for liver biopsy is optional and will require a separate consent from participant. Additional safety assessments may be required as per local practice and guidelines prior to the liver biopsy (refer to study operations manual).

[s] Pre-dose plasma ADA sample

Appendix 9-Table 4 Schedule of Activities for siRNA (100 mg or 200 mg) + NUC Treatment Arm (Follow-up Period)

	Follow-up period											VB/VR	ET/UV [i]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24[k]**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Physical examination, vital signs [a, b]									x		x	x	x
ECG									x		x		
Abdominal ultrasound									x		x		
Alfa-fetoprotein									x		x		
Alcohol and drugs of abuse screen [c]													x
Pregnancy test [d]		x		x		x	x	x	x	x	x		x
Thyroid function tests									x		x		
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry	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
GLDH	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
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x	x	x	x	x	x	x	x	x	x	x	x	x
HBV DNA quantitative[l]	x	x	x	x	x	x	x	x	x	x	x	x	x
Total HBsAg [e]		x		x		x		x	x		x	x	
HBcrAg		x		x		x		x	x		x	x	
Total anti-HBc quantitative						x			x		x		
HBV RNA quantitative		x		x		x		x	x		x	x	
HBV DNA sequencing												x	
Plasma PK (siRNA)													

Appendix 9-Table 4 Schedule of Activities for siRNA (100 mg or 200 mg) + NUC Treatment Arm (Follow-up Period) (cont.)

	Follow-up period											VB/VR	ET/UV [i]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24[k]**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Plasma PK (NUC) [f]												x	
Plasma ADA (siRNA)						x			x	x	x	x	x
Liver biopsy [j]									x				
RBR [g]												x	
Diary review	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events & concomitant medications [h]	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA=anti-drug antibodies; ARFI = acoustic radiation force impulse; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics; RBR = Research Biosample Repository; RNA = ribonucleic acid; ; siRNA= short interfering ribonucleic acid; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

Note: If participants discontinue NUC later in the follow-up, additional visits *should* be scheduled with a frequency of every 2 weeks for the first three months and every 4 weeks up to week 48 of follow-up period.

[a] Full physical examination at screening and at the end-of-treatment. Limited symptom-directed physical examination at other visits and as clinically indicated.

[b] Blood pressure, pulse rate, respiratory rate, and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

[c] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[d] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[e] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb/components of HBsAg.

[f] During the PK assessments for VB/VR visits, only one sample is required for collection, no other time points required. Pre-dose if on NUC therapy.

Appendix 9-Table 4 Schedule of Activities for siRNA (100 mg or 200 mg) + NUC Treatment Arm (Follow-up period) (cont.)

[g] RBR samples collected only from RBR-consenting participants.

[h] Pre-treatment, only serious adverse events should be reported.

[i] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

[j] Only for participants in the liver biopsy sub-study. Liver biopsy sample will be collected during the follow-up period on Day 168. Participation for liver biopsy is optional and will require a separate consent from participant. Additional safety assessments may be required as per local practice and guidelines prior to the liver biopsy (refer to study operations manual).

[k] *Visit window may be extended to +6 weeks in extreme circumstances such as pandemic, natural disasters, supply chain disruption, outbreak of hostilities.*

[l] *Participants with HBV DNA > 2,000 IU/mL during the follow-up period will undergo weekly monitoring. Participants with HBV DNA >20 IU/mL but < 2,000 IU/mL, should undergo monitoring every two weeks. Participants, who have discontinued NUC therapy, should have monthly visits from follow-up Week 24 to Week 48, instead of the 3 monthly follow-up visits shown in SoA, which are relevant for participants on NUC therapy, to enable early detection and appropriate management of HBV DNA rebound. At these additional unscheduled monitoring visits, the following laboratory assessments should be performed using the unscheduled lab kit: hematology, chemistry, coagulation, GLDH, urinalysis, HBV serology, HBV DNA quantitative, total HBsAg, HBcrAg, and HBV RNA quantitative.*

Appendix 10
Study Details Specific to siRNA (RO7445482) + PEG-IFN + NUC Arm

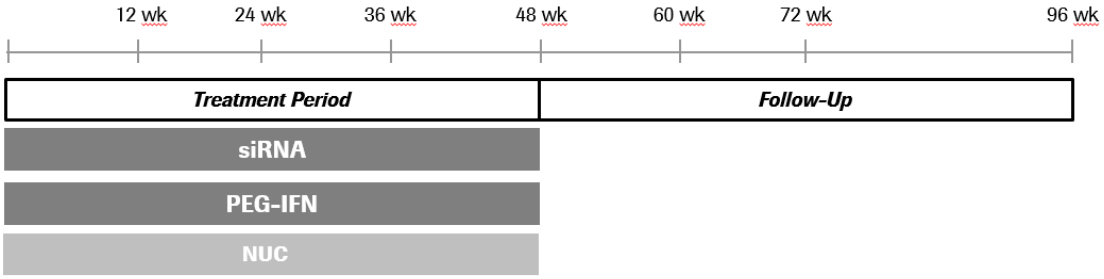
An overview of short interfering RNA (siRNA) + pegylated interferon-alpha (PEG-IFN) + nucleos(t)ide (NUC) treatment arm is shown in Appendix 10-Figure 1.

Participants will receive RO7445482 (also known as DCR-HBVS; 200 mg every 4 weeks [Q4W]) in addition to their background NUC therapy for the 48-week treatment period. PEG-IFN at a dose of 180 µg will be administered once weekly (QW) for 48 weeks. At the end of the treatment period, participants will continue NUC treatment during the follow-up unless the NUC discontinuation criteria have been met (see Section 6.8).

Approximately 30 participants will be randomized to this treatment arm.

If a 30% delta for hepatitis B surface antigen (HBsAg) loss is observed at Week 48 (end-of-treatment [EOT]) or follow-up Weeks 12 or 24 (primary endpoint) the treatment arm may be expanded to accrue additional efficacy and safety data, and to contribute to Phase 3 design planning. If a successful interim analysis is observed at Weeks 12 or 24, shorter treatment duration arms (12 and 24 weeks' duration) and/or a response-guided therapy (RGT) arm may be added.

Appendix 10-Figure 1 siRNA + PEG-IFN+ NUC Treatment Arm



A10.1 BACKGROUND SPECIFIC TO SIRNA + PEG-IFN+ NUC ARM

A10.1.1 BACKGROUND ON RO7445482

RO7445482 (DCR-HBVS) is an siRNA conjugated to N-acetyl-D-galactosamine (GalNAc), which enables liver targeting through binding to the asialoglycoprotein receptor (ASGPR) that is highly expressed in the liver. After forming the RNA-induced silencing complex (RISC), the RO7445482 antisense strand targets hepatitis B virus (HBV) RNA for degradation by triggering RNAi-mediated cleavage within the HBsAg coding sequence, thereby inhibiting HBV gene expression.

Literature indicates that HBV antigens suppress the host immune response through several pathways, including the direct effects of long-term exposure to high concentration of viral antigens resulting in T-cell immune tolerance and T-cell exhaustion (Hai-Jun et al 2015). Depletion of viral antigens through inhibition of HBV gene expression may therefore facilitate the restoration of the host immune response.

Non-clinical studies with RO7445482 have shown potent antiviral activity. HBsAg reductions of up to 3.5 $\log_{10}$ for more than 7 weeks, as well as significant reductions in HBcAg, were observed after a single translationally relevant dose in mice, demonstrating duration of action suitable for infrequent dosing.

To date, clinical experience with RO7445482 is based on a Phase I clinical study (DCR-HBVS-101) involving healthy volunteers and participants with CHB.

A10.1.2 BACKGROUND ON PEG-IFN (PEGASYS®)

PEG-IFN is a chemically modified alpha interferon formed by the covalent attachment of a 40-kilodalton single branched methoxy polyethylene glycol (PEG) moiety to recombinant IFN alfa-2a.

PEG-IFN is an inducer of the innate antiviral immune response through binding to the human type 1 interferon receptor. Subsequent activation of multiple intracellular signal transduction pathways results in broad pleiotropic biological effects.

PEG-IFN is currently approved for the treatment of CHB.

A10.2 BENEFIT/RISK ASSESSMENT SPECIFIC TO siRNA+ PEG-IFN + NUC ARM

The 48-week treatment with RO7445482 and PEG-IFN treatment in combination with NUC aims to result in therapeutic benefit for participants, including possibly higher functional cure rates than observed currently with standard-of-care therapies (monotherapy with NUC or PEG-IFN). The concurrent RO7445482 and PEG-IFN administrations aim is to test the scientific hypothesis whether concurrent direct-acting antiviral and immunomodulatory agent combination therapy, maximizes the efficacy outcomes.

The concept of the combination of a direct anti-viral with an immunomodulatory agent is supported by in vivo nonclinical combination of a HBV-targeting locked nucleic acid (LNA)-based antisense oligonucleotide (HBV-LNA ASO) and toll-like receptor 7 (TLR7)-agonist, RO7020531, using a recombinant adeno-associated virus carrying HBV genome (AAV-HBV) mouse model. The combination resulted in (a) delayed and reduced rebound in HBsAg and HBV DNA, (b) transient increase in frequency of anti-HBsAg

positive mice, and (c) robust induction of anti-viral B-cell response. In detail, RO7020531 and HBV-LNA combination resulted in significant delay (up to 4 weeks) in rebound and lower off-treatment levels of HBsAg. Three out of 8 mice in the HBV-LNA ASO and RO7020531 (QOD) combo group showed sustained HBsAg loss (< 1.4 log_{10} IU/ml). HBV DNA levels in the combination group remained at lower levels compared to monotherapy groups up to 9 weeks off-treatment. In addition, combination treatment further increases the number of animals exhibiting a transient elevation in anti-HBsAg response as well as long-term memory B-cell response. These data provides pre-clinical evidence that combination of a direct anti-viral with an immunomodulatory agent potentially increases cure rates in CHB patients (Blaising et al 2019).

The data from the combination of RO7049389 (a direct antiviral agent that works as a core protein allosteric modulator) and toll-like receptor 7 (TLR7)-agonist, RO7020531 (an immune modulator) demonstrated significantly greater HBV DNA and hepatitis B surface antigen (HBsAg) reductions post treatment (Day 84) than either agent as monotherapy further supports this concept (see Section A8.2).

Interim Phase 1 data have shown significant and durable antiviral activity with four monthly doses of RO7445482 in NUC-suppressed participants with CHB. At Day 112, mean HBsAg log_{10} IU/mL reduction from baseline were 1.39, 1.80 and 1.84 for participants who received 1.5 mg/kg, 3.0 mg/kg, or 6 mg/kg, respectively. Approximately 80% of participants achieved > 1.5 log_{10} IU/mL reduction (irrespective of HBeAg-status), 60% had HBsAg levels < 100 IU/mL, and durability of response was demonstrated up to Day 392.

Based on the interim Phase 1 data, RO7445482 was safe and well tolerated in healthy volunteers (HV) and CHB patients. The safety profile appears to be similar between HVs and patient participants, and there were no safety signals or dose related trends identified. No severe or serious treatment-emergent adverse events (TEAEs) or TEAEs leading to treatment discontinuation, apart from generally mild injection site reactions (ISRs), there was absence of other potential oligonucleotide class effects.

RO7445482 has shown acceptable safety/tolerability in the Phase 1 study involving healthy volunteers and CHB participants, and non-clinical toxicology and safety pharmacology studies support the proposed 48-week combination regimen.

For details, refer to the RO7445482 Investigator's Brochure, Pegasys® local prescribing information, NUC local prescribing information, and the Pharmacy Manuals.

A10.3 JUSTIFICATION FOR DOSE SPECIFIC TO siRNA + PEG-IFN + NUC ARM

For RO7445482, fixed dose of 200 mg Q4W (equivalent to 3 mg/kg monthly) has been selected for Phase 2 study in combination with other IMPs/NMEs. This dose is within the anticipated therapeutic dose-range in humans and is expected to be safe and well tolerated. A summary of the key data supporting the selected dose is provided below:

- The dose-response trend in the HBsAg declines, together with PK/PD modeling of interim Phase 1 data, supports the proposed 200 mg Q4W dosing regimen. Preliminary PK/PD modeling predicts that the proportion of participants who will achieve > 1.5 and > 2 $\log_{10}$ IU/mL reductions in HBsAg, following Q4W doses up to Week 12, will be higher with a 200 mg Q4W regimen (97% and 56%, respectively) compared to a 100 mg Q4W regimen (89% and 6%, respectively).

- The non-clinical chronic toxicology studies provide acceptable safety margins for the 200 mg Q4W fixed dose (3 mg/kg equivalent) for treatment period of 48 weeks.

- PK/PD modelling supports use of fixed (200 mg) instead of weight based (3 mg/kg) RO7445482 dosing.

For PEG-IFN, the approved regimen for the treatment of CHB (i.e., 180 mcg QW for 48 weeks) will be used.

For details, refer to the RO7445482 Investigator's Brochure, Pegasys® local prescribing information, NUC local prescribing information, and the Pharmacy Manuals.

A10.4 INCLUSION/EXCLUSION CRITERIA SPECIFIC TO siRNA + PEG-IFN + NUC ARM

Participants must meet the following criterion for inclusion in the siRNA + PEG-IFN + NUC treatment arm:

Sex

1. Female participants:

   A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

   - Woman of non-childbearing potential (WONCBP).
   - Woman of childbearing potential (WOCBP), who:

– Agrees to remain abstinent (refrain from heterosexual intercourse) or use 2 acceptable contraceptive methods, of which at least 1 is considered highly effective (result in a failure rate of < 1% per year) during the treatment period and for at least 6 months after the final dose of study treatment (see A10.7 and Appendix 5).

– Has a negative pregnancy test at screening (Day -14 to -7). In addition, willing to undergo a urine pregnancy test at Day 1 and every month during treatment and up to 6 months follow-up, thereafter every 3 months until end of follow-up.

Participants are excluded from the siRNA + PEG-IFN + NUC arm if any of the following criteria apply or if there is any condition which would preclude the patient from being treated with PEG-IFN, according to the Pegasys® local prescribing information:

Medical Conditions

1. Known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis, or Stevens-Johnson syndrome, to alpha interferons, including Pegasys®, or any of its components
2. Current symptoms of depression or history of severe psychiatric condition, particularly severe depression, suicidal ideation, or suicidal attempt.
3. History of autoimmune hepatitis or other autoimmune disorders.
4. Diabetes that is not well controlled (HbA1c $\geq$ 7% at screening)
5. Pre-existing ophthalmologic disorders (known history or as assessed by eye examination at screening), which in the opinion of the investigator would increase the likelihood of clinical significance of potential drug-induced retinopathy (e.g., diabetic or hypertensive retinopathy, glaucoma, dense cataract, visual field abnormalities, severe retinopathy).
6. History of pulmonary disorders including interstitial pneumonitis, bronchiolitis obliterans, pulmonary hypertension, and sarcoidosis.
7. History of pancreatitis.
8. Participants with history or present evidence of orthostatic hypotension.

A10.5 SAFETY ASSESSMENTS SPECIFIC TO SIRNA + PEG-IFN + NUC ARM

Physical Examinations

Eye examination will be performed at screening, preferably by an ophthalmologist, and will include funduscopic examination with dilation, visual acuity, assessment, visual field testing, and color visual testing.

Vital signs

Assessment of orthostatic hypotension will be done at screening. To assess the presence of orthostatic hypotension, blood pressure will be measured both while the participant is sitting and while standing. Participants will be excluded if a drop of 20 millimeters of mercury (mm Hg) in systolic blood pressure or a drop of 10 mm Hg in diastolic blood pressure within two to five minutes of standing up, or if standing causes signs and symptoms of hypotension.

A10.6 LIFESTYLE CONSIDERATIONS SPECIFIC TO siRNA + PEG-IFN + NUC ARM

Participants who take PEG-IFN should brush their teeth thoroughly twice daily and have regular dental examinations, as described in the local prescribing information.

NUCs will be given according to the local prescribing information.

For CHB participants, who routinely take herbal medicines that, in the Investigator's opinion, may have immune-modulatory effects, herbal medicines should strongly be discouraged.

A10.7 CONTRACEPTIVE REQUIREMENTS SPECIFIC TO siRNA + PEG-IFN + NUC ARM

For WOCBP: agreement to remain abstinent (refrain from heterosexual intercourse) or use 2 acceptable contraceptive methods of which at least 1 is considered highly effective (see Appendix 5), during the study and for at least 6 months after the last dose of study drug.

- Examples of acceptable highly effective contraceptive methods (< 1% failure rate per year) include combined or progesterone-only hormonal contraception, intrauterine device, and vasectomized partner.
- Examples of acceptable not as highly effective contraceptive methods (> 1% failure rate per year) include progesterone only hormonal contraception (where inhibition of ovulation is not the primary mode of action) and male or female condoms with or without spermicide.

For men: agreement to remain abstinent (refrain from heterosexual intercourse) or agree to use contraceptive measures, and agree to refrain from donating sperm, as defined below:

- Men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of study drug to avoid exposing the embryo.
- Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial 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 contraception.

A10.8 TREATMENT ADMINISTERED SPECIFIC TO siRNA + PEG-IFN + NUC ARM

Appendix 10-Table 1 summarizes the treatments administered.

Appendix 10-Table 1 Summary of Treatments Administered for siRNA + PEG-IFN + NUC Treatment Arm

Study Treatment Name	siRNA (RO7445482)	Pegasys®	NUC
IMP and NIMP	IMP	IMP	NIMP*
Dose Formulation	Sterile colorless to yellow solution of drug substance RO7445482 in water for injection	peginterferon alfa-2a is a clear and colourless to light yellow sterile liquid	film-coated tablet
Unit Dose Strength(s)/Dosage Level(s)	120 mg/mL, 2 mL filled in a 6 mL vial	Each prefilled syringe of 0.5 mL solution contains 180 µg peginterferon alfa-2a	Refer to local prescription information
Dose:	Fixed dose 200 mg Q4W	180 µg QW	ETV: 0.5 mg OD TDF: 300 mg OD TAF: 25 mg OD
Route of Administration	SC	SC	oral
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor or locally by the study site
Packaging and Labeling	Study treatment will be provided in vials, packaged, and labeled as required per local regulation.	Study treatment will be provided as prefilled syringes as single use. Will be packaged and labeled as required per local regulation.	Study treatment will be packaged and labeled as required per local regulation.

*NUC are considered IMP in the UK only.

RO7445482 and PEG-IFN administrations will be via the SC route utilizing sterile technique. RO7445482 doses will be administered at the study clinic preferably in the morning by investigational staff.

The SC administration site (e.g., left abdomen, right abdomen etc.) should be rotated between visits or when multiple injections are administered during a single visit. On study days where RO7445482 and PEG-IFN are both administered (e.g., Day 1), PEG-IFN SC administration should be administered after RO7445482 SC administration within an interval of 1 - 24 hours.

Guidelines for dosage modification and treatment interruption/discontinuation are provided in Section A10.11 (in this Appendix).

For more details, refer to the RO7445482 Investigator's Brochure, Pegasys® local prescribing information, NUC local prescribing information, and the Pharmacy Manuals.

A10.9 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non serious AESIs 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 documents listed below:

Drug	Document
RO7445482	RO7445482 Investigator's Brochure
PEG-IFN	Pegasys® Summary of Product Characteristics

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.

A10.10 MANAGEMENT OF ADVERSE EVENTS SPECIFIC TO siRNA + PEG-IFN + NUC ARM

A10.10.1 PEG-IFN RELATED AES

As PEG-IFN results in broad pleiotropic biological effects, PEG-IFN treatment is associated with a broad/heterogeneous adverse event (AE) profile. Commonly observed AEs in CHB participants include pyrexia (54%), headache (27%), fatigue (24%), myalgia (26%), alopecia (18%), and anorexia (16%).

If severe adverse reactions or laboratory abnormalities develop during combination PEG-IFN therapy, the dose should be modified until the adverse reactions abate. If intolerance persists after dose adjustment, PEG-IFN therapy should be discontinued.

Approximately 5% and 40% of participants discontinue PEG-IFN therapy early or require modification of the PEG-IFN dose, respectively. The most common reasons for dose modification are laboratory abnormalities, including neutropenia (20%), thrombocytopenia (13%), and ALT elevation (11%).

A10.11 DOSE MODIFICATION

When dose modification of PEG-IFN is required for adverse reactions (clinical and/or laboratory), an initial dose reduction to 135 µg (adjustment to the corresponding graduation mark for the prefilled syringes) is recommended. Dose reduction to 90 µg (adjustment to the corresponding graduation mark for the prefilled syringes) may be needed if the adverse reaction persists or recurs. Following improvement of the adverse reaction, re-escalation of the dose may be considered. Appendix 10-Table 2 provides guidelines for dose modifications and discontinuation of PEG-IFN for laboratory abnormalities as well as other NME dose interruption/discontinuation criteria.

Appendix 10-Table 2 Summary of Dose Interruption/Modification/Discontinuation Guidelines for siRNA+PEG-IFN+NUC Combination Arm

Laboratory/Clinical Parameters	Recommendation	Reference
siRNA-related AEs		
No laboratory and clinical parameters have been identified yet	No dose modification recommedations for siRNA	N/A
General criteria for dose interruptions/discontinuations for all NMEs		
Liver transaminases and liver function test	See Section 7.1	Section 8.3.8.3
Confirmed virological breakthrough	**Discontinue** NMEs and continue treatment according to local standards	Section 8.3.8.1
Others	See Section 7.1	
PEG-IFN-related AEs (only listed the most common AEs)*		
Neutropenia	ANC <750 cells/mm^3: **Reduce** PEG-IFN to 135 µg. ANC <500 cells/mm^3: **Discontinue** PEG-IFN until ANC >1000 cells/mm^3. Resume PEG-IFN at 90 µg and monitor ANC.	Appendix 10 (Section A10.10) ***For details of management of PEG-IFN-related AEs, please follow local prescribing information***
Thrombocytopenia	<50,000 cells/mm^3: **Reduce** PEG-IFN to 90 µg. <25,000 cells/mm^3: **Discontinue** PEG-IFN	
Persistent ALT elevation ≥5 - <10 × ULN	**Reduce** PEG-IFN to 135 µg. Monitor ALT weekly (further modifying dose if necessary) until ALT is stable or decreases	
Persistent ALT values >10 × ULN	Temporarily **interrupt,** based on laboratory result consider re-introducing therapy	
New or worsening ophthalmologic disorders	**Discontinue** PEG-IFN	
Severe depression or suicidal ideation	**Discontinue** PEG-IFN and psychiatric intervention as appropriate	
Patients who deoelop or experience exacerbations of psoriasis	*Discontinuation of PEG-IFN should be considered*	

For participants who discontinue PEG-IFN early because of intolerability, the NUC and RO7445482 treatment should be continued up to 48 weeks. The reasons for discontinuation of PEG-IFN and length of treatment duration will be recorded in the eCRF.

A10.12 PHARMACODYNAMICS AND BIOMARKERS ANALYSES SPECIFIC TO siRNA + PEG-IFN + NUC ARM

A10.12.1 SIRNA + PEG-IFN + NUC ACTIVITY BIOMARKERS

To characterize PEG-IFN PD biomarkers (secondary objective), blood samples will be collected at time points according to the SoA (see Appendix 10-Table 3 and Appendix 10-Table 4) to measure cytokines including IP-10, IL-6 and TNF-α as well as a panel of transcriptional response of Interferon Stimulated Genes (ISG15, OAS1, MX1, and TLR7) if appropriate. Following review of these PD biomarkers and the AEs, further cytokines may be tested using a separate aliquot collected at the same time points including, IL-1, IL-10, and IFN-γ.

A10.12.2 CLINICAL GENOTYPING

If safety or activity rationales develop, clinical genotyping will be performed (see Sections 8.7.4.1 and 8.8.1.1) if appropriate. This exploratory objective will aim at evaluating the association of genetic polymorphisms in known candidate genes with the PK profiles of the NME and with primary and secondary endpoints. Known candidate genes of interest that are specific to siRNA/PEG-IFN include ASGR1. Further genes may be queried from the data based on progressing knowledge on these NME/IMP and their targets.

A10.13 SCHEDULE OF ACTIVITIES siRNA + PEG-IFN + NUC ARM

An overview of the schedule of the activities is provided in Appendix 10-Table 3 and Appendix 10-Table 4.

Appendix 10-Table 3 Schedule of Activities for siRNA + PEG-IFN + NUC Treatment Arm (Screening and Treatment Periods)

	Screening		Treatment Period														VB/VR	ET/UV[r]
Week			**1**	**3**	**5**	**9**	**13[o, q]**	**17**	**21**	**25[p, q]**	**29**	**33**	**37**	**41**	**45**	**49 [q]**		
Day	**-56 to -7**	**-14 to -7**	**1**	**15 (±2)**	**29 (±3)**	**57 (±3)**	**85 (±3)**	**113 (±3)**	**141 (±3)**	**169 (±3)**	**197 (±3)**	**225 (±3)**	**253 (±3)**	**281 (±3)**	**309 (±3)**	**337 (±3)**		
Informed consent	x																	
Demography, medical history	x																	
Physical examination, vital signs [a, b]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ophthalmic Exam [a]	x																	
Randomization			x															
ECG	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Transient elastography/ARFI/MR [c]	x																	
Abdominal ultrasound	x									x						x		
Alfa-fetoprotein	x									x						x		
HAV, HCV, HDV, HEV, HIV	x																	
Autoantibodies [d]	x																	
Alcohol and drugs of abuse screen [e]		x														x		x
Pregnancy test [f]		x	x		x	x	x	x	x	x	x	x	x	x	x	x		x
Thyroid function tests	x						x			x			x			x		
Hematology (includes HbA1c[g])	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry		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
GLDH	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	x
Clinical genotyping [h]			x															

Appendix 10-Table 3 Schedule of Activities for siRNA + PEG-IFN + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

	Screening		Treatment Period														VB/VR	ET/UV[r]
Week			**1**	**3**	**5**	**9**	**13[o,q]**	**17**	**21**	**25[p,q]**	**29**	**33**	**37**	**41**	**45**	**49 [q]**		
Day	**-56 to -7**	**-14 to -7**	**1**	**15 (±2)**	**29 (±3)**	**57 (±3)**	**85 (±3)**	**113 (±3)**	**141 (±3)**	**169 (±3)**	**197 (±3)**	**225 (±3)**	**253 (±3)**	**281 (±3)**	**309 (±3)**	**337 (±3)**		
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
HBV DNA quantitative	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Total HBsAg [i]			x		x		x			x			x			x	x	
HBcrAg			x		x		x			x			x			x	x	
Total anti-HBc quantitative			x				x			x			x			x		
HBV RNA quantitative			x		x		x			x			x			x	x	
HBV RNA sequencing [h]			x															
HBV DNA sequencing [j]																	x	
Plasma PK (siRNA) [k]			x				x			x			x			x	x	
Serum PK (PEG-IFN) [k]			x				x			x			x			x	x	
Plasma PK (NUC) [k]			x				x			x			x			x	x	
Plasma ADA (siRNA) [s]			x				x			x			x			x	x	x
Serum ADA (PEG-IFN) [s]			x				x			x			x			x	x	x
Cytokine panel [l]			x				x			x			x			x		x
ISG panel [l]			x				x			x			x			x		x
RBR [m]			x							x			x			x	x	
Clinic siRNA 200 mg sc Q4W treatment administration			x		x	x	x	x	x	x	x	x	x	x	x	x		

Appendix 10-Table 3 Schedule of Activities for siRNA + PEG-IFN + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

	Screening		Treatment Period														VB/VR	ET/UV[r]
Week			**1**	**3**	**5**	**9**	**13[o,q]**	**17**	**21**	**25[p,q]**	**29**	**33**	**37**	**41**	**45**	**49 [q]**		
Day	**-56 to -7**	**-14 to -7**	**1**	**15 (±2)**	**29 (±3)**	**57 (±3)**	**85 (±3)**	**113 (±3)**	**141 (±3)**	**169 (±3)**	**197 (±3)**	**225 (±3)**	**253 (±3)**	**281 (±3)**	**309 (±3)**	**337 (±3)**		
PEG-IFN treatment administration QW			x															
NUC treatment administration OD			x															
Adverse events & concomitant medications & diary review [n]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibodies; ARFI = acoustic radiation force impulse; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IFN- α+ interferon alpha; IP-10 = interferon gamma-induced protein 10; ISG = interferon-stimulated genes; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics; RBR = Research Biosample Repository; RNA = ribonucleic acid; siRNA= short interfering ribonucleic acid; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

[a] Full physical examination at screening and at the end-of-treatment. Limited symptom-directed physical examination at other visits and as clinically indicated. Height at screening only. Weight at screening, Day 1, and Weeks 13, 25, 37, and 49. Eye examination (including fundoscopy) only at screening.

[b] Blood pressure, pulse rate, respiratory rate, and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

[c] Historical liver biopsy or transient elastography/ARFI/MR/2D-shear wave elastography [2D-SWE] results obtained within 6 months prior to randomization are also acceptable. During screening transient elastography/ARFI/MR/2D-SWE are acceptable.

[d] Autoantibodies refer to ANA, AMA, ASMA, and a-TPO.

[e] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[f] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[g] HbA1c should be included in hematology and is required only at screening.

[h] If not collected at Day 1, samples for clinical genotyping and HBV RNA sequencing can be collected at any subsequent time point. *The sample for HBV RNA sequencing aims at determining the HBV genotype. The HBV genotype may also be inferred using alternative approaches, such as serovariant determination.*

Appendix 10-Table 3 Schedule of Activities for siRNA + PEG-IFN + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

[i] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb complexes/components of HBsAg.

[j] HBV DNA sequencing will be collected in case of virological breakthrough/relapse, blood sample to be collected up to 6 times.

[k] Plasma PK samples for siRNA to be collected at pre-dose, 1-3 and 4-6 hours post-dose. Plasma PK samples for NUC to be collected at pre-dose. Serum PK samples for PEG-IFN is collected pre-dose. During the PK assessments for VB/VR visits, only 1 pre-dose sample is required for collection; no other points required.

[l] Cytokine panel (IP-10, IL-1, IL-6, IL-10, IFN-γ, and TNF-α) and ISG panel to be collected at pre-dose and 6 hours post-dose of PEG-IFN. At an unscheduled visit or early termination visit, preferably a pre-dose, otherwise, just a sample for cytokine and ISG panels should be collected if the visit is linked to a PEG-IFN related adverse reaction (e.g., influenza-like symptoms). No samples are required, for unscheduled visit or early termination visit not linked to PEG-IFN related adverse reaction (e.g., influenza-like symptoms).

[m] RBR samples collected only from RBR-consenting participants.

[n] Pre-treatment, only serious adverse events should be reported.

[o] End-of-treatment visit for participants in the 12-week finite treatment arm (if commenced after an interim analysis).

[p] End-of-treatment visit for participants in the 24-week finite treatment arm (if commenced after an interim analysis).

[q] End-of-treatment visit for participants with HBsAg loss in the 48-week response-guided therapy arm (if commenced after an interim analysis).

[r] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

[s] Pre-dose plasma ADA sample.

Appendix 10-Table 4 Schedule of Activities for siRNA + PEG-IFN + NUC Treatment Arm (Follow-up Period)

	Follow-up period											VB/VR	ET/UV[i]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24[j]**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Physical examination, vital signs [a, b]									x		x	x	x
ECG									x		x		
Abdominal ultrasound									x		x		
Alfa-fetoprotein									x		x		
Alcohol and drugs of abuse screen [c]													x
Pregnancy test [d]		x		x		x	x	x	x	x	x		x
Thyroid function tests									x		x		
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry	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
GLDH	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
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x	x	x	x	x	x	x	x	x	x	x	x	x
HBV DNA quantitative[k]	x	x	x	x	x	x	x	x	x	x	x	x	x
Total HBsAg[e]		x		x		x		x	x		x	x	
HBcrAg		x		x		x		x	x		x	x	
Total anti-HBc quantitative						x			x		x		
HBV RNA quantitative		x		x		x		x	x		x	x	
HBV DNA sequencing												x	
Plasma PK (siRNA)													

Appendix 10-Table 4 Schedule of Activities for siRNA + PEG-IFN + NUC Treatment Arm (Follow-up Period) (cont.)

	Follow-up period											VB/VR	ET/UV[i]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24[j]**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Serum PK (PEG-IFN)													
Plasma PK (NUC)[f]												x	
Plasma ADA (siRNA)						x			x	x	x	x	x
Serum ADA (PEG-IFN)						x			x	x	x	x	x
RBR[g]												x	
Diary review	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events & concomitant medications[h]	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA= anti-drug antibodies; ARFI = acoustic radiation force impulse; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IP-10 = interferon gamma-induced protein 10; ISG = interferon-stimulated genes; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics; RBR = Research Biosample Repository; RNA = ribonucleic acid; siRNA= short interfering ribonucleic acid; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

Note: If participants discontinue NUC later in the follow-up, additional visits *should* be scheduled with a frequency of every 2 weeks for the first three months and every 4 weeks up to week 48 of follow-up period.

[a] Full physical examination at screening and at the end-of-treatment. Limited symptom-directed physical examination at other visits and as clinically indicated.

[b] Blood pressure, pulse rate, respiratory rate, and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

[c] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[d] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[e] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb/components of HBsAg.

Appendix 10-Table 4 Schedule of Activities for siRNA + PEG-IFN + NUC Treatment Arm (Follow-up Period) (cont.)

[f] During the PK assessments for VB/VR visits, only 1 sample is required for collection; no other time points required. Pre-dose if on NUC therapy.

[g] RBR samples collected only from RBR-consenting participants.

[h] Pre-treatment, only serious adverse events should be reported.

[i] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

[j] *Visit window may be extended to +6 weeks in extreme circumstances such as pandemic, natural disasters, supply chain disruption, outbreak of hostilities.*

[k] *Participants with HBV DNA > 2,000 IU/mL during the follow-up period will undergo weekly monitoring. Participants with HBV DNA >20 IU/mL but < 2,000 IU/mL, should undergo monitoring every two weeks. Participants, who have discontinued NUC therapy, should have monthly visits from follow-up Week 24 to Week 48, instead of the 3 monthly follow-up visits shown in SoA, which are relevant for participants on NUC therapy, to enable early detection and appropriate management of HBV DNA rebound. At these additional unscheduled monitoring visits, the following laboratory assessments should be performed using the unscheduled lab kit: hematology, chemistry, coagulation, GLDH, urinalysis, HBV serology, HBV DNA quantitative, total HBsAg, HBcrAg, and HBV RNA quantitative.*

Appendix 11
Study Details Specific to siRNA (RO7445482) + CpAM (RO7049389) + NUC Arm

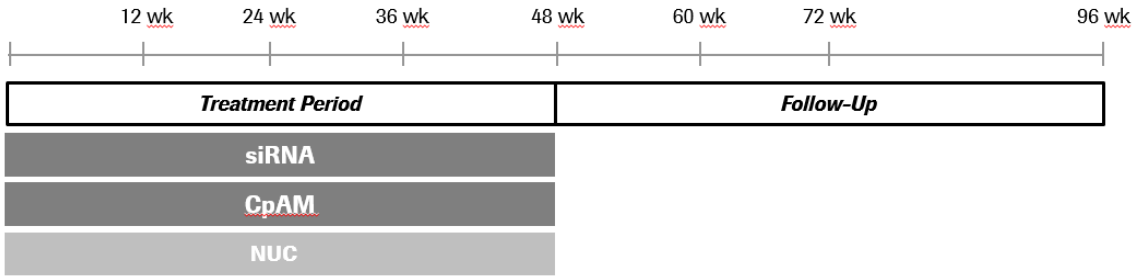
An overview of short interfering RNA (siRNA) + core protein allosteric modulator (CpAM) + nucleos(t)ide (NUC) treatment arm is shown in Appendix 11-Figure 1.

Participants will receive RO7445482 (also known as DCR-HBVS; 200 mg every 4 weeks [Q4W]) and RO7049389 (600 mg once a day [QD]) in addition to their background NUC therapy for the 48-week treatment period. At the end of the treatment period, participants will continue NUC treatment during the follow-up unless the NUC discontinuation criteria have been met (see Section 6.8).

Approximately 30 participants will be randomized to this treatment arm.

If a 30% delta for hepatitis B surface antigen (HBsAg) loss is observed at Week 48 (end-of-treatment [EOT]) or follow-up Weeks 12 or 24 (primary endpoint) the treatment arm may be expanded to accrue additional efficacy and safety data, and to contribute to Phase 3 design planning. If a successful interim analysis is observed at Weeks 12 or 24, shorter treatment duration arms (12 and 24 weeks' duration) and/or a response-guided therapy (RGT) arm may be added.

Appendix 11-Figure 1 siRNA + CpAM + NUC Treatment Arm



A11.1 BACKGROUND SPECIFIC TO siRNA + CpAM + NUC ARM

A11.1.1 BACKGROUND ON RO7445482

RO7445482 (DCR-HBVS) is an siRNA conjugated to N-acetyl-D-galactosamine (GalNAc), which enables liver-targeting through binding to the asialoglycoprotein receptor (ASGPR) that is highly expressed in the liver. After forming the RNA-induced silencing complex (RISC), the RO7445482 antisense strand targets hepatitis B virus (HBV) RNA for degradation by triggering RNAi-mediated cleavage within the HBsAg coding sequence, thereby inhibiting HBV gene expression.

Literature indicates that HBV antigens suppress the host immune response through several pathways, including the direct effects of long-term exposure to high concentration of viral antigens resulting in T-cell immune tolerance and T-cell exhaustion (Hai-Jun et al 2015). Depletion of viral antigens through inhibition of HBV gene expression may therefore facilitate the restoration of the host immune response.

Non-clinical studies with RO7445482 have shown potent antiviral activity. HBsAg reductions of up to 3.5 $\log_{10}$ for more than 7 weeks, as well as significant reductions in HBcAg, were observed after a single dose in mice, demonstrating duration of action suitable for infrequent dosing.

To date, clinical experience with RO7445482 is based on a Phase I clinical study (DCR-HBVS-101) involving healthy volunteers and participants with chronic hepatitis B (CHB).

A11.1.2 BACKGROUND ON RO7049389

RO7049389 is a CpAM and belongs to the well-studied class of heteroaryldihydropyrimidine (HAP) compounds. This class of compounds induces formation of abnormal HBV core protein aggregates, which are subsequently recognized and depleted. Depleting functional core protein results in interruption of viral assembly and inhibition of HBV replication.

The HBV core protein is involved in multiple steps of the viral life cycle such as encapsulation of pre-genomic ribonucleic acid (pgRNA), subsequent initiation of reverse transcription, and is an important component of covalently closed circular DNA (cccDNA) mini-chromosome. Furthermore, literature suggests that the HBV core protein may play a role in suppressing host innate immune responses (Twu et al 1988; Fernandez et al 2003; Gruffaz et al 2013). Depletion of functional core protein may therefore facilitate host immune restoration. RO7049389 can therefore potentially provide anti-HBV benefits by both direct inhibition of viral replication and augmentation of host immune responses against the virus.

RO7049389 has shown potent antiviral activity through the induction of HBV core protein misassembly and subsequent degradation, and has a high degree of selectivity against HBV. RO7049389 demonstrated activity against most prevalent HBV genotypes (A, B, C, D) and against a panel of NUC analogue-resistant HBV variants tested in vitro.

To date, clinical experience with RO7049389 includes three Phase 1 clinical studies: an entry-into-human (EIH) study in healthy volunteers (HV) and patients (YP39364), a study in HVs of Chinese descent (YP39406), and a drug-drug interaction (DDI) study in HVs (YP40218).

A11.2 BENEFIT/RISK ASSESSMENT SPECIFIC TO siRNA+ CpAM + NUC ARM

The 48-week treatment with RO7445482 and RO7049389 in combination with NUC aims to result in therapeutic benefit for participants, including possibly higher functional cure rates than observed currently with standard-of-care therapies (monotherapy with NUC or PEG-IFN). The concurrent RO7445482 and RO7049389 administrations aim is to test the hypothesis whether prolonged reduction in HBV antigens, including but not limited to HBsAg, will result in immune-restoration and potentially functional cure.

In non-clinical rodent pharmacology studies, RO7445482 (DCR-HBVS) treatment resulted in a lowering of serum HBsAg of up to 3.5 $\log_{10}$ for > 7 weeks after a single, translationally relevant dose. Serum HBsAg levels did not return to within 2 $\log_{10}$ of baseline for at least 4 months, demonstrating duration of action suitable for infrequent dosing. These data support the use of DCR-HBVS in patients with CHB, who will require a sustained host response to achieve a functional cure.

Emerging clinical trial data shows that CpAM exerts additional anti-viral activity when combined with NUC (Man-Fung Yuen et al 2020). This was demonstrated by the greater decline in HBV DNA and pgRNA levels, as well as the proportion of patients achieving undetectable HBV DNA and pgRNA levels.

Interim Phase 1 data have shown significant and durable antiviral activity with 4 monthly doses of RO7445482 in NUC-suppressed participants with CHB. At Day 112, mean HBsAg $\log_{10}$ IU/mL reduction from baseline were 1.39, 1.80, and 1.84 for participants who received 1.5 mg/kg, 3.0 mg/kg or 6 mg/kg, respectively. Approximately 80% of participants achieved > 1.5 $\log_{10}$ IU/mL reduction (irrespective of HBeAg-status), 60% had HBsAg levels < 100 IU/mL, and durability of response was demonstrated up to Day 392.

Based on the interim Phase 1 data, RO7445482 was safe and well tolerated in healthy volunteers (HV) and CHB patients. The safety profile appears to be similar between HVs and patient participants, and there were no safety signals or dose related trends identified. No severe or serious treatment-emergent adverse events (TEAEs) or TEAEs leading to treatment discontinuation, apart from generally mild injection site reactions (ISRs), there was absence of other potential oligonucleotide class effects.

RO7445482 and RO7049389 have shown acceptable safety/tolerability in the Phase 1 studies involving healthy volunteers and CHB participants, and non-clinical toxicology and safety pharmacology studies support the proposed 48-week combination regimen.

For details, refer to the RO7445482 and RO7049389 Investigator's Brochures.

A11.3 JUSTIFICATION FOR DOSE SPECIFIC TO siRNA+ CpAM + NUC ARM

For RO7445482, fixed dose of 200 mg Q4W (equivalent to 3 mg/kg monthly) has been selected for Phase 2 study in combination with other IMPs/NMEs. This dose is within the anticipated therapeutic dose-range in humans and is expected to be safe and well tolerated. A summary of the key data supporting the selected dose is provided below:

- The dose-response trend in the HBsAg declines, together with PK/PD modeling of interim Phase 1 data, supports the proposed 200 mg Q4W dosing regimen. Preliminary PK/PD modeling predicts that the proportion of participants who will achieve > 1.5 and > 2 $\log_{10}$ IU/mL reductions in HBsAg, following Q4W doses up to Week 12, will be higher with a 200 mg Q4W regimen (97% and 56%, respectively) compared to a 100 mg Q4W regimen (89% and 6%, respectively).
- The non-clinical chronic toxicology studies provide acceptable safety margins for the 200 mg Q4W fixed dose (3 mg/kg equivalent) for treatment period of 48 weeks.
- PK/PD modelling supports use of fixed (200 mg) instead of weight based (3 mg/kg) RO7445482 dosing

For RO7049389, a dose of 600 mg QD has been selected for this Phase 2 study. This dose is within the predicted therapeutic dose-range in humans and is expected to be safe and well tolerated. A summary of the key data supporting the selected dose is provided below:

- RO7049389 doses up to 1000 mg QD (for 28 days), 800 mg BID (for 6 days) and 2500 mg (single dose) have been observed to be safe and well tolerated in three Phase 1 studies involving healthy volunteers and CHB participants.
- Although 200 mg to 600 mg QD doses resulted in robust pharmacodynamic effects (HBV DNA decline 2.66 – 3.2 $\log_{10}$ IU/mL) in the Phase 1 studies, a trend of increased HBV DNA decline was observed with higher doses. In addition, disease-modelling utilizing non-clinical and clinical PK/PD data predicts an increased PD effect with the 600 mg QD dose.
- The non-clinical chronic toxicology studies provide acceptable safety margins for the 600 mg QD dose.

Further details are provided in the RO7445482 and RO7049389 Investigator's Brochures.

A11.4 INCLUSION/EXCLUSION CRITERIA SPECIFIC TO siRNA + CpAM + NUC ARM

Participants must meet the following criterion for inclusion in the siRNA + CPAM + NUC treatment arm:

Sex

1. Female Participants:

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

   - Woman of non-childbearing potential (WONCBP).
   - Woman of childbearing potential (WOCBP), who:
     - Agrees to remain abstinent (refrain from heterosexual intercourse) or use 2 acceptable contraceptive methods, of which at least one is considered highly effective (result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the final dose of study treatment (ref A11.6 and Appendix 5).
     - Has a negative pregnancy test at screening (Day -14 to -7). In addition, willing to undergo a urine pregnancy test at Day 1 and every month during treatment and up to 6 months follow-up, thereafter every 3 months until end of follow-up.

A11.5 LIFESTYLE CONSIDERATIONS SPECIFIC TO siRNA + CpAM + NUC ARM

RO7049389 will be given in fasted state (at least 2 hours after a meal or 2 hours before the next meal). NUCs will be given according to the local prescribing information.

For RO7049389, any nutrients known to modulate activity of CYP enzymes (e.g., grapefruit- or Seville orange-containing products) will be prohibited within 3 days before Day -1 through to the last dose of RO7049389.

For CHB participants who routinely take herbal medicines that in Investigator's opinion may have immune-modulatory effects, herbal medicines should strongly be discouraged.

A11.6 CONTRACEPTIVE REQUIREMENTS SPECIFIC TO siRNA + CpAM + NUC ARM

For WOCBP: agreement to remain abstinent (refrain from heterosexual intercourse) or use 2 acceptable contraceptive methods of which at least 1 is considered highly effective (see Appendix 5), during the study and for at least 6 months after the last dose of study drug.

- Examples of acceptable highly effective contraceptive methods (< 1% failure rate per year) include combined or progesterone-only hormonal contraception, intrauterine device, and vasectomized partner.
- Examples of acceptable not as highly effective contraceptive methods (> 1% failure rate per year) include progesterone only hormonal contraception (where inhibition of ovulation is not the primary mode of action) and male or female condoms with or without spermicide.

For men: agreement to remain abstinent (refrain from heterosexual intercourse) or agree to use contraceptive measures, and agree to refrain from donating sperm, as defined below:

- Men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of study drug to avoid exposing the embryo.
- Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial 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 contraception.

A11.7 TREATMENT ADMINISTERED SPECIFIC TO siRNA + CpAM + NUC ARM

Appendix 11-Table 1 summarizes the treatments administered.

Appendix 11-Table 1 Summary of Treatments Administered for siRNA + CPAM + NUC Treatment Arm

Study Treatment Name	siRNA (RO7445482)	CpAM (RO7049389)	NUC
IMP and NIMP	IMP	IMP	NIMP*
Dose Formulation	Sterile colorless to yellow solution of drug substance RO7445482 in water for injection	film-coated tablet	film-coated tablet
Unit Dose Strength(s)/Dosage Level(s)	120 mg/mL, 2 mL filled in a 6 mL vial	200 mg	Refer to local prescription information
Dose:	Fixed dose 200 mg Q4W	600 mg OD	ETV: 0.5 mg OD TDF: 300 mg OD TAF: 25 mg OD
Route of Administration	SC	Oral	oral
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor or locally by the study site
Packaging and Labeling	Study treatment will be provided in vials, packaged, and labeled as required per local regulation.	Study treatment will be packaged and labeled as required per local regulation.	Study treatment will be packaged and labeled as required per local regulation.

*NUC are considered IMP in the UK only.

RO7445482 administrations will be via the SC route utilizing sterile technique. RO7445482 doses will be administered at the study clinic preferably in the morning by investigational staff.

The SC administration site (e.g., left abdomen, right abdomen etc.) should be rotated between visits.

Guidelines for dosage modification and treatment interruption/discontinuation are in Section A11.8 (in this Appendix).

For more details, refer to the RO7445482 and RO7049389 Investigator's Brochures, NUC local prescribing information, and the Pharmacy Manuals.

A11.8 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non serious AESIs 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 documents listed below:

Drug	Document
RO7049389	RO7049389 Investigator's Brochure
RO7445482	RO7445482 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.

A11.9 DOSE MODIFICATIONS

Appendix 11-Table 2 summarizes the dose interruption/discontinuation guidelines for the siRNA+CpAM+NUC combination arm.

Appendix 11-Table 2 Dose Interruption/Discontinuation Guidelines for siRNA+CpAM+NUC Combination Arm

Laboratory/Clinical Parameters	Recommendation	Reference
siRNA-related AEs		
No laboratory or clinical parameters have been identified yet	No dose modification recommendations for siRNA	N/A
CpAM-related AEs		
No laboratory or clinical parameters have been identified yet	No dose modification recommedations for CpAM	N/A
General criteria for dose interruptions/discontinuations for all NMEs		
Liver transaminases and liver function test	See Section 7.1	Section 8.3.8.3
Confirmed virological breakthrough	**Discontinue** NMEs and continue treatment according to local standards	Section 8.3.8.1
Others	See Section 7.1	

A11.10 CONCOMITANT THERAPY SPECIFIC TO siRNA + CpAM + NUC ARM

The following concomitant medications are prohibited:

- Inducers of CYP3A enzyme: e.g., efavirenz, nevirapine, pioglitazone, rifampin, rifabutin, troglitazone, phenobarbital, phenytoin, carbamazepine, and St. John's wort within 14 days or 5 half-lives (whichever is longer) before the first administration of RO7049389 and while on study treatment with RO7049389.
- Inhibitors of CYP3A enzyme: e.g., indinavir, nelfinavir, clarithromycin, itraconazole, ketoconazole, nefazodone, ketoconazole, verapamil, suboxone, diltiazem, cimetidine, amiodarone, fluvoxamine, troleandomycin, and voriconazole within 7 days or 5 half-lives (whichever is longer) before the first administration of RO7049389 and while on study treatment with RO7049389.
- Strong inducers of UDP-glucuronosyltransferase (UGT) 1A3 enzymes: e.g., carbamazepine and nicotine within 14 days, or 5 half-lives (whichever is longer) before the first administration of RO7049389 and while on study treatment with RO7049389.
- Strong inhibitors of UGT1A3/1A1 enzymes: e.g., atazanavir, gemfibrozil, indinavir, and ketoconazole within 7 days, or 5 half-lives (whichever is longer) before the first administration of RO7049389 and while on study treatment with RO7049389.
- Inhibitors of OATP1B transporters: e.g., cyclosporine, rifampicin, eltrombopag, lapatinib, lopinavir, ritonavir within 7 days, or 5 half-lives (whichever is longer) before the first administration of RO7049389 and while on study treatment with RO7049389.

The following concomitant medications are to be used with caution, and the Sponsor should be informed before these drugs are administered. When coadministered with

RO7049389, the recommendation is to use the lowest necessary dose of the substrate, titrate the dose carefully, and monitor closely for substrate-associated adverse reactions.

- Substrates of OATP1B: e.g., atrasentan, bosentan, ezetimibe, irinotecan, statins (e.g., atorvastatin, rosuvastatin, simvastatin, pitavastatin, pravastatin), repaglinide, rifampin, valsartan, and olmesartan.
- CYP3A4 substrates with a narrow therapeutic range.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication when determining whether a certain medication inhibits or induces above mentioned enzymes or transporter. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications that are not listed above.

A11.11 PHARMACODYNAMICS AND BIOMARKERS ANALYSES SPECIFIC TO siRNA + CpAM + NUC ARM

A11.11.1 CLINICAL GENOTYPING

If safety or activity rationales develop, clinical genotyping will be performed (see Sections 8.7.4.1 and 8.8.1.1) if appropriate. This exploratory objective will aim at evaluating the association of genetic polymorphisms in known candidate genes with the PK profiles of the two NMEs and with primary and secondary endpoints. Known candidate genes of interest that are specific to CpAM/siRNA include AOX1, UGT1A1, PGP, OATP1B1, OATP1B3, CYP3A4, UGT1A3, and ASGR1. Further genes may be queried from the data based on progressing knowledge on these NMEs and their targets.

A11.12 SCHEDULE OF ACTIVITIES siRNA + CpAM + NUC ARM

An overview of the schedule of the activities is provided in Appendix 11-Table 3 and Appendix 11-Table 4.

Appendix 11-Table 3 Schedule of Activities for siRNA + CPAM + NUC Treatment Arm (Screening and Treatment Periods)

	Screening		Treatment Period														VB/VR	ET/UV[q]
Week			**1**	**3**	**5**	**9**	**13[n,p]**	**17**	**21**	**25[o,p]**	**29**	**33**	**37**	**41**	**45**	**49[p]**		
Day	**-56 to -7**	**-14 to -7**	**1**	**15 (±2)**	**29 (±3)**	**57 (±3)**	**85 (±3)**	**113 (±3)**	**141 (±3)**	**169 (±3)**	**197 (±3)**	**225 (±3)**	**253 (±3)**	**281 (±3)**	**309 (±3)**	**337 (-2)**		
Informed consent	x																	
Demography, medical history	x																	
Physical examination, vital signs [a, b]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization			x															
ECG	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Transient elastography/ARFI/MR [c]	x																	
Abdominal ultrasound	x									x						x		
Alfa-fetoprotein	x									x						x		
HAV, HCV, HDV, HEV, HIV	x																	
Autoantibodies [d]	x																	
Alcohol and drugs of abuse screen [e]		x														x		x
Pregnancy test [f]		x	x		x	x	x	x	x	x	x	x	x	x	x	x		x
Thyroid function tests	x						x			x			x			x		
Hematology (includes HbaA1c)[g]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry		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
GLDH	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	x
Clinical genotyping [h]			x															

Appendix 11-Table 3 Schedule of Activities for siRNA + CPAM + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

	Screening		Treatment Period														VB/VR	ET/UV[q]
Week			**1**	**3**	**5**	**9**	**13[n,p]**	**17**	**21**	**25[o,p]**	**29**	**33**	**37**	**41**	**45**	**49[p]**		
Day	**-56 to -7**	**-14 to -7**	**1**	**15 (±2)**	**29 (±3)**	**57 (±3)**	**85 (±3)**	**113 (±3)**	**141 (±3)**	**169 (±3)**	**197 (±3)**	**225 (±3)**	**253 (±3)**	**281 (±3)**	**309 (±3)**	**337 (-2)**		
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
HBV DNA quantitative	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Total HBsAg[i]			x		x		x			x			x			x	x	
HBcrAg			x		x		x			x			x			x	x	
Total anti-HBc quantitative			x				x			x			x			x		
HBV RNA quantitative			x		x		x			x			x			x	x	
HBV RNA sequencing [h]			x															
HBV DNA sequencing [j]																	x	
Plasma PK (siRNA) [k]			x				x			x			x			x	x	
Plasma PK (CpAM) [k]			x				x			x			x			x	x	
Plasma PK (NUC) [k]			x				x			x			x			x	x	
Plasma ADA (siRNA)[r]			x				x			x			x			x	x	x
RBR [l]			x							x			x			x	x	
Clinic siRNA 200 mg sc Q4W treatment administration			x		x	x	x	x	x	x	x	x	x	x	x	x		
CpAM treatment administration OD			x															
NUC treatment administration OD			x															
Adverse events & concomitant medications & diary review [m]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibodies; ARFI = acoustic radiation force impulse; CpAM = Core protein allosteric modulator; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics;

Appendix 11-Table 3 Schedule of Activities for siRNA + CPAM + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

RBR = Research Biosample Repository; RNA = ribonucleic acid; siRNA= short interfering ribonucleic acid; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

[a] Full physical examination at screening and at the end-of-treatment. Limited symptom-directed physical examination at other visits and as clinically indicated. Height at screening only. Weight at screening, Day 1, and Weeks 13, 25, 37, and 49.

[b] Blood pressure, pulse rate, respiratory rate, and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

[c] Historical liver biopsy or transient elastography/ARFI/MR/2D- shear wave elastography [2D-SWE] results obtained within 6 months prior to randomization are also acceptable. During screening transient elastography/ARFI/MR/2D-SWE are acceptable.

[d] Autoantibodies refer to ANA, AMA, ASMA, and a-TPO.

[e] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[f] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[g] HbA1c should be included in hematology and is required only at screening.

[h] If not collected at Day 1, samples for clinical genotyping and HBV RNA sequencing can be collected at any subsequent time point. *The sample for HBV RNA sequencing aims at determining the HBV genotype. The HBV genotype may also be inferred using alternative approaches, such as serovariant determination.*

[i] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb complexes/components of HBsAg.

[j] HBV DNA sequencing will be collected in case of virological breakthrough/relapse, blood sample to be collected up to 6 times.

[k] Plasma PK samples for CpAM and siRNA to be collected at pre-dose,1-3 and 4-6 hours post-dose. Plasma PK samples for NUC to be collected at pre-dose. During the PK assessments for VB/VR visits, only one pre-dose sample is required for collection, no other points required.

[l] RBR samples collected only from RBR-consenting participants.

[m] Pre-treatment, only serious adverse events should be reported.

[n] End-of-treatment visit for participants in the 12-week finite treatment arm (if commenced after an interim analysis).

[0] End-of-treatment visit for participants in the 24-week finite treatment arm (if commenced after an interim analysis).

[p] End-of-treatment visit for participants with HBsAg loss in the 48-week response-guided therapy arm (if commenced after an interim analysis).

[q] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

[r] Pre-dose plasma ADA sample.

Appendix 11-Table 4 Schedule of Activities for siRNA + CPAM + NUC Treatment Arm (Follow-up Period)

	Follow-up period											VB/VR	ET/UV[i]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Physical examination, vital signs [a, b]									x		x	x	x
ECG									x		x		
Abdominal ultrasound									x		x		
Alfa-fetoprotein									x		x		
Alcohol and drugs of abuse screen [c]													x
Pregnancy test [d]		x		x		x	x	x	x	x	x		x
Thyroid function tests									x		x		
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry	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
GLDH	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
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x	x	x	x	x	x	x	x	x	x	x	x	x
HBV DNA quantitative	x	x	x	x	x	x	x	x	x	x	x	x	x
Total HBsAg[e]		x		x		x		x	x		x	x	
HBcrAg		x		x		x		x	x		x	x	
Total anti-HBc quantitative						x			x		x		
HBV RNA quantitative		x		x		x		x	x		x	x	
HBV DNA sequencing												x	
Plasma PK (siRNA)													
Plasma PK (CpAM)													

Appendix 11-Table 4 Schedule of Activities for siRNA + CPAM + NUC Treatment Arm (Follow-up Period) (cont.)

	Follow-up period											VB/VR	ET/UV[i]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Plasma PK (NUC)[f]												x	
Plasma ADA (siRNA)						x			x	x	x	x	x
RBR[g]												x	
Diary review	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events & concomitant medications[h]	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; ARFI = acoustic radiation force impulse; CpAM = Core protein allosteric modulator; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics; RBR = Research Biosample Repository; RNA = ribonucleic acid ; siRNA= short interfering ribonucleic acid; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

Note: If participants discontinue NUC later in the follow-up, additional visits can be scheduled with a frequency of every 2 weeks for the first three months and every 4-12 weeks up to week 48 of follow-up period, similarly to the monitoring proposed for those who will discontinue NUC, siRNA, and CpAM at week 48 at the end-of-treatment period.

[a] Full physical examination at screening and at the end-of-treatment. Limited symptom-directed physical examination at other visits and as clinically indicated.

[b] Blood pressure, pulse rate, respiratory rate, and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

[c] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[d] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[e] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb/components of HBsAg.

[f] During the PK assessments for VB/VR visits, only one sample is required for collection, no other time points required. Pre-dose if on NUC therapy.

[g] RBR samples collected only from RBR-consenting participants.

[h] Pre-treatment, only serious adverse events should be reported.

[i] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

Appendix 12
Study Details Specific to siRNA (RO7445482) + TLR7 (RO7020531) + NUC Arm

An overview of short interfering RNA (siRNA) + toll-like receptor 7 (TLR7) + nucleos(t)ide NUC treatment arm is shown in Appendix 12-Figure 1.

Participants will receive RO7445482 (also known as DCR-HBVS; 200 mg Q4W) in addition to their background NUC therapy for the 48-week treatment period. RO7020531 (150 mg once every other day [QOD]) will be administered during Weeks 13-24 and Weeks 37-48 (i.e., 2 treatment cycles of 12 weeks' duration each and 42 doses of RO7020531 for each cycle). At the end of the treatment period, participants will continue NUC treatment during the follow-up unless the NUC discontinuation criteria have been met (see Section 6.8).

Approximately 30 participants will be randomized to this treatment arm.

If a 30% delta for HBsAg loss is observed at Week 48 (EOT) or follow-up Weeks 12 or 24 (primary endpoint) the treatment arm may be expanded to accrue additional efficacy and safety data, and to contribute to Phase 3 design planning. If a successful interim analysis is observed at Weeks 12 or 24, shorter treatment duration arms (12 and 24 weeks' duration) and/or a response-guided therapy (RGT) arm may be added.

Appendix 12-Figure 1 siRNA + TLR7 + NUC Treatment Arm

A12.1 BACKGROUND SPECIFIC TO siRNA + TLR7 + NUC ARM

A12.1.1 BACKGROUND ON RO7445482

RO7445482 (DCR-HBVS) is an siRNA conjugated to N-acetyl-D-galactosamine (GalNAc), which enables liver-targeting through binding to the asialoglycoprotein receptor (ASGPR) that is highly expressed in the liver. After forming the RNA-induced silencing complex (RISC), the RO7445482 antisense strand targets hepatitis B virus (HBV) RNA for degradation by triggering RNAi-mediated cleavage within the hepatitis B surface antigen (HBsAg) coding sequence, thereby inhibiting HBV gene expression.

Literature indicates that HBV antigens suppress the host immune response through several pathways, including the direct effects of long-term exposure to high concentration of viral antigens resulting in T-cell immune tolerance and T-cell exhaustion (Hai-Jun et al 2015). Depletion of viral antigens through inhibition of HBV gene expression may therefore facilitate the restoration of the host immune response.

Non-clinical studies with RO7445482 have shown potent antiviral activity. HBsAg reductions of up to 3.5 $\log_{10}$ for more than 7 weeks, as well as significant reductions in HBcAg, were observed after a single dose in mice, demonstrating duration of action suitable for infrequent dosing.

To date, clinical experience with RO7445482 is based on a Phase I clinical study (DCR-HBVS-101) involving healthy volunteers and participants with CHB.

A12.1.2 BACKGROUND ON RO7020531

RO7020531 is an oral double prodrug of the TLR7-specific agonist RO7011785. A prodrug approach was chosen for oral delivery of the TLR7 agonist RO7011785 in order to improve bioavailability and limit TLR7 activation in the gastrointestinal (GI) tract, which may be associated with GI intolerability.

TLRs are a family of pathogen-recognition receptors that activate the innate immune response. The stimulation of TLR7 mediates an endogenous type I IFN response, which is critical in development of a broad, effective, and protective immunity against hepatitis viruses (Horscroft et al 2012, Funk et al 2014). Compared to pegylated interferon-alfa (PEG-IFN-α) therapy, treatment with a TLR7 agonist induces broader immunomodulatory effects that are likely to lead to more effective control and functional cure of chronic HBV infection (Strader et al 2004, Isogawa et al 2005). TLR7 agonists induce the production of multiple isotypes of IFN from plasmacytoid dendritic cells (pDCs) which have been shown in vitro to possess additive or synergistic antiviral effects compared to exogenous PEG-IFN.

Non-clinical studies with RO7020531 suggest that it is rapidly converted to the active metabolite RO7011785, and data from in vivo studies with RO7020531 and in vitro studies with RO7011785 support immune activation as the mechanism of action.

To date, clinical experience with RO7020531 includes two Phase 1 clinical studies: an EIH study in HVs and CHB participants (NP39305) and a study in HVs of Chinese descent (YP39553).

A12.2 BENEFIT/RISK ASSESSMENT SPECIFIC TO siRNA+ TLR7 + NUC ARM

The 48-week treatment with RO7445482 and RO7020531 in combination with NUC aims to result in therapeutic benefit for participants, including possibly higher functional cure rates than observed currently with standard-of-care therapies (monotherapy with NUC or PEG-IFN). The concurrent RO7445482 and RO7020531 administrations aim is to test the scientific hypothesis whether concurrent direct-acting antiviral and immunomodulatory agent combination therapy maximizes the efficacy outcomes.

Given that reduction in viral antigens is anticipated to result in functional immune recovery, the potency of an immunomodulatory agent is expected to increase if administered following a reduction in HBsAg. Consequently, in this treatment arm, the RO7020531 12-week treatment cycles will commence at week 13 and week 37 following administration of RO7445482 i.e., 'off/on' immunomodulatory treatment approach.

This concept is supported by in vivo non-clinical data, whereby in a recombinant adeno-associated virus carrying HBV genome (AAV-HBV) mouse model the combination of RO7049389 (a direct antiviral agent that works as a core protein allosteric modulator) and toll-like receptor 7 (TLR7)-agonist, RO7020531 (an immune modulator) resulted in significantly greater HBV DNA and hepatitis B surface antigen (HBsAg) reductions post treatment (Day 84) than either agent as monotherapy (Appendix 12-Table 1). HBsAg loss (< lower limit of quantification [LLOQ]) was observed in 5 of 7 mice by the end of the 6-week combination treatment and sustained in the 6-week off-treatment period but in none of the monotherapy groups, suggesting a transformational efficacy impact with the direct-acting antiviral and immunomodulatory agent combination therapy.

Appendix 12-Table 1 Summary of Viral Marker Reductions (AAV-HBV Mouse Model)

Treatment	HBV DNA Reduction (Log)			HBsAg Reduction (Log)		
	Day 14	Day 42	Day 84	Day 14	Day 42	Day 84
RO7020531: 100 mg/kg QOD	1.2±0.2	1.9±0.4	0.2±0.1	0.6±0.4	1.6±0.5	0.4±0.2
RO7049389: 20 mg/kg QD	3.5±0.1	3.8±0.1	1.5±0.2	0.0±0.1	1.5±0.2	1.9±0.3
Combination therapy	3.8±0.1	4.1±0.1	3.4±0.5	0.9±0.5	3.1±0.3	3.1±0.3
Vehicle	0.0±0.1	0.0±0.1	0.0±0.1	0.0±0.1	0.0±0.2	0.0±0.2

Notes: Day 84 is 42 days post-treatment. Data presented as mean ± SEM (7 mice per group).

Furthermore, the combination of HBV-LNA ASO (a gene expression inhibitor) and TLR7 agonist (an immune modulator) led to a delayed and reduced off-treatment rebound of HBsAg and HBV DNA in AAV-HBV mice than either agent alone (Blaising et al 2019).

Interim Phase 1 data have shown significant and durable antiviral activity with 4 monthly doses of RO7445482 in NUC-suppressed participants with CHB. At Day 112, mean HBsAg $\log_{10}$ IU/mL reduction from baseline were 1.39, 1.80 and 1.84 for participants who received 1.5 mg/kg, 3.0 mg/kg or 6 mg/kg, respectively. Approximately 80% of participants achieved > 1.5 $\log_{10}$ IU/mL reduction (irrespective of HBeAg-status), 60% had HBsAg levels < 100 IU/mL, and durability of response was demonstrated up to Day 392.

Based on the interim Phase 1 data, RO7445482 was safe and well tolerated in healthy volunteers (HV) and CHB patients. The safety profile appears to be similar between HVs and patient participants, and there were no safety signals or dose related trends identified. No severe or serious treatment-emergent adverse events (TEAEs) or TEAEs leading to treatment discontinuation, apart from generally mild injection site reactions (ISRs), there was absence of other potential oligonucleotide class effects.

RO7445482 and RO7020531 separately, have shown acceptable safety/tolerability in the Phase 1 studies involving healthy volunteers and CHB participants, and non-clinical toxicology and safety pharmacology studies support the proposed 48-week combination regimen.

For details, refer to the RO7445482 and RO7020531 Investigator's Brochures.

A12.3 JUSTIFICATION FOR DOSE SPECIFIC TO siRNA+ TLR7 + NUC ARM

For RO7445482, fixed dose of 200 mg Q4W (equivalent to 3 mg/kg monthly) has been selected for Phase 2 study in combination with other IMPs/NMEs. This dose is within the anticipated therapeutic dose-range in humans and is expected to be safe and well tolerated. A summary of the key data supporting the selected dose is provided below:

- The dose-response trend in the HBsAg declines, together with PK/PD modeling of interim Phase 1 data, supports the proposed 200 mg Q4W dosing regimen. Preliminary PK/PD modeling predicts that the proportion of participants who will achieve > 1.5 and > 2 $\log_{10}$ IU/mL reductions in HBsAg, following Q4W doses up to Week 12, will be higher with a 200 mg Q4W regimen (97% and 56%, respectively) compared to a 100 mg Q4W regimen (89% and 6%, respectively).
- The non-clinical chronic toxicology studies provide acceptable safety margins for the 200 mg Q4W fixed dose (3 mg/kg equivalent) for treatment period of 48 weeks.
- PK/PD modelling supports use of fixed (200 mg) instead of weight based (3 mg/kg) RO7445482 dosing.

For RO7020531, a dose of 150 mg QOD has been selected for this Phase 2 study, to be administered continuously over two 12-week cycles separated by a 12-week dosing holiday (for RO7020531 only). This dose and regimen is within the predicted therapeutic

dose-range in humans and is expected to be safe and with acceptable tolerability. A summary of the key data supporting the selected dose is provided below:

- RO7020531 doses up to 170 mg QOD and 150 mg QOD (both for 6 weeks) have been observed to be safe and with acceptable tolerability in two Phase 1 studies involving healthy volunteers and CHB participants.
- Pharmacodynamic effects consistent with TLR7 activation was observed in the 100-170 mg QOD dose-range, with increasing magnitude of response associated with higher doses.

Further details are provided in the RO7445482 and RO7020531 Investigator's Brochures.

A12.4 INCLUSION/EXCLUSION CRITERIA SPECIFIC TO siRNA + TLR7 + NUC ARM

Participants must meet the following criterion for inclusion in the siRNA + TLR7 + NUC treatment arm:

Sex

1. Female Participants:

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

   - Woman of non-childbearing potential (WONCBP).
   - Woman of childbearing potential (WOCBP), who:
     – Agrees to remain abstinent (refrain from heterosexual intercourse) or use 2 acceptable contraceptive methods, of which at least 1 is considered highly effective (result in a failure rate of < 1% per year) during the treatment period and for at least 6 months after the final dose of study treatment (Appendix 5).
     – Has a negative pregnancy test at screening (Day -14 to -7). In addition, willing to undergo a urine pregnancy test at Day 1 and every month during treatment and up to 6 months follow-up, thereafter every 3 months until end of follow-up.

Participants are excluded from the siRNA + TLR7 + NUC arm if any of the following criteria apply:

Weight

1. Body mass index < 21 and weight at screening: $<$55 kg for men or < 45 kg for women

Medical Conditions

2. Current symptoms of depression or history of depression requiring treatment.
3. History of autoimmune hepatitis or other autoimmune disorders.
4. Diabetes that is not well controlled (HbA1c$\geq$7% at screening)
5. Pre-existing ophthalmologic disorders (known history or as assessed by eye examination at screening), which in the opinion of the investigator would increase the likelihood of clinical significance of potential drug-induced retinopathy (e.g., diabetic or hypertensive retinopathy, glaucoma dense cataract, visual field abnormalities, severe retinopathy).
6. History of pulmonary disorders including interstitial pneumonitis, bronchiolitis obliterans, pulmonary hypertension, and sarcoidosis.
7. History of pancreatitis.
8. Participants with history or present evidence of orthostatic hypotension.

A12.5 SAFETY ASSESSMENTS SPECIFIC TO SIRNA + TLR7 + NUC ARM

Physical Examinations

Eye examination will be performed at screening, preferably by an ophthalmologist, and will include funduscopic examination with dilation, visual acuity, assessment, visual field testing, and color visual testing.

Vital signs

Assessment of orthostatic hypotension will be done at screening. To assess the presence of orthostatic hypotension, blood pressure will be measured both while the participant is sitting and while standing. Participants will be excluded if a drop of 20 millimeters of mercury (mm Hg) in systolic blood pressure or a drop of 10 mm Hg in diastolic blood pressure within 2 to 5 minutes of standing up or if standing causes signs and symptoms of hypotension.

A12.6 LIFESTYLE CONSIDERATIONS SPECIFIC TO siRNA + TLR7 + NUC ARM

RO7020531 will be given in fasted state (at least 2 hours after a meal or 2 hours before the next meal). NUCs will be given according to the local prescribing information.

For RO7020531, consumption of green tea beverages should be minimized during the treatment period, as these may inhibit aldehyde oxidase activity (Tayama et al 2011).

For CHB participants who routinely take herbal medicines that in Investigator's opinion may have immune-modulatory effects, herbal medicines should strongly be discouraged.

A12.7 CONTRACEPTIVE REQUIREMENTS SPECIFIC TO siRNA + TLR7 + NUC ARM

For WOCBP: agreement to remain abstinent (refrain from heterosexual intercourse) or use 2 acceptable contraceptive methods of which at least 1 is considered highly effective (see Appendix 5), during the study and for at least 6 months after the last dose of study drug.

- Examples of acceptable highly effective contraceptive methods (< 1% failure rate per year) include combined or progesterone-only hormonal contraception, intrauterine device, and vasectomized partner.
- Examples of acceptable not as highly effective contraceptive methods (> 1% failure rate per year) include progesterone-only hormonal contraception (where inhibition of ovulation is not the primary mode of action) and male or female condoms with or without spermicide.

For men: agreement to remain abstinent (refrain from heterosexual intercourse) or agree to use contraceptive measures, and agree to refrain from donating sperm, as defined below:

- Men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of study drug to avoid exposing the embryo.
- Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial 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 contraception.

A12.8 TREATMENT ADMINISTERED SPECIFIC TO siRNA + TLR7 + NUC ARM

Appendix 12-Table 2 summarizes the treatments administered. Paracetamol/acetaminophen is considered non investigational medicinal products (NIMPs).

Appendix 12-Table 2 Summary of Treatments Administered for siRNA + TLR7 + NUC Treatment Arm

Study Treatment Name	siRNA (RO7445482)	TLR7 (RO7020531)	NUC
IMP and NIMP	IMP	IMP	NIMP*
Dose Formulation	Sterile colorless to yellow solution of drug substance RO7445482 in water for injection	film-coated tablet	film-coated tablet
Unit Dose Strength(s)/Dosage Level(s)	120 mg/mL, 2 mL filled in a 6 ml vial	150 mg 100 mg	Refer to local prescription information
Dose:	Fixed dose 200 mg Q4W	150 mg QOD 100 mg QOD 100 mg QW	ETV: 0.5 mg OD TDF: 300 mg OD TAF: 25 mg OD
Route of Administration	SC	oral	oral
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor or locally by the study site
Packaging and Labeling	Study treatment will be provided in vials, packaged, and labeled as required per local regulation.	Study treatment will be packaged and labeled as required per local regulation.	Study treatment will be packaged and labeled as required per local regulation.

*NUC are considered IMP in the UK only.

RO7445482 administrations will be via the SC route utilizing sterile technique. RO7445482 doses will be administered at the study clinic preferably in the morning by investigational staff.

The SC administration site (e.g., left abdomen, right abdomen etc.) should be rotated between visits.

Guidelines for dosage modification and treatment interruption/discontinuation are in Section A12. (in this Appendix).

For more details, refer to the RO7445482 and RO7020531 Investigator's Brochures, NUC local prescribing information, and the Pharmacy Manual.

A12.9 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non serious AESIs 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 documents listed below:

Drug	Document
RO7020531	RO7020531 Investigator's Brochure
RO7445482	RO7445482 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.

A12.10 CONCOMITANT THERAPY SPECIFIC TO siRNA + TLR7 + NUC ARM

The following concomitant medications are prohibited:

- Inhibitors of Organic Anion Transporter 1 and 3 (OAT 1 and OAT 3): e.g., p-aminohippuric acid (PAH), probenecid, teriflunomide within 7 days, or 5 half-lives (whichever is longer) before the first administration of RO7020531 and while on study treatment with RO7020531.
- Inhibitors of P-gp transporters: e.g., amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil within 7 days, or 5 half-lives (whichever is longer) before the first administration of RO7020531 and while on study treatment with RO7020531.

The following concomitant medications are to be used with caution, and the Sponsor should be informed before these drugs are administered. When coadministered with study drugs, the recommendation is to use the lowest necessary dose of the substrate, titrate the dose carefully, and monitor closely for substrate-associated adverse reactions

- Drugs metabolized by aldehyde oxidase including famciclovir and/or inhibiting this enzyme including tamoxifen, raloxifen, cimetidine, promethazine, clozapine, and chlorpromazine, which could decrease the formation of RO7011785.
- Drugs that reduce renal function or compete for active tubular secretion that may increase serum concentrations of RO7011785 study drug.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication when determining whether a certain medication inhibits or induces above mentioned enzymes or transporter or renal function. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications that are not listed above.

A12.11 MANAGEMENT OF ADVERSE EVENTS SPECIFIC TO siRNA + TLR7 + NUC ARM

TLR-RELATED AES

TLR7 agonist activates innate and adaptive immune responses, and these mechanisms include induction of type I interferon (IFNα). Safety data from the ongoing Phase 1 studies showed IFN-related flu-like symptoms (headache, pyrexia, chills, myalgia, nausea), mostly of mild intensity; and in some participants, hematological abnormalities (e.g., neutropenia, lymphopenia). During the two clinical studies with RO7020531 (NP39305 and YP39553), all hematological abnormalities were asymptomatic and in most cases reversible within 24 to 48 hours.

TLR7 agonists as a class may have the potential, in a dose-dependent manner, to lead to hypotension and distributive shock due to excessive cytokine release (cytokine release syndrome [CRS])—e.g., IL-1,IL-6,IL-10, IFN-γ, TNF-α etc.—by immune activation. CRS can present with a variety of symptoms, from mild symptoms overlapping with mild flu-like symptoms to severe or life-threatening manifestations. Mild symptoms of CRS include fever, fatigue, headache, rash, arthralgia, and myalgia. More severe cases are characterized by hypotension that requires vasopressor treatment and/or hypoxia that requires medical intervention. They can progress to an uncontrolled systemic inflammatory response with circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi–organ-system failure. Flu-like symptoms were observed during the two clinical studies with RO7020531 (NP39305 and YP39553) at 140 mg to 170 mg single or multiple QOD doses up to 6 weeks. These symptoms overlap with and are not distinguishable from mild cases of CRS.

A12.12 ENHANCED SAFETY MONITORING DURING COMBINATION TREATMENT WITH SIRNA + TLR7 + NUC ARM

Based on the emerging data from Phase 1 studies NP39305 (HV and patient cohorts) and YP39553 (single– and multiple–ascending-dose clinical study in Chinese HVs), it became evident that in all cases of flu-like symptoms, the initial onsets emerged within the initial 3 doses of RO7020531. For this reason, pre-dose laboratory analyses and optional extended in-hospital stay with frequent vital sign monitoring (every 2 to 4 hours) and ECGs (pre-dosing and 6 to 8 hours after dosing at each visit) are scheduled for the initial 3 doses of each combination cycle and guided by emerging AEs as follows:

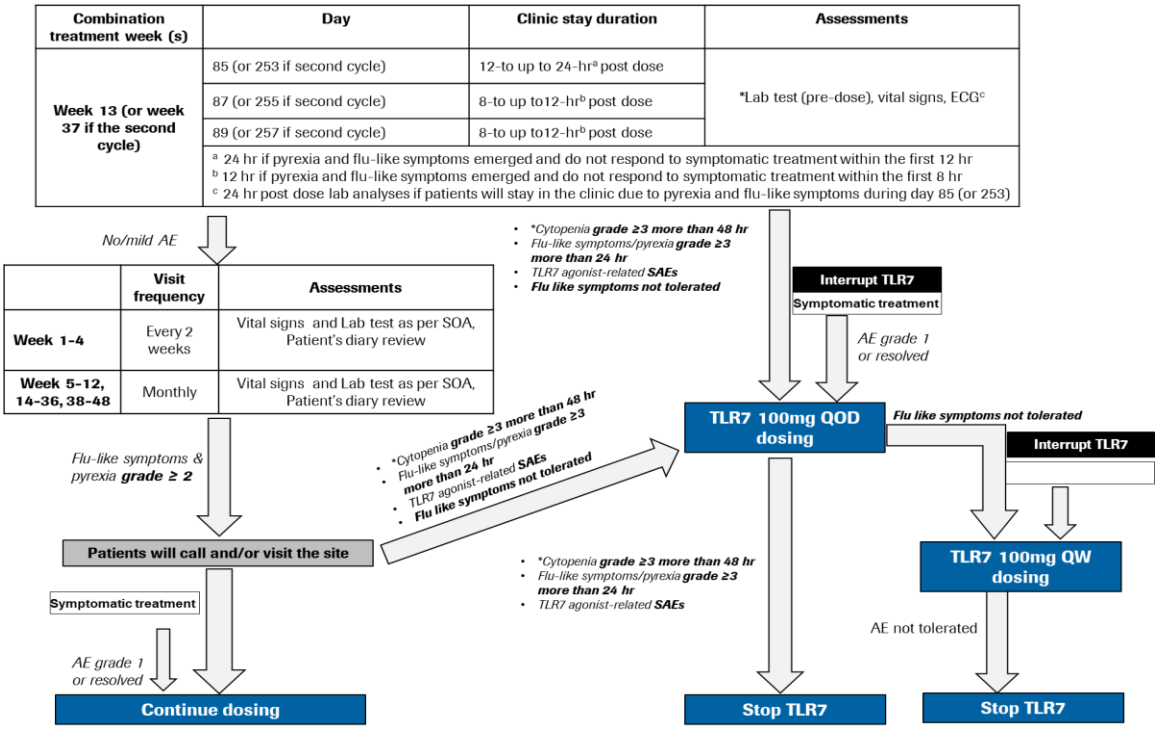
- On Day 85 and/or Day 253 (first day of each cycle of TLR7 dosing), participants will stay in the clinical unit for 12 hours with an option to stay in the clinic for up to 24 hours (at the Investigator's discretion) in case pyrexia and additional flu-like symptom(s) emerge and do not respond to symptomatic treatment (paracetamol/acetaminophen up to 2 g/day) during the first 12 hours post-combination dosing. For those participants who stay up to 24 hours, an additional 24 hours post-dose laboratory assessment will be done on Day 2 and Day 170, respectively.
- On Day 87 and Day 255 (third day of each cycle of TLR7 dosing), participants will stay in the clinical unit for 8 hours with an option to stay in the clinic for up to 12 hours (at the Investigator's discretion) in case pyrexia and additional flu-like symptom(s) emerged and would not respond to symptomatic treatment (paracetamol/acetaminophen up to 2 g/day) during the first 8 hours post-combination dosing.
- On Day 89 and Day 257 (fifth day of each cycle of TLR7 dosing), participants will stay in the clinical unit for 8 hours with an option to stay in the clinic for up to 12 hours (at the Investigator's discretion) in case pyrexia and additional flu-like symptom(s) emerged during the first 8 hours and would not respond to symptomatic treatment (paracetamol/acetaminophen up to 2 g/day) during the first 8 hours post-combination dosing.

The Sponsor will promptly communicate to the Investigator any change to the proposed enhanced monitoring plan based on emerging data and interim safety evaluations. In case the prolonged hospital stay is not required but participants live far away and may need to be back on the following day, the investigator may decide to allow them to stay at a hotel nearby.

The Sponsor will provide participants a thermometer to use for temperature self-monitoring in case flu-like symptoms and pyrexia emerge. If at any time during the combination cycles (siRNA + TLR7 + NUC) participants experience flu-like symptoms with pyrexia (Grade 2 or above), it will be recommended to call the site and the PI or the medical personnel on site:

- may recommend participants visit the clinic for an unscheduled visit according to the SOA in Appendix 12.
- may recommend symptomatic treatment with paracetamol/ acetaminophen up to 2 g/day.

Appendix 12-Figure 2. Safety Monitoring and RO7020531 Dosing Interruption for Flu-like Symptoms and Cytopenia during Combination Treatment with siRNA + TLR7 + NUC



*Based either on central laboratory (as per the SoA in Appendix 12) and/or local laboratory if performed for participant management and/or decision-making. In such a scenario, if local laboratory tests are performed, an additional sample will be sent to the central laboratory, but decisions will be based on local laboratory results.

A12.13 DOSE MODIFICATION

Dose reduction to 100 mg QOD with RO7020531 for intolerability associated with adverse events should be considered by the Investigator during the treatment phase in the following situations:

- Grade 3 (severe) TLR7 agonist-related AEs of flu-like symptoms that persist > 24 hours despite prophylactic and/or symptomatic treatment with acetaminophen (paracetamol)
- Grade 3 (severe) hematological (e.g., cytopenia) laboratory abnormalities that persist for > 48 hours
- TLR7 agonist-related SAE
- Flu-like symptoms that are not tolerated

In the above situations, RO7020531 150 mg QOD dosing should be interrupted until AEs, laboratory abnormalities, or SAEs improve to Grade 1 or less, before initiating a dose reduction to RO7020531 100 mg QOD.

For repetitive/recurrent flu-like symptoms/pyrexia (either responsive or unresponsive despite symptomatic treatment with acetaminophen or poorly manageable despite prophylactic treatment with acetaminophen) or other TLR7 agonist-related AEs (including repetitive AEs) which are not well manageable, the Investigator in discussion with the participant should consider a RO7020531 dose reduction to 100 mg QOD. The Medical Monitor is available to the PI to answer any medical questions.

Following the RO7020531 dose reduction to 100 mg QOD, the Investigator should interrupt RO7020531 dosing if any of the following situations occur:

- Grade 3 (severe) TLR7 agonist-related AEs of flu-like symptoms that persist for > 24 hours despite prophylactic and/or symptomatic treatment with acetaminophen (paracetamol)
- Grade 3 (severe) hematological (e.g., cytopenia) laboratory abnormalities that persist for > 48 hours
- TLR7 agonist-related SAE

Following the RO7020531 dose reduction to 100 mg QOD, if flu-like symptoms are still not tolerated by the participants, a reduction of the dosing frequency of RO7020531 to 100 mg QW (once a week) should be considered.

Appendix 12-Table 3 summarizes the dose interruption/modification/discontinuation guidelines for the siRNA+TLR7+NUC combination arm.

Appendix 12-Table 3. Dose Interruption/Modification/Discontinuation Guidelines for the siRNA+TLR7+NUC Combination Arm

Laboratory/Clinical Parameters	Recommendation	Reference
TLR7-related AEs		
Grade 3 flu-like symptoms >24 hr despite prophylactic and/or symptomatic treatment, or, repetitive flu-like symptoms that are poorly tolerated	**Interrupt** RO7020531 dosing (150 mg QOD). **Reduce** RO7020531 to **100 mg QOD** when AEs improved to Grade 1 or SAE resolved. Following dose reduction (100 mg QOD), if similar Grade 3 AEs or laboratory abnormalities occur, interrupt RO7020531. In general, consider **switching to 100 mg QW** (at least 5 days after the last dose) prior to drug discontinuation (case-by-case basis).	Appendix 8 (Section A12.12)
Grade 3 hematological abnormalities that persist >48 hr		
TLR7 agonist-related SAE		
siRNA-related AEs		
No laboratory or clinical parameters have been identified yet	No dose modification recommendations for siRNA	N/A
General criteria for dose interruptions/discontinuations for all NMEs		
Liver transaminases and liver function test	See Section 7.1	Section 8.3.8.3
Confirmed virological breakthrough	**Discontinue** NMEs and continue treatment according to local standards	Section 8.3.8.1
Others	See Section 7.1	

In general, when addressing tolerability issues with RO7020531, prior to the investigator making a decision to discontinue study treatment or participant withdrawal of consent from study treatment, a dose reduction should be discussed and evaluated if considered in the participant's best interest. The Medical Monitor is available to the Investigator to answer any medical questions.

The first dose of RO7020531 100 mg QOD should be administered in the clinic, and participants should be monitored for at least 8 hours as per SoA (with pre-dose safety laboratory assessment, every 2 to 4 hours for vital signs, and ECG assessment at pre-dose and 6 to 8 hours post-dose). This first visit should be synchronized with the participant's current RO7020531 QOD dosing schedule.

In case participants are changed to 100 mg QW dosing, at least 5 days should have elapsed since the last dose. If Grade 2 flu-like symptoms occur, the Investigator may recommend symptomatic treatment with paracetamol/ acetaminophen. If symptoms respond to symptomatic treatment and the treatment is tolerable, participants will continue QW dosing. If there is poor tolerability, participants will permanently discontinue further RO7020531 dosing. Participants changed to the QW dosing will follow the same SOA of participants in the QOD dosage, with two 12-week combination treatment cycles (Weeks 13 to 25 and 37 to 49) and a 12-week holiday period in between.

Participants who change to 100 mg QW dosing or discontinue because of non-safety reasons may be replaced at the sponsor's discretion. This is to ensure the number per arm of the randomized QOD dose regimen remains close to the planned 30 participants.

Participants on RO7020531 100 mg QOD will follow the SoA as included in Appendix 12. In case of RO7020531 100 mg QW dosing, participants will follow the SoA as included in Appendix 12, but QW dosing administration will be aligned with SoA visits.

For ALT elevations, refer to Section 8.3.8.3.

A12.14 PHARMACODYNAMICS AND BIOMARKERS ANALYSES SPECIFIC TO siRNA + TLR7 + NUC ARM

A12.14.1 TLR7 ACTIVITY BIOMARKERS

TLR7 is expressed on human pDC and B-cells, and its activation induces both humoral and cellular changes (Iwasaki and Medzhitov 2004, Lester and Li 2014). These changes include the production of cytokines and chemokines such as IFN- α, IL-6, TNF-α, IL-10, IL-12p40, IP-10, and changes in the expression of ISGs, e.g., ISG15, OAS-1 and myxovirus resistance 1 gene (MX1) and of the TLR7 gene itself (Fidock et al 2011), as well as changes in markers of immune stimulation such as neopterin.

To characterize TLR7 PD biomarkers (secondary objective), blood samples will be collected at time points according to the SoA (see Appendix 12-Table 4 and Appendix 12-Table 5) to measure cytokines including INF-α, IP-10, IL-6 and TNF-α as well as a panel of transcriptional response of Interferon Stimulated Genes (ISG15, OAS1, MX1, and TLR7) if appropriate. Following review of these PD biomarkers and the AEs, further cytokines may be tested using a separate aliquot collected at the same time points including, IL-1, IL-10, and IFN-γ.

A12.14.2 CLINICAL GENOTYPING

If safety or activity rationales develop, clinical genotyping will be performed (see Sections 8.7.4.1 and 8.8.1.1) if appropriate. This exploratory objective will aim at evaluating the association of genetic polymorphisms in known candidate genes with the PK profiles of the two NMEs and with primary and secondary endpoints. Known candidate genes of interest that are specific to siRNA/TLR7 include AOX1, TLR7, UGT1A1, and ASGR1. Further genes may be queried from the data based on progressing knowledge on these NMEs and their targets.

A12.15 SCHEDULE OF ACTIVITIES siRNA + TLR7 + NUC ARM

An overview of the schedule of the activities is provided in Appendix 12-Table 4 and Appendix 12-Table 5.

Appendix 12-Table 4 Schedule of Activities for siRNA + TLR7 + NUC Treatment Arm (Screening and Treatment Periods)

	Screening		Treatment Period																		100 mg QOD [u]	VB/VR	ET/UV [v]
Week			**1**	**3**	**5**	**9**	**13 [o, q]**			**17**	**21**	**25 [p,q]**	**29**	**33**	**37**			**41**	**45**	**49 [q]**		**-**	**-**
Day	**-56 to -7**	**-14 to -7**	**1**	**15 (±2)**	**29 (±3)**	**57 (±3)**	**85 (±1)**	**+2 [s]**	**+2 [s]**	**113 (±3)**	**141 (±3)**	**169 (-5[r])**	**197 (±3)**	**225 (±3)**	**253 (±2)**	**+2 [s]**	**+2 [s]**	**281 (±3)**	**309 (±3)**	**337 (-6[r])**			
Informed consent	x																						
Demography, medical history	x																						
Physical examination, vital signs [a, b]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ophthalmic Exam [a]	x																						
Randomization			x																				
ECG	x		x	x	x	x	x [t]	x [t]	x [t]	x	x	x	x	x	x [t]	x [t]	x [t]	x	x	x	x [t]		
Transient elastography/ARFI/MR [c]	x																						
Abdominal ultrasound	x											x								x			
Alfa-fetoprotein	x											x								x			
HAV, HCV, HDV, HEV, HIV	x																						
Autoantibodies [d]	x																						
Alcohol and drugs of abuse screen [e]		x																		x			x
Pregnancy test [f]		x	x		x	x	x			x	x	x	x	x	x			x	x	x			x
Thyroid function tests	x						x					x								x			
Hematology (includes HbA1c)[g]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 12-Table 4 Schedule of Activities for siRNA + TLR7 + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

	Screening		Treatment Period																		100 mg QOD [u]	VB/VR	ET/UV [v]
Week			1	3	5	9	13 [o, q]			17	21	25 [p,q]	29	33	37			41	45	49 [q]		-	-
Day	-56 to -7	-14 to -7	1	15 (±2)	29 (±3)	57 (±3)	85 (±1)	+2 [s]	+2 [s]	113 (±3)	141 (±3)	169 (-5 [r])	197 (±3)	225 (±3)	253 (±3)	+2 [s]	+2 [s]	281 (±3)	309 (±3)	337 (-6 [r])			
Coagulation	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
GLDH	x		x	x	x	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	x	x	x	x	x	x
Clinical genotyping [h]			x																				
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x		x	x	x	x	x			x	x	x	x	x	x			x	x	x		x	x
HBV DNA quantitative	x		x	x	x	x	x			x	x	x	x	x	x			x	x	x		x	x
Total HBsAg [i]			x		x		x					x			x					x		x	
HBcrAg			x		x		x					x			x					x		x	
Total anti-HBc quantitative			x				x					x			x					x			
HBV RNA quantitative			x		x		x					x			x					x		x	
HBV RNA sequencing [h]			x																				
HBV DNA sequencing [j]																						x	
Plasma PK (TLR7) [k]							x	x	x			x			x	x	x			x	x	x	
Plasma PK (siRNA) [k]			x				x	x				x			x	x				x		x	
Plasma PK (NUC) [k]			x				x					x			x					x		x	
Plasma ADA (siRNA)[w]			x				x					x			x					x		x	x

Appendix 12-Table 4 Schedule of Activities for siRNA + TLR7 + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

	Screening		Treatment Period																			100 mg QOD [u]	VB/VR	ET/UV [v]
Week			**1**	**3**	**5**	**9**	**13 [o, q]**			**17**	**21**	**25[p,q]**	**29**	**33**	**37**			**41**	**45**	**49[q]**			**-**	**-**
Day	**-56 to -7**	**-14 to -7**	**1**	**15 (±2)**	**29 (±3)**	**57 (±3)**	**85 (±1)**	**+2 [s]**	**+2 [s]**	**113 (±3)**	**141 (±3)**	**169 (-5[r])**	**197 (±3)**	**225 (±3)**	**253 (±3)**	**+2 [s]**	**+2 [s]**	**281 (±3)**	**309 (±3)**	**337 (-6[r])**				
24 hour pooled urine PK[x] (siRNA)							x								x									
Cytokine panel [l]			x				x	x	x			x			x	x	x			x	x		x
ISG panel [l]			x				x	x	x			x			x	x	x			x	x		x
RBR [m]			x									x			x					x		x	
Clinic siRNA 200mg sc Q4W treatment administration			x		x	x	x			x	x	x	x	x	x			x	x	x				
TLR7 treatment administration QOD							x								x									
NUC treatment administration OD			x																					
Adverse events & concomitant medications & dairy review [n]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; ARFI = acoustic radiation force impulse; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IFN- α+ interferon alpha; IP-10 = interferon gamma-induced protein 10; ISG = interferon-stimulated genes; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics;

Appendix 12-Table 4 Schedule of Activities for siRNA + TLR7 + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

RBR = Research Biosample Repository; RNA = ribonucleic acid; siRNA= short interfering ribonucleic acid; TLR = toll-like receptor; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

[a] Full physical examination at screening and at the end-of-treatment. Limited symptom-directed physical examination at other visits and as clinically indicated. Height at screening only. Weight at screening, Day 1, and Weeks 13, 25, 37, and 49. Eye examination (including fundoscopy) only at screening.

[b] Blood pressure, pulse rate, respiratory rate and body temperature obtained at least 5 minutes after participant has been in supine/sitting position. Orthostatic hypotension test only at screening. Vital signs assessments on Days 85 and 253: predose, 2-4 hours, 4-6 hours, 6-8 hours and 8-12 hours; Vital signs assessments on day of the second and third RO7020531 dose of the first cycle , on the first day of those switching to QW dosing, and on the days of the second and third RO7020531 dose in the second cycle: predose, 2-4 hours, 4-6 hours, 6-8 hours (and 8-12 hours optional in case of extended in-clinic stay).

[c] Historical liver biopsy or transient elastography/ARFI/MR/2D- shear wave elastography [2D-SWE] results obtained within 6 months prior to randomization are also acceptable. During screening transient elastography/ARFI/MR/2D-SWE are acceptable.

[d] Autoantibodies refer to ANA, AMA, ASMA, and a-TPO.

[e] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[f] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[g] HbA1c should be included in hematology, and is required only at screening.

[h] If not collected at Day 1, samples for clinical genotyping and HBV RNA sequencing can be collected at any subsequent time point. *The sample for HBV RNA sequencing aims at determining the HBV genotype. The HBV genotype may also be inferred using alternative approaches, such as serovariant determination.*

[i] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb complexes/components of HBsAg.

[j] HBV DNA sequencing will be collected in case of virological breakthrough/relapse, blood sample to be collected up to 6 times.

[k] Plasma PK samples for TLR7 to be collected at pre-dose, 1-3 and 4-6 hours post-dose. Plasma PK samples for NUC to be collected at pre-dose. Plasma PK samples for siRNA D85 and D253 at pre-dose, 1, 2, 4, 6, 8 and 48 hours post-dose; For D1, D169 and D337 to be collected at pre-dose, 1-3 and 4-6 hours post-dose. During the PK assessments for VB/VR visits, only one pre-dose sample is required for collection, no other points required.

Appendix 12-Table 4 Schedule of Activities for siRNA + TLR7 + NUC Treatment Arm (Screening and Treatment Periods) (cont.)

[l] Cytokine panel (INF-α, IP-10, IL-1, IL-6, IL-10, IFN-γ, and TNF-α) and ISG panel to be collected at pre-dose and 6 hours post-dose of TLR7. On Day 1, only a pre-dose cytokine and ISG panels should be collected. At an unscheduled visit or early termination visit, preferably a pre-dose, otherwise, just a sample for cytokine and ISG panels should be collected if the visit is linked to a TLR7 related adverse reaction (e.g., influenza-like symptoms). No samples are required, for unscheduled visit or early termination visit not linked to TLR7 related adverse reaction (e.g., influenza-like symptoms).

[m] RBR samples collected only from RBR-consenting participants.

[n] Pre-treatment, only serious adverse events should be reported.

[o] End-of-treatment visit for participants in the 12-week finite treatment arm (if commenced after an interim analysis).

[p] End-of-treatment visit for participants in the 24-week finite treatment arm (if commenced after an interim analysis).

[q] End-of-treatment visit for participants with HBsAg loss in the 48-week response-guided therapy arm (if commenced after an interim analysis).

[r] visit will be on dosing days for PK and PD sampling: -7 if the patient is on QW dosing.

[s] Not applicable to participants who switched to QW RO7020531 dosing.

[t] ECGs to be assessed predose and 6-8hrs post-dose on the first 3 doses of each 12-week RO7020531 cycle and on first dose if 100 mg QOD dosing is started.

[u] For patients who move from 150 mg QOD to 100 mg QOD, this first dose of 100 mg QOD should be administered in the clinic and should be synchronized with the patients' current RO7020531 QOD dosing schedule e.g., if the next current QOD dosing falls over the weekend, then it would be acceptable to miss doses for the first dose visit to take place outside the weekend.

[v] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

[w] Pre-dose plasma ADA sample.

[x] *Timed urine collected for PK analyses of siRNA concentration and potential drug metabolites (if feasible). Participants will have provided a urine sample for safety analysis predose (urinalysis) and should then have an empty bladder. The 24 hours pooled (0-24 hours) urine collection to commence with first void and following siRNA administration and up to 24 hours post dose.*

Appendix 12-Table 5 Schedule of Activities for siRNA + TLR7 + NUC Treatment Arm (Follow-up Period)

	Follow-up period											VB/VR	ET/UV[i]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24[j]**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Physical examination, vital signs [a, b]									x		x	x	x
ECG									x		x		
Abdominal ultrasound									x		x		
Alfa-fetoprotein									x		x		
Alcohol and drugs of abuse screen [c]													x
Pregnancy test [d]		x		x		x	x	x	x	x	x		x
Thyroid function tests									x		x		
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry	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
GLDH	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
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x	x	x	x	x	x	x	x	x	x	x	x	x
HBV DNA quantitative[k]	x	x	x	x	x	x	x	x	x	x	x	x	x
Total HBsAg [e]		x		x		x		x	x		x	x	
HBcrAg		x		x		x		x	x		x	x	
Total anti-HBc quantitative						x			x		x		
HBV RNA quantitative		x		x		x		x	x		x	x	
HBV DNA sequencing												x	
Plasma PK (TLR7)													

Appendix 12-Table 5 Schedule of Activities for siRNA + TLR7 + NUC Treatment Arm (Follow-up Period) (cont.)

	Follow-up period											VB/VR	ET/UV[i]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24[j]**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Plasma PK (siRNA)													
Plasma PK (NUC) [f]												x	
Plasma ADA (siRNA)						x			x	x	x	x	x
RBR [g]												x	
Diary review	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events & concomitant medications [h]	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; ARFI = acoustic radiation force impulse; CpAM = Core protein allosteric modulator; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IP-10 = interferon gamma-induced protein 10; ISG = interferon-stimulated genes; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics; RBR = Research Biosample Repository; RNA = ribonucleic acid; siRNA= short interfering ribonucleic acid; TLR = toll-like receptor; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

Note: If participants discontinue NUC later in the follow-up, additional visits *should* be scheduled with a frequency of every 2 weeks for the first three months and every 4 weeks up to week 48 of follow-up period.

[a] Full physical examination at screening and at the end-of-treatment. Limited symptom-directed physical examination at other visits and as clinically indicated

[b] Blood pressure, pulse rate, respiratory rate and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

[c] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[d] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[e] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb complexes/components of HBsAg.

Appendix 12-Table 5 Schedule of Activities for siRNA + TLR7 + NUC Treatment Arm (Follow-up Period) (cont.)

[f] During the PK assessments for VB/VR visits, only one sample is required for collection, no other time points required. Pre-dose if on NUC therapy.
[g] RBR samples collected only from RBR-consenting participants.
[h] Pre-treatment, only serious adverse events should be reported.
[i] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.
[j] Visit window may be extended to +6 weeks in extreme circumstances such as pandemic, natural disasters, supply chain disruption, outbreak of hostilities.
[k] Participants with HBV DNA > 2,000 IU/mL during the follow-up period will undergo weekly monitoring. Participants with HBV DNA >20 IU/mL but < 2,000 IU/mL, should undergo monitoring every two weeks. Participants, who have discontinued NUC therapy, should have monthly visits from follow up Week 24 to Week 48, instead of the 3 monthly follow up visits shown in SoA, which are relevant for participants on NUC therapy, to enable early detection and appropriate management of HBV DNA rebound. At these additional unscheduled monitoring visits, the following laboratory assessments should be performed using the unscheduled lab kit: hematology, chemistry, coagulation, GLDH, urinalysis, HBV serology, HBV DNA quantitative, total HBsAg, HBcrAg, and HBV RNA quantitative.

Appendix 13
Study Details Specific to siRNA (RO7445482) + PD-L1 LNA (RO7191863) + NUC Arms

An overview of short interfering RNA (siRNA) + programmed death ligand-1 locked nucleic acid (PD-L1 LNA) + nucleos(t)ide (NUC) treatment arms is shown in Appendix 13-Figure 1.

Participants will receive RO7445482 (also known as DCR-HBVS; 200 mg every 4 weeks [Q4W]) and RO7191863 [redacted] in addition to their background NUC therapy in one of two treatment arms that will run in parallel.

- One treatment arm will evaluate a 24-week treatment duration where RO7445482 (200 mg Q4W) will be given during Weeks 1-24 and RO7191863 [redacted] will be given during Weeks 13-24.

- A second treatment arm will evaluate a 36-week treatment duration where RO7445482 (200 mg Q4W) will be given during Weeks 1-24 and RO7191863 [redacted] will be given during Weeks 25-36.

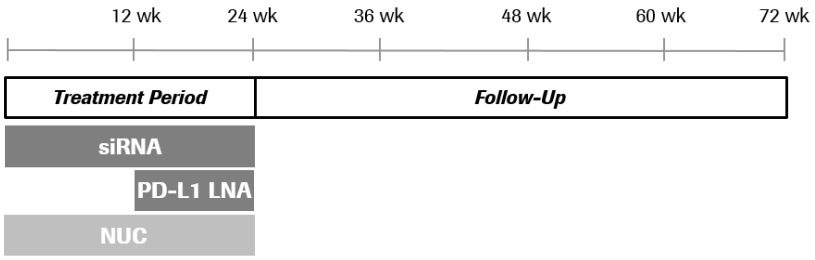
In both treatment arms, participants will receive their background NUC therapy for the duration of study treatment. At the end of the treatment period, participants will continue NUC treatment during the follow-up unless the NUC discontinuation criteria have been met (see Section 6.8).

Approximately 30 participants will be randomized to each treatment arm.

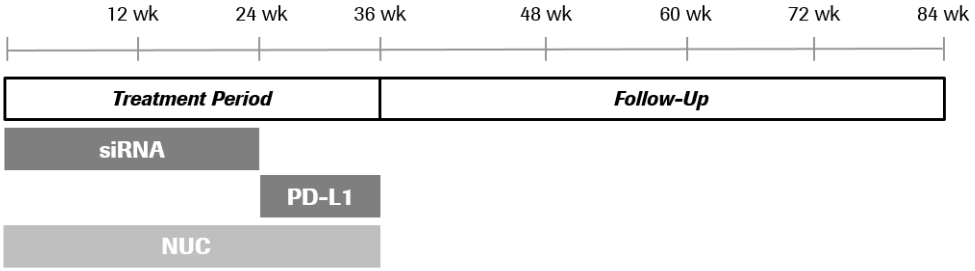
If a 30% delta for hepatitis B surface antigen (HBsAg) loss is observed at end-of-treatment (EOT) or follow-up Weeks 12 or 24 (primary endpoint) the treatment arm may be expanded to accrue additional efficacy and safety data, and to contribute to Phase 3 design planning.

Appendix 13-Figure 1 siRNA + PD-L1 LNA + NUC Treatment Arms

24-Week Concurrent Treatment Arm



36-Week Sequential Treatment Arm



A13.1 BACKGROUND SPECIFIC TO siRNA + PD-L1 LNA + NUC ARM

A13.1.1 BACKGROUND ON RO7445482

RO7445482 (DCR-HBVS) is a short interfering RNA (siRNA) conjugated to N-acetyl-D-galactosamine (GalNAc), which enables liver-targeting through binding to the asialoglycoprotein receptor (ASGPR) that is highly expressed in the liver. After forming the RNA-induced silencing complex (RISC), the RO7445482 antisense strand targets HBV RNA for degradation by triggering RNAi-mediated cleavage within the HBV surface coding sequence, thereby inhibiting HBV gene expression.

Literature indicates that hepatitis B virus (HBV) antigens suppress the host immune response through several pathways, including the direct effects of long-term exposure to high concentration of viral antigens resulting in T-cell immune tolerance and T-cell exhaustion (Hai-Jun et al 2015). Depletion of viral antigens through inhibition of HBV gene expression may therefore facilitate the restoration of the host immune response.

Non-clinical studies with RO7445482 have shown potent antiviral activity. HBsAg reductions of up to 3.5 $\log_{10}$ for more than 7 weeks, as well as significant reductions in HBcAg, were observed after a single dose in mice, demonstrating duration of action suitable for infrequent dosing.

To date, clinical experience with RO7445482 is based on a Phase I clinical study (DCR-HBVS-101) involving healthy volunteers and participants with chronic hepatitis B (CHB) infection.

A13.1.2 BACKGROUND ON RO7191863

RO7191863 is a locked nucleic acid (LNA) antisense oligonucleotide (ASO) that induces RNAse H-mediated intracellular degradation of the messenger RNA (mRNA) encoding the host protein programmed death ligand-1 (PD-L1). In patients with CHB, increased expression of PD-L1 has been demonstrated on hepatocytes and non-parenchymal liver cells (NPLCs) including intra-hepatic antigen presenting cells (Chen et al 2011). RO7191863 is expected to result in the targeted inhibition of PD-L1 expression in the liver by conjugation of the LNA ASO with GalNAc. This mediates specific uptake by hepatocytes through engagement of the ASGPR, which is expressed predominantly by hepatocytes, with low to no expression in other cell types. (Stockert 1995; Zelensky et al 2005; Gupta 2012). To a lesser extent, uptake is also expected to occur in NPLCs based on non-clinical in vivo data.

Non-clinical in vivo data indicate that the inhibition of PD-L1 expression with GalNAc-conjugated PD-L1 LNA results in the intra-hepatic expansion of immune cells, induction of HBV-specific immune responses in the liver (which are proposed to include CD8 T-lymphocyte–mediated cytotoxic activity and cytokine release), and concomitant antiviral responses measurable in blood, including a decline of hepatitis B surface antigen, hepatitis B e antigen (HBeAg), and HBV DNA, which is sustained for several weeks off treatment.

To date, clinical experience with RO7191863 includes a Phase 1 entry-into-human study in CHB participants (NP40479).

A13.2 BENEFIT/RISK ASSESSMENT SPECIFIC TO siRNA+ PD-L1 LNA + NUC ARM

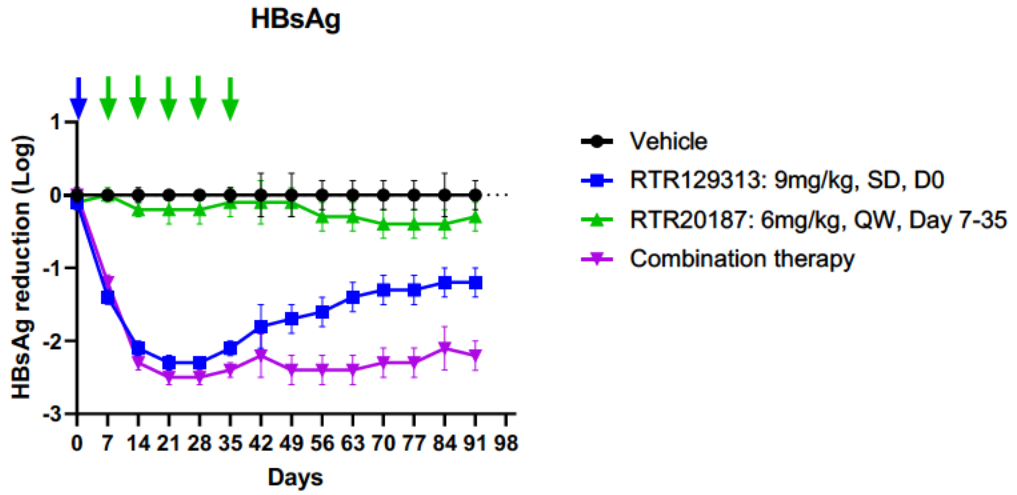
The 24-week and 36-week treatment with RO7445482 and RO7191863, in combination with ongoing nucleos(t)ide analogue (NUC) treatment, aims to result in therapeutic benefit for participants by achieving higher functional cure rates (HBsAg loss) than observed currently with standard-of-care therapies (NUC or pegylated interferon-alpha [PEG-IFNa]). The administration of RO7445482 and RO7191863 in combination aims to test the scientific hypothesis that concurrent or sequential administration of a direct-

acting antiviral agent that reduces HBV antigen load and an immunomodulatory agent that counteracts immune-inhibition will synergistically maximize efficacy outcomes. The potency of the immunomodulatory agent is expected to increase if the immunomodulator is administered during and/or following a reduction in HBV antigen load including HBsAg. Thus, reduction in HBV antigen load with RO7445482 is anticipated to enable the optimal activity of RO7191863.

This concept is supported by in vivo preliminary data generated in AAV-HBV mice in a new pilot study. The combination therapy showed synergistic effects of PD-L1 (mouse surrogate RTR20187, 5 weekly doses) when administered 1 week after HBV siRNA (RTR129313, tool compound, single dose) on HBsAg (Appendix 13-Figure 2 and Appendix 13-Table 1), HBeAg (Appendix 13-Figure 3 and Appendix 13-Table 2) and HBV DNA (Appendix 13-Figure 4 and Appendix 13-Table 3) levels (up to additional 1, 0.9 and 1.8 log drop respectively), compared to siRNA treatment alone 8 weeks after the last dose. The synergistic effect was maintained for up to 9 weeks after the last dose suggesting a transformational efficacy impact with the direct-acting antiviral and immunomodulatory agent combination therapy. No safety findings were observed during the in-life phase (no body weight loss, no clinical signs, no mortality). Another efficacy study is currently ongoing to confirm these results and includes additional safety parameters in the serum to evaluate liver and kidney functional markers (blood chemistry panel for AST, ALP, GGT, BUN, total protein, albumin, creatinine, K+, P, and Ca2+).

The sustained antiviral response may be associated with the recovery of the antigen specific immune response as demonstrated in another study where mice receiving 5 weekly doses of RTR20187 and showed an increased number of intrahepatic liver immune cells (primarily B- and T-lymphocytes, natural killer (NK) cells and antigen presenting cells) observed 1 week after the last dose (Day 35), together with an increase of IFN-gamma responses to stimulation of total liver immune cells with HBV surface and core peptide pools. No significant Interferon (IFN)-gamma responses were measured in non-infected mice treated with RTR20187 (RDR No. 1089260) (Appendix 13-Table 4).

Appendix 13-Figure 2 HBsAg reduction level in AAV-HBV mice treated with HBV siRNA and PD-L1 LNA



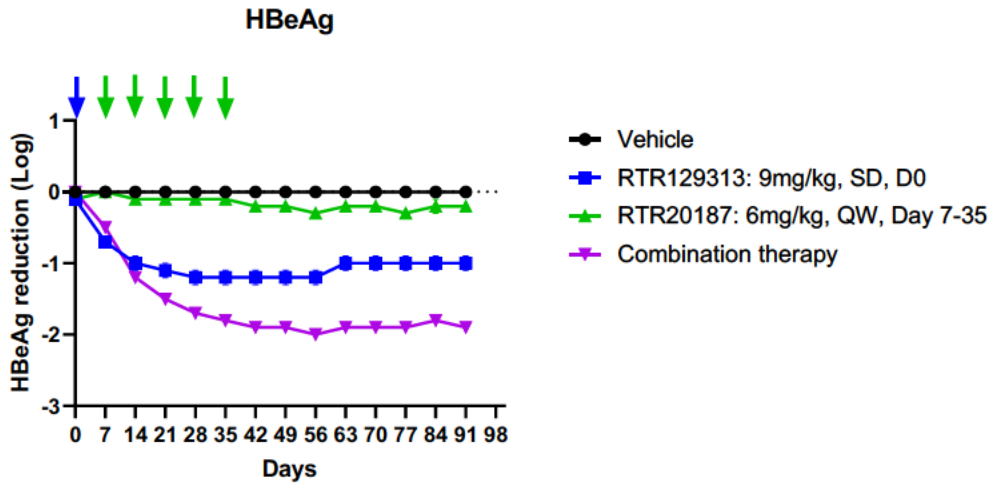
QW = Weekly, SD=Single Dose, D0 = Day 0 post first dosing, , mg/kg = milligram per kilogram, HBsAg = HBV surface antigen. Data presented as mean ± SEM (6 mice per group) reduction to vehicle group

Appendix 13-Table 1 Summary of HBsAg reduction (Log reduction)

	Summary of HBsAg reduction (Log reduction)							
	Vehicle		*RTR129313: 9mg/kg, SD, D0*		*RTR20187: 6mg/kg, QW, Day 7-35*		*Combination therapy*	
Days	*mean*	*± SEM*	*mean*	*± SEM*	*mean*	*± SEM*	*mean*	*± SEM*
0	*0.0*	*0.1*	*-0.1*	*0.1*	*-0.1*	*0.1*	*0.0*	*0.0*
7	*0.0*	*0.0*	*-1.4*	*0.1*	*0.0*	*0.1*	*-1.2*	*0.1*
14	*0.0*	*0.1*	*-2.1*	*0.1*	*-0.2*	*0.1*	*-2.3*	*0.1*
21	*0.0*	*0.0*	*-2.3*	*0.1*	*-0.2*	*0.2*	*-2.5*	*0.1*
28	*0.0*	*0.0*	*-2.3*	*0.0*	*-0.2*	*0.2*	*-2.5*	*0.1*
35	*0.0*	*0.1*	*-2.1*	*0.1*	*-0.1*	*0.2*	*-2.4*	*0.1*
42	*0.0*	*0.3*	*-1.8*	*0.3*	*-0.1*	*0.3*	*-2.2*	*0.3*
49	*0.0*	*0.3*	*-1.7*	*0.2*	*-0.1*	*0.2*	*-2.4*	*0.2*
56	*0.0*	*0.2*	*-1.6*	*0.2*	*-0.3*	*0.2*	*-2.4*	*0.2*
63	*0.0*	*0.2*	*-1.4*	*0.2*	*-0.3*	*0.2*	*-2.4*	*0.2*
70	*0.0*	*0.2*	*-1.3*	*0.2*	*-0.4*	*0.2*	*-2.3*	*0.2*
77	*0.0*	*0.2*	*-1.3*	*0.2*	*-0.4*	*0.2*	*-2.3*	*0.2*
84	*0.0*	*0.3*	*-1.2*	*0.2*	*-0.4*	*0.2*	*-2.1*	*0.3*
91	*0.0*	*0.2*	*-1.2*	*0.2*	*-0.3*	*0.2*	*-2.2*	*0.2*

QW = Weekly, SD=Single Dose, mg/kg = milligram per kilogram, Data presented as mean ± SEM (6 mice per group) reduction to vehicle group

Appendix 13-Figure 3 HBeAg level in AAV-HBV mice treated with HBV siRNA and PD-L1 LNA



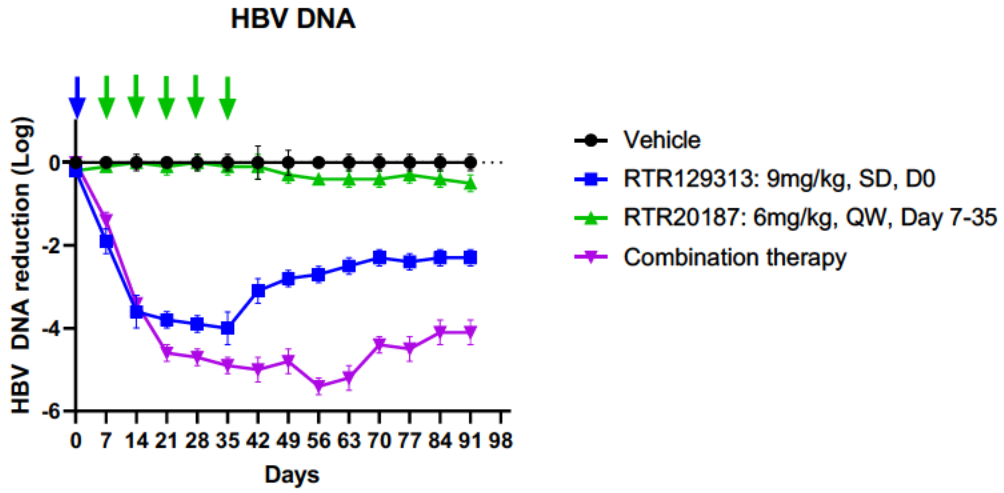
QW = Weekly, SD=Single Dose, D0 = Day 0 post first dosing, mg/kg = milligram per kilogram, HBeAg = HBV e antigen. Data presented as mean ± SEM (6 mice per group) reduction to vehicle group

Appendix 13-Table 2 Summary of HBeAg reduction (Log reduction)

	Summary of HBeAg reduction (Log reduction)							
	Vehicle		*RTR129313: 9mg/kg, SD, D0*		*RTR20187: 6mg/kg, QW, Day 7-35*		*Combination therapy*	
Days	*mean*	*± SEM*	*mean*	*± SEM*	*mean*	*± SEM*	*mean*	*± SEM*
0	*0.0*	*0.0*	*-0.1*	*0.0*	*-0.1*	*0.0*	*0.0*	*0.0*
7	*0.0*	*0.0*	*-0.7*	*0.0*	*0.0*	*0.0*	*-0.5*	*0.0*
14	*0.0*	*0.0*	*-1.0*	*0.1*	*-0.1*	*0.0*	*-1.2*	*0.0*
21	*0.0*	*0.0*	*-1.1*	*0.1*	*-0.1*	*0.0*	*-1.5*	*0.0*
28	*0.0*	*0.0*	*-1.2*	*0.1*	*-0.1*	*0.0*	*-1.7*	*0.0*
35	*0.0*	*0.0*	*-1.2*	*0.1*	*-0.1*	*0.0*	*-1.8*	*0.0*
42	*0.0*	*0.0*	*-1.2*	*0.1*	*-0.2*	*0.0*	*-1.9*	*0.0*
49	*0.0*	*0.0*	*-1.2*	*0.1*	*-0.2*	*0.0*	*-1.9*	*0.0*
56	*0.0*	*0.0*	*-1.2*	*0.1*	*-0.3*	*0.0*	*-2.0*	*0.0*
63	*0.0*	*0.0*	*-1.0*	*0.1*	*-0.2*	*0.0*	*-1.9*	*0.0*
70	*0.0*	*0.0*	*-1.0*	*0.1*	*-0.2*	*0.0*	*-1.9*	*0.0*
77	*0.0*	*0.0*	*-1.0*	*0.1*	*-0.3*	*0.0*	*-1.9*	*0.0*
84	*0.0*	*0.0*	*-1.0*	*0.1*	*-0.2*	*0.1*	*-1.8*	*0.0*
91	*0.0*	*0.0*	*-1.0*	*0.1*	*-0.2*	*0.0*	*-1.9*	*0.0*

QW = Weekly, SD=Single Dose, mg/kg = milligram per kilogram, Data presented as mean ± SEM (6 mice per group) reduction to vehicle group

Appendix 13-Figure 4 HBV DNA level in AAV-HBV mice treated with HBV siRNA and PD-L1 LNA



QW = Weekly, SD=Single Dose, D0 = Day 0 post first dosing, mg/kg = milligram per kilogram. Data presented as mean ± SEM (6 mice per group) reduction to vehicle group

Appendix 13-Table 3 Summary of HBV DNA reduction (Log reduction)

	Summary of HBV DNA reduction (Log reduction)							
	Vehicle		RTR129313: 9mg/kg, SD, D0		RTR20187: 6mg/kg, QW, Day 7-35		Combination therapy	
Days	mean	± SEM	mean	± SEM	mean	± SEM	mean	± SEM
0	0.0	0.1	-0.2	0.1	-0.2	0.1	0.0	0.1
7	0.0	0.1	-1.9	0.3	-0.1	0.1	-1.4	0.2
14	0.0	0.2	-3.6	0.4	0.0	0.1	-3.4	0.2
21	0.0	0.1	-3.8	0.2	-0.1	0.2	-4.6	0.2
28	0.0	0.2	-3.9	0.2	0.0	0.2	-4.7	0.2
35	0.0	0.2	-4.0	0.4	-0.1	0.2	-4.9	0.2
42	0.0	0.4	-3.1	0.3	-0.1	0.3	-5.0	0.3
49	0.0	0.3	-2.8	0.2	-0.3	0.2	-4.8	0.3
56	0.0	0.1	-2.7	0.2	-0.4	0.1	-5.4	0.2
63	0.0	0.2	-2.5	0.2	-0.4	0.2	-5.2	0.3
70	0.0	0.2	-2.3	0.2	-0.4	0.2	-4.4	0.2
77	0.0	0.2	-2.4	0.2	-0.3	0.2	-4.5	0.3
84	0.0	0.2	-2.3	0.2	-0.4	0.2	-4.1	0.3
91	0.0	0.2	-2.3	0.2	-0.5	0.2	-4.1	0.3

QW = Weekly, SD=Single Dose, mg/kg = milligram per kilogram, Data presented as mean ± SEM (6 mice per group) reduction to vehicle group

Appendix 13-Table 4 ***IFN-gamma Response to HBV Surface and Core Overlapping Peptide Pools of Liver Immune Cells Isolated from AAV HBV Mice After 5 Weekly Doses of Either RTR20187 at 5mg/kg or Vehicle Control (at Day 35, 1 week after last dose)***

	Vehicle			*PD-L1 LNA (Mouse RTR29187)*		
	mean (SFU)	*SEM*	*N*	*mean (SFU)*	*SEM*	*N*
HBs peptides	*9.2*	*3.54*	*8*	*372.94*	*114.61*	*8*
HBc peptides	*40.43*	*7.87*	*8*	*179.64*	*60.31*	*8*
HBs + HBc peptides	*15.62*	*5.76*	*8*	*396.72*	*142.43*	*8*

SFU: spot forming unit
Sem: standard error of mean
N: number of mice

For RO7445482, interim Phase 1 data have shown significant and durable antiviral activity with 4 monthly SC doses in NUC-suppressed participants with CHB. At Day 112, mean HBsAg $\log_{10}$ IU/mL reductions from baseline were 1.39, 1.80, and 1.84 for participants who received 1.5 mg/kg, 3.0 mg/kg, or 6 mg/kg, respectively. Approximately 80% of participants achieved > 1.5 $\log_{10}$ IU/mL reduction (irrespective of HBeAg-status), 60% had HBsAg levels < 100 IU/mL, and durability of response was demonstrated up to Day 392.

Based on interim Phase 1 data, RO7445482 was safe and well tolerated in healthy volunteers (HV) and CHB patients. The safety profile appears to be similar between HVs and patient participants, and there were no safety signals or dose-related trends identified. No severe or serious treatment-emergent adverse events (TEAEs) or TEAEs leading to treatment discontinuation were reported. Apart from generally mild injection site reactions (ISRs), there were no other potential oligonucleotide class effects.

For RO7191863*, interim* Phase 1 *data have shown significant antiviral activity in NUC-suppressed participants with CHB, with an exposure-response relationship. At the highest dosing regimen explored* [redacted] *the mean maximum HBsAg reduction from baseline was 0.5 log10 IU/mL. Approximately 43% of participants (3 out of 7) achieved marked declines in HBsAg in the range of 0.9 - 1.1 log10 IU/mL reduction from baseline.*

Based on the interim Phase 1 data, RO7191863 was safe in CHB patients *with an overall acceptable tolerability profile*. No serious or immune-related adverse events (AEs) were observed and *there was no evidence of* potential oligonucleotide class effects *(e.g., renal toxicity events). An exposure-response relationship with ALT elevations was evident, which is consistent with the RO7191863 mechanism of action and anticipated effects of checkpoint inhibition on the restoration of a HBV-specific immune response. The ALT elevations predominantly occurred* [redacted] *were mostly low grade <5x ULN and often associated with concurrent decline in HBsAg, and all cases showed*

preserved hepatic function. In consideration of the data available from the Phase 1 study, further PK/PD modeling was carried out to select an optimal dose, as discussed in Section A13.3.

RO7445482 and RO7191863 separately, have shown acceptable safety and tolerability in the Phase 1 studies *involving healthy volunteers and/or* CHB participants, and non-clinical toxicology and safety pharmacology studies support the proposed 24 and 36-week combination regimens.

For details, refer to the RO7445482 and RO7191863 Investigator's Brochures*, and the RO7191863 Interim Data Memo.*

A13.3 JUSTIFICATION FOR DOSE SPECIFIC TO siRNA+ PD-L1 LNA + NUC ARM

For RO7445482, the fixed dose of 200 mg SC (equivalent to 3.0 mg/kg) Q4W has been selected for Phase 2 study in combination with other IMPs/NMEs. This dose is within the anticipated therapeutic dose-range in humans and is expected to be safe and well tolerated. A summary of the key data supporting the selected dose is provided below:

- The dose-response trend in the HBsAg declines, together with pharmacokinetic (PK)/pharmacodynamic (PD) modeling of interim Phase 1 data, supports the proposed 200 mg Q4W dosing regimen. Preliminary PK/PD modeling predicts that the proportion of participants who will achieve > 1.5 and > 2 $\log_{10}$ IU/mL reductions in HBsAg, following Q4W doses up to Week 12, will be higher with a 200 mg Q4W regimen (97% and 56%, respectively) compared to a 100 mg Q4W regimen (89% and 6%, respectively).
- The non-clinical chronic toxicology studies provide acceptable safety margins for the 200 mg Q4W fixed dose for a treatment period of 48 weeks.
- PK/PD modelling supports use of fixed (200 mg) instead of weight based (3.0 mg/kg) RO7445482 dosing.

For RO7191863, a dose of [redacted] SC [redacted] has been selected for this Phase 2 study, to be administered over 12 weeks. This dose and regimen are predicted to be efficacious in humans and is expected to be safe and with acceptable tolerability. A summary of the key data supporting the selected dose is provided below:

- The non-clinical toxicology studies of RO7191863 support [redacted] for a treatment period of 12 weeks.
- *RO7191863 doses* [redacted] *for 12 weeks have been observed to be safe and with acceptable tolerability in the Phase 1 study. Low-grade transient ALT elevations were frequent at the highest dosing regimen.*

- *The exposure-response trends in HBsAg declines as well as ALT elevation, together with PK/PD modeling supports* [redacted] *for 12 weeks.*
    - *PopPK modeling predicts that* [redacted] *is expected to result in a 34% reduction in the mean cumulative liver AUC compared to the* [redacted]*, which is anticipated to meaningfully reduce ALT liability without overtly impacting the HBsAg response.*
    - *PK/PD modeling predicts that the* [redacted] *will result in a clinically meaningful reduction in the proportion of subjects that exceed the ALT >5x ULN threshold compared to the* [redacted] *(~11% vs ~17%).*

In the 24-week concurrent treatment arm where administration between RO7445482 and RO7191863 overlaps and dosing days coincide, RO7191863 will be administered first, followed by RO7445482. RO7445482 should be administered no earlier than 24 hours after RO7191863 and no later than 48 hours prior to the subsequent dose of RO7191863 to avoid any potential competition between both drugs for ASGPR-mediated drug uptake.

Further details are provided in the RO7445482 and RO7191863 Investigator's Brochures, *and the RO7191863 Interim Data Memo*.

A13.4 INCLUSION/EXCLUSION CRITERIA SPECIFIC TO siRNA + PD-L1 LNA + NUC ARM

Participants must meet the following criterion for inclusion in the siRNA + PD-L1 LNA + NUC treatment arm:

Sex

1. Male and Female Participants:

    a. Female Participants

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

    - Woman of non-childbearing potential (WONCBP).
    - Woman of childbearing potential (WOCBP), who:

        - Agrees to remain abstinent (refrain from heterosexual intercourse) or use *two acceptable contraceptive methods, of which at least one is considered* highly *effective* (result in a failure rate of < 1% per year) before, during the treatment period, and for at least 6 months after the final dose of study treatment (see Appendix 5).

- Hormonal contraception must be in use at least 30 days prior to first study drug administration, and
- Barrier methods must be in use for at least 14 days prior to first study drug administration.
- A vasectomized partner must have had the vasectomy at least 3 months prior to the first study drug administration or there must be confirmation of a zero sperm count.

- Has a negative pregnancy test at screening (Day -14 to -7). In addition, willing to undergo a urine pregnancy test at Day 1 and every month during treatment and up to 6 months follow-up, *thereafter every 3 months until end of follow-up*.

b. Male Participants

During the treatment period and for at least 6 months after the final dose of study treatment, agree to:

- Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year, with a partner who is a woman of childbearing potential (WOCBP). For a vasectomy to be considered a highly effective contraceptive method it must have been performed 3 months before first study drug administration or there must be confirmation of a zero sperm count.
- With pregnant female partner, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.
- Refrain from donating sperm.

Participants are excluded from the siRNA + PD-L1 LNA + NUC arm if any of the following criteria apply:

Medical Conditions

1. History and/or evidence of autoimmune hepatitis or other autoimmune disorders.

A13.5 LIFESTYLE CONSIDERATIONS SPECIFIC TO siRNA + PD-L1 LNA + NUC ARM

NUCs will be given according to the local prescribing information.

For CHB participants who routinely take herbal medicines that in Investigator's opinion may have immune-modulatory effects, herbal medicines should strongly be discouraged.

A13.6 CONTRACEPTIVE REQUIREMENTS SPECIFIC TO siRNA + PD-L1 LNA + NUC ARM

See Appendix 13-Section 13.4.

A13.7 TREATMENT ADMINISTERED SPECIFIC TO siRNA + PD-L1 LNA + NUC ARM

Appendix 13-Table *5* summarizes the treatments administered.

Appendix 13-*Table 5* **Summary of Treatments Administered for siRNA + PD-L1 LNA + NUC Treatment Arm**

Study Treatment Name	siRNA (RO7445482)	PD-L1 LNA (RO7191863)	NUC
IMP and NIMP	IMP	IMP	NIMP*
Dose Formulation	Sterile colorless to yellow solution of drug substance RO7445482 in water for injection	Yellow, brownish yellow or greenish sterile liquid	Film-coated tablet
Unit Dose Strength(s)/Dosage Level(s)	120 mg/mL, 2 mL filled in a 6 ml vial	[redacted]	Refer to local prescription information
Dose:	Fixed dose 200 mg Q4W	[redacted]	ETV: 0.5 mg OD or TDF: 300 mg OD or TAF: 25 mg OD
Route of Administration	SC	SC	oral
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor or locally by the study site
Packaging and Labeling	Study treatment will be provided in vials, packaged, and labeled as required per local regulation.	Study treatment will be provided in vials, packaged, and labeled as required per local regulation.	Study treatment will be packaged and labeled as required per local regulation.

*NUC are considered IMP in the UK only.

RO7191863 and RO7445482 administrations will be via the SC route utilizing sterile technique. RO7191863 and RO7445482 should be administered at the study clinic preferably in the morning by investigational staff. On weeks where dosing of RO7191863 and RO7445482 overlap (Weeks 13, 17, and 21), RO7191863 must be administered first, and RO7445482 can be administered no earlier than 24 hours after dosing of RO7191863. RO7445482 dose can be administered on a different day that week, but no later than 48 hours before the next planned dose of RO7191863 (see Appendix 13-*Table 7*, Appendix 13-*Table 8*, and Appendix 13-*Table 9*).

The SC administration site (e.g., left abdomen, right abdomen etc.) should be rotated between visits and different sites should be used for administration of RO7191863 and RO7445482 (on weeks where dosing overlaps).

Guidelines for dosage modification and treatment interruption/discontinuation are in Section A13.9.

For more details, refer to the RO7445482 and RO7191863 Investigators Brochures, NUC local prescribing information, and the Pharmacy Manual.

A13.8 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non-serious AESIs 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 documents listed below:

Drug	Document
RO7191863	RO7191863 Investigator's Brochure
RO7445482	RO7445482 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.

A13.9 DOSE MODIFICATION

Appendix 13-*Table 6* summarizes the dose interruption/discontinuation guidelines for the siRNA+PD-L1 LNA+NUC combination arm.

Appendix 13-*Table 6* **Dose Interruption/Discontinuation Guidelines for siRNA+PD-L1 LNA+NUC Combination Arm**

Laboratory/Clinical Parameters	Recommendation	Reference
siRNA-related AEs and/or PD-L1-related AEs		
No laboratory or clinical parameters have been identified yet	No dose modification recommendations for siRNA and/or PD-L1 LNA	N/A
General criteria for dose interruptions/discontinuations for all NMEs		
Liver transaminases and liver function test	See Section 7.1	Section 8.3.8.3
Confirmed virological breakthrough	**Discontinue** NMEs and continue treatment according to local standards	Section 8.3.8.1
Others	See Section 7.1	

A13.10 PHARMACOKINETICS ANALYSES SPECIFIC TO siRNA + PD-L1 LNA + NUC ARM

A13.10.1 OPTIONAL LIVER BIOPSY SUB-STUDY

At one or more selected sites with established expertise, participants may be offered to participate in a liver biopsy sub-study, which will involve collection of a liver biopsy sample. This procedure will be performed at the *end of the* treatment. Liver biopsy tissue will be used to measure intra-hepatic RO7445482 and RO7191863 exposure levels (including metabolites, if applicable). Participation in the liver biopsy sub-study will require a separate consent and will involve a select number of participants.

For further details, refer to the study operations manual.

A13.11 BIOMARKER ANALYSES SPECIFIC TO siRNA + PD-L1 LNA + NUC ARM

A13.11.1 SAFETY BIOMARKERS

Blood samples will be collected during the course of the study for the analysis of exploratory *liver* safety biomarkers (see Appendix 13-*Table 8*, and Appendix 13-*Table 9*) *given a* potential safety risk of LNA ASOs and of RO7191863 is hepatic injury. The standard liver injury markers (ALT and AST) have several limitations in terms of specificity (e.g., AST is not liver-specific), sensitivity (the rise in ALT and AST indicates that liver injury has already occurred), and prognostic value (the magnitude of the ALT elevation does not predict the patient's subsequent course). This study will evaluate several emerging liver injury biomarkers (e.g., GLDH, MCSFR1, OPN, CK-18, ccK-18, and total HMGB1) that may complement ALT and AST and standard measures of liver function for the early detection of liver injury. Due to the exploratory nature of the tests, the results will only be analyzed retrospectively and will not be used for decision making.

This information may provide an improved understanding of the safety profile of RO7191863 and of the association between ALT increases and PD activity.

A13.11.2 PD-L1 ACTIVITY BIOMARKERS

The PD biomarker assessment plan specific for PD-L1-LNA comprises measures of target engagement, antiviral activity, and immunity.

In addition to virological assessments described in Section 8.1, levels of soluble PD-L1 will be monitored in plasma as an alternative potential readout of target engagement and/or PD effects, based on preliminary data from the Phase 1 study NP40479.

Targeting the PD-1/PD-L1 inhibitory pathway is proposed to restore HBV-specific T-cell immunity at the site of infection. It is currently unclear whether this will translate into measurable HBV specific immune responses in peripheral blood at some time during or after the end of dosing. HBV-specific cellular immune function will be explored ex-vivo using cryopreserved PBMC collected at timepoints indicated in the SoA (see Appendix 13-*Table 8*, and Appendix 13-*Table 9*). These analyses will be considered as an exploratory optional objective, taking into consideration the logistic and technical challenges that might be experienced with the collection of viable PBMC during the conduct of a multi-center trial. Additionally, cellular immune phenotyping (by flow cytometry) will be performed at regular intervals during the study, using peripheral blood to study potential modulation by treatment.

In an effort to measure intrahepatic target engagement using peripheral blood, blood samples will be collected from CHB participants for the extraction of liver-derived extracellular vesicles (EVs, predominantly exosomes). Liver origin can be determined based on the presence of the ASGPR in the EVs. It is assumed that multiple doses in the CHB population may induce a measurable reduction of EV-associated PD-L1. The application of this biomarker in this study will be gated based on the assessment of feasibility currently ongoing within the Phase 1 study NP40479.

Liver targeting of RO7191863 is expected to reduce immune related risks associated with systemic exposure; nevertheless, soluble markers of immune activation and inflammation (soluble cytokines and chemokines which may include but are not limited to e.g., IFN-gamma, TNF-alpha, CXCL10/IP-10) will be assessed in participants. Measures of systemic immune activation and inflammation will be correlated with the safety profile and pharmacodynamic effects of siRNA and PD-L1 LNA in participants.

A13.11.3 FINE NEEDLE ASPIRATE (FNA) SUB-STUDY - OPTIONAL

At one or more selected sites with established expertise, participants will be offered serial FNAs of the liver at four timepoints to explore one or more intra-hepatic PD

effects. The cellular material obtained with FNAs includes primarily immune cells with some hepatocytes, and these will be used for exploring PD-L1 and PD-1 expression, immune phenotype, immune genotype, and potentially viral parameters (e.g., HBV covalently closed circular deoxyribonucleic acid [cccDNA], integrated HBV DNA) as well as RO7191863 and RO7445482 exposure levels intra-hepatically. This will provide improved scientific understanding of the mechanism of action of RO7191863 as a liver-target immune enhancer. Analysis techniques may include, but are not limited to, flow cytometry and gene expression. DNA and/or RNA will be extracted for exploratory research on immunological response modulated by the inhibition of PD-L1/PD-1 pathway. A peripheral blood mononuclear cell sample obtained as part of the main study may be used for comparison tests with the intra hepatic measurements.

A13.11.4 CLINICAL GENOTYPING

If safety or activity rationales develop, clinical genotyping will be performed (see Sections 8.7.4.1 and 8.8.1.1) if appropriate. This exploratory objective will aim at evaluating the association of genetic polymorphisms in known candidate genes with the PK profiles of the two NMEs and with primary and secondary endpoints. Known candidate genes of interest that are specific to siRNA, PD-L1, and ASGR1. Further genes may be queried (e.g., immune genotype) from the data based on progressing knowledge on these NMEs and their targets.

A13.12 SCHEDULE OF ACTIVITIES siRNA + PD-L1 LNA + NUC ARM

An overview of the schedule of the activities is provided in Appendix 13-*Table 7*, Appendix 13-*Table 8*, and Appendix 13-*Table 9*.

Appendix 13-*Table 7* Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm - 24 Week (Screening and Treatment Periods)

	Screening		Treatment Period																			VB/VR	ET/ UV[u]
Week			1	5	9	13		14	15	16	17		18	19	20	21		22	23	24	25		
Day	-56 to -7	-14 to -7	1	29 (±2)	57 (±3)	85 (±3)	89 (-4)	92 (±3)	99 (±3)	106 (±3)	113 (±3)	117 (-4)	120 (±3)	127 (±3)	134 (±3)	141 (±3)	145 (-4)	148 (±3)	155 (±3)	162 (±3)	169 (±3)		
Informed consent	x																						
Demography, medical history	x																						
Physical examination, vital signs [a, b]	x		x	x	x	x		x	x	x	x		x	x	x	x		x	x	x	x	x	x
Randomization			x																				
ECG	x		x	x	x	x					x					x					x		
Transient elastography/ARFI/MR[c]	x																						
Abdominal ultrasound	x																				x		
Alfa-fetoprotein	x																				x		
HAV, HCV, HDV, HEV, HIV	x																						
Autoantibodies [d]	x																						
Alcohol and drugs of abuse screen [e]		x																			x		x
Pregnancy test [f]		x	x	x	x	x					x					x					x		x
Thyroid function tests	x					x															x		
Hematology (includes HbA1c [g])	x		x	x	x	x		x	x	x	x		x	x	*x*	x		*x*	x	*x*	x	x	x
Chemistry		x	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	x
GLDH	x		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	x	x	x
Clinical genotyping [h]			x																				
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x		x	x	x	x			x		x			x		x			x		x	x	x

Appendix 13-*Table 7* Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm – 24 Week (Screening and Treatment Periods) (cont.)

	Screening		Treatment Period																		VB/VR	ET/UV[u]
Week			**1**	**5**	**9**	**13**		**14**	**15**	**16**	**17**		**18**	**19**	**20**	**21**		**22**	**23**	**24**	**25**		
Day	**-56 to -7**	**-14 to -7**	**1**	**29 (±2)**	**57 (±3)**	**85 (±3)**	**89 (-4)**	**92 (±3)**	**99 (±3)**	**106 (±3)**	**113 (±3)**	**117 (-4)**	**120 (±3)**	**127 (±3)**	**134 (±3)**	**141 (±3)**	**145 (-4)**	**148 (±3)**	**155 (±3)**	**162 (±3)**	**169 (±3)**		
HBV DNA quantitative	x		x			x					x										x	x	x
Total HBsAg [i]			x			x					x					x					x	x	
HBcrAg			x	x	x	x					x			x		x			x		x	x	
Total anti-HBc quantitative			x			x					x					x					x		
HBV RNA quantitative			x	x	x	x					x			x		x			x		x	x	
HBV RNA sequencing [h]			x																				
HBV DNA sequencing [j]																						x	
Plasma PK (siRNA) [k]			x				x										x				x	x	
Plasma PK (PD-L1 LNA) [k]						x										x					x	x	
Plasma PK (NUC) [k]			x			x										x					x	x	
Plasma ADA (siRNA) [l]			x				x										x				x	x	x
Plasma ADA (PD-L1 LNA) [l]						x										x					x	x	x
Liver injury markers			x			x			x		x			x					x			*x*	
Extracellular vesicles			x			x					x			x		x			x		x		*x*
Circulating immune phenotyping			x			x					x			x		x			x		x		x
Soluble PD-L1			x	x	x	x					x			x		x			x		x		x
Cytokine panel [m]			x	x	x	x					x					x					x		x
PBMC [n]			x			x															x		
FNA [o]			x			x															x		

Appendix 13-*Table 7* **Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm – 24 Week (Screening and Treatment Periods) (cont.)**

	Screening		Treatment Period																		VB/ VR	ET/ UV[u]
Week			**1**	**5**	**9**	**13**		**14**	**15**	**16**	**17**		**18**	**19**	**20**	**21**		**22**	**23**	**24**	**25**		
Day	**-56 to -7**	**-14 to -7**	**1**	**29 (±2)**	**57 (±3)**	**85 (±3)**	**89 (-4)**	**92 (±3)**	**99 (±3)**	**106 (±3)**	**113 (±3)**	**117 (-4)**	**120 (±3)**	**127 (±3)**	**134 (±3)**	**141 (±3)**	**145 (-4)**	**148 (±3)**	**155 (±3)**	**162 (±3)**	**169 (±3)**		
Liver Biopsy [p]																					x		
RBR [q]			x			x										x					x	x	
Clinic siRNA 200 mg sc Q4W treatment administration [r]			x	x	x		x[r]					x[r]					x[r]						
Clinic PD-L1 LNA [redacted] sc [redacted] treatment administration [r, s]			[redacted]																				
NUC treatment administration OD			x																				
Adverse events, concomitant medications, and diary review [t]			x	x	x	x		x	x	x	x		x	x	x	x		x	x	x	x	x	x

Appendix 13-*Table 7* Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm – 24 Week (Screening and Treatment Periods) (cont.)

ADA = anti-drug antibodies; ARFI = acoustic radiation force impulse; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; FNA = fine needle aspirate; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics; RBR = Research Biosample Repository; RNA = ribonucleic acid; siRNA= short interfering ribonucleic acid; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

[a] Full physical examination at screening and at the end-of-treatment. Limited symptom-directed physical examination at other visits and as clinically indicated. Height at screening only. Weight at screening, Day 1, and Weeks 13, 17, 21, and 25.

[b] Blood pressure, pulse rate, respiratory rate, and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

[c] Historical liver biopsy or transient elastography/ARFI/MR/2D- shear wave elastography [2D-SWE] results obtained within 6 months prior to randomization are also acceptable. During screening transient elastography/ARFI/MR /2D-SWE are acceptable.

[d] Autoantibodies refer to ANA, AMA, ASMA, and a-TPO.

[e] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[f] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[g] HbA1c should be included in hematology and is required only at screening.

[h] If not collected at Day 1, samples for clinical genotyping and HBV RNA sequencing can be collected at any subsequent time point. *The sample for HBV RNA sequencing aims at determining the HBV genotype. The HBV genotype may also be inferred using alternative approaches, such as serovariant determination.*

[i] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb complexes/components of HBsAg.

[j] HBV DNA sequencing will be collected in case of virological breakthrough/relapse; blood sample to be collected up to 6 times.

[k] Plasma PK samples for PD-L1 LNA and siRNA should be collected pre-dose, 1-3 and 4-6 hours post-dose at all indicated visits, with the exception of EOT where only one PK timepoint is required. Plasma PK samples for NUC should be collected pre-dose. During the PK assessment for VB/BR visits, only one pre-dose sample is required for collection.

[l] ADA is collected pre-dose.

Appendix 13-*Table 7* Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm – 24 Week (Screening and Treatment Periods) (cont.)

[m] Cytokine panel (e.g., INF-α, IP-10, IL-1, IL-6, IL-10, IFN-γ, and TNF-α) to be collected pre-dose.

[n] PBMC at selected sites only, three collections: Days 1, 85, and 169. The exact days of collection may be adjusted by the Sponsor based on emerging data.

[o] Optional sub-study FNA at selected sites only. The days of collection may be adjusted by the Sponsor based on emerging data.

[p] Only for participants in the liver biopsy sub-study. Participation for liver biopsy is optional and will require a separate consent from the participant. Additional safety assessments may be required as per local practice and guidelines prior to the liver biopsy (refer to study operations manual).

[q] RBR samples collected only from RBR-consenting participants.

[r] On weeks where dosing of RO7191863 and RO7445482 overlap (Weeks 13, 17, and 21), RO7191863 must be administered first, and RO7445482 can be administered no earlier than 24 hours after dosing of RO7191863 (Days 85, 113, and 141). RO74445482 dose can be administered on a different day that week (e.g., Days 89, 117, 145), but no later than 48 hours before the next planned dose of RO7191863. It should be noted that on the overlapping weeks, PK and ADA samples for RO7445482 should be collected on the same day as dosing of RO7445482. Different injection sites should be used for SC administration.

[s] *The PD-L1 LNA dose is weight based and should be calculated using the most recent per protocol assessment of participant weight at each dosing visit.*

[t] Pre-treatment, only serious adverse events should be reported.

[u] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

Appendix 13 -*Table 8* Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm – 36 Week (Screening and Treatment Periods)

	Screening		Treatment Period																		VB/VR	ET/UV[t]
Week			**1**	**5**	**9**	**13**	**17**	**21**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**		
Day	**-56 to -7**	**-14 to -7**	**1**	**29 (±2)**	**57 (±3)**	**85 (±3)**	**113 (±3)**	**141 (±3)**	**169 (±3)**	**176 (±3)**	**183 (±3)**	**190 (±3)**	**197 (±3)**	**204 (±3)**	**211 (±3)**	**218 (±3)**	**225 (±3)**	**232 (±3)**	**239 (±3)**	**246 (±3)**	**253 (±3)**		
Informed consent	x																					
Demography, medical history	x																					
Physical examination, vital signs [a, b]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization			x																			
ECG	x		x	x	x	x	x	x	x				x				x				x	
Transient elastography/ARFI/MR [c]	x																					
Abdominal ultrasound	x																				*x*	
Alfa-fetoprotein	x																					
HAV, HCV, HDV, HEV, HIV	x																					
Autoantibodies [d]	x																					
Alcohol and drugs of abuse screen [e]		x																			x	x
Pregnancy test [f]		x	x	x	x	x	x	x	x				x				x				x	x
Thyroid function tests	x								x												x	
Hematology (includes HbA1c [g])	x		x	x	x	x	x	x	x	*x*	x	*x*	x	*x*	x	*x*	x	*x*	x	*x*	x	x	x
Chemistry		x	x	x	x	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	*x*	x	x	x
GLDH	x		x	x	x	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	*x*	x	*x*	x	x	x
Clinical genotyping [h]			x																			
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x		x	x	x	x	x	x	x		x		x		x		x		x		x	x

Appendix 13 -*Table 8* Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm – 36 Week (Screening and Treatment Periods) (cont.)

	Screening		Treatment Period																		VB/VR	ET/UV[t]
Week			**1**	**5**	**9**	**13**	**17**	**21**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**		
Day	**-56 to -7**	**-14 to -7**	**1**	**29 (±2)**	**57 (±3)**	**85 (±3)**	**113 (±3)**	**141 (±3)**	**169 (±3)**	**176 (±3)**	**183 (±3)**	**190 (±3)**	**197 (±3)**	**204 (±3)**	**211 (±3)**	**218 (±3)**	**225 (±3)**	**232 (±3)**	**239 (±3)**	**246 (±3)**	**253 (±3)**		
HBV DNA quantitative	x		x				x		x				x								x	x	x
Total HBsAg [i]			x			x			x				x				x				x	x	
HBcrAg			x	x	x	x	x	x	x				x		x		x		x		x	x	
Total anti-HBc quantitative			x			x			x				x				x				x		
HBV RNA quantitative			x	x	x	x	x	x	x				x		x		x		x		x	x	
HBV RNA sequencing [h]			x																				
HBV DNA sequencing [j]																						x	
Plasma PK (siRNA) [k]			x			x		x														x	
Plasma PK (PD-L1 LNA) [k]									x				x				x				x	x	
Plasma PK (NUC) [k]			x			x		x	x				x				x				x	x	
Plasma ADA (siRNA) [l]			x			x		x	x												x	x	x
Plasma ADA (PD-L1 LNA) [l]									x				x				x				x	x	x
Liver injury markers			x						x				x				x				x	*x*	
Extracellular vesicles			x						x				x		x		x		x		x		*x*
Circulating immune phenotyping			x			x			x				x		x		x		x		x		x
Soluble PD-L1			x	x	x	x	x	x	x				x		x		x		x		x		x

Appendix 13-*Table 8* **Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm – 36 Week (Screening and Treatment Periods) (cont.)**

	Screening		Treatment Period																			VB/ VR	ET/UV[t]
Week			**1**	**5**	**9**	**13**	**17**	**21**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**		
Day	**-56 to -7**	**-14 to -7**	**1**	**29 (±2)**	**57 (±3)**	**85 (±3)**	**113 (±3)**	**141 (±3)**	**169 (±3)**	**176 (±3)**	**183 (±3)**	**190 (±3)**	**197 (±3)**	**204 (±3)**	**211 (±3)**	**218 (±3)**	**225 (±3)**	**232 (±3)**	**239 (±3)**	**246 (±3)**	**253 (±3)**		
Cytokine panel [m]			x	x	x	x	x	x	x				x				x				x		x
PBMC [n]			x						x												x		
FNA [o]			x						x												x		
Liver Biopsy [p]																					x		
RBR [q]			x						x								x				x	x	
Clinic siRNA 200 mg sc Q4W treatment administration			x	x	x	x	x	x															
Clinic PD-L1 LNA [redacted] sc [redacted] treatment administration [r]			[redacted]																				
NUC treatment administration OD			x																				
Adverse events, concomitant medications, and diary review [s]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibodies; ARFI = acoustic radiation force impulse; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; FNA = fine needle aspirate; GLDH = glutamate dehydrogenase; HAV/HBV/HCV/HDV/HEV = hepatitis A/B/C/D/E virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; MR = magnetic resonance; NUC = nucleos(t)ide analogue; PK = pharmacokinetics; RBR = Research Biosample Repository; RNA = ribonucleic acid; siRNA= short interfering ribonucleic acid; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

[a] Full physical examination at screening and at the end-of-treatment. Limited symptom-directed physical examination at other visits and as clinically indicated. Height at screening only. Weight at screening, Day 1, and Weeks 25, 29, 33, and 37.

[b] Blood pressure, pulse rate, respiratory rate, and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

Appendix 13 -*Table 8* **Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm (Screening and Treatment Periods) (cont.)**

[c] Historical liver biopsy or transient elastography/ARFI/MR/2D- shear wave elastography [2D-SWE] results obtained within 6 months prior to randomization are also acceptable. During screening transient elastography/ARFI/MR /2D-SWE are acceptable.

[d] Autoantibodies refer to ANA, AMA, ASMA, and a-TPO.

[e] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[f] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[g] HbA1c should be included in hematology and is required only at screening.

[h] If not collected at Day 1, samples for clinical genotyping and HBV RNA sequencing can be collected at any subsequent time point. *The sample for HBV RNA sequencing aims at determining the HBV genotype. The HBV genotype may also be inferred using alternative approaches, such as serovariant determination.*

[i] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb complexes/components of HBsAg.

[j] HBV DNA sequencing will be collected in case of virological breakthrough/relapse; blood sample to be collected up to 6 times.

[k] Plasma PK samples for PD-L1 LNA and siRNA should be collected pre-dose, 1-3 and 4-6 hours post-dose at all indicated visits, with the exception of EOT where only one PK timepoint is required. Plasma PK samples for NUC should be collected pre-dose. During the PK assessment for VB/BR visits, only one pre-dose sample is required for collection.

[l] ADA is collected pre-dose.

[m] Cytokine panel (e.g., INF-α, IP-10, IL-1, IL-6, IL-10, IFN-γ, and TNF-α) to be collected pre-dose.

[n] PBMC at selected sites only, three collections: Days 1, 169, and 253. The exact timepoints for collection may be adjusted by the Sponsor based on emerging data.

[o] Optional sub-study FNA at selected sites only. The timepoints for collection may be adjusted by the Sponsor based on emerging data.

[p] Only for participants in the liver biopsy sub-study. Participation for liver biopsy is optional and will require a separate consent from the participant. Additional safety assessments may be required as per local practice and guidelines prior to the liver biopsy (refer to study operations manual).

[q] RBR samples collected only from RBR-consenting participants.

[r] *The PD-L1 LNA dose is weight based and should be calculated using the most recent per protocol assessment of participant weight at each dosing visit.*

[s] Pre-treatment, only serious adverse events should be reported.

[t] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

Appendix 13-*Table 9* **Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm – 24 and 36 Week (Follow-up Period)**

	Follow-up period											VB/VR	ET/UV[k]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24[l]**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Physical examination, vital signs [a, b]									x		x	x	x
ECG									x		x		
Abdominal ultrasound									x		x		
Alfa-fetoprotein									x		x		
Alcohol and drugs of abuse screen [c]													x
Pregnancy test [d]		x		x		x	x	x	x	x	x		x
Thyroid function tests									x		x		
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry	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
GLDH	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
HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBe)	x	x	x	x	x	x	x	x	x	x	x	x	x
HBV DNA quantitative[m]	x	x	x	x	x	x	x	x	x	x	x	x	x
Total HBsAg [e]		x		x		x			x		x	x	
HBcrAg		x		x		x	x	x	x	x	x	x	
Total anti-HBc quantitative						x			x		x		
HBV RNA quantitative		x		x		x	x	x	x	x	x	x	
HBV DNA sequencing												x	
Plasma PK (siRNA) [f]													
Plasma PK (PD-L1 LNA) [f]													
Plasma PK (NUC) [f]												x	
Plasma ADA (siRNA)						x			x	x	x	x	x
Plasma ADA (PD-L1 LNA)						x			x	x	x	x	x
RBR [g]												x	
Extracellular vesicles		x		x		x	x	x	x	x	x		x
Circulating immune phenotyping		x		x		x	x	x	x	x	x		x
Soluble PD-L1		x		x		x	x	x	x	x	x		x

Appendix 13-*Table 9* Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm – 24 and 36 Week (Follow-up Period) (cont.)

	Follow-up period											VB/VR	ET/UV[k]
Week	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24[l]**	**36**	**48**		**-**
Day	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**70 (±3)**	**84 (±7)**	**112 (±7)**	**140 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**		
Cytokine panel [h]		x		x		x		x	x	x	x		x
PBMC [i]						x			x				
FNA [j]						x							
Diary review	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events & concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibodies; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET=early termination; FNA = fine needle aspirate; GLDH = glutamate dehydrogenase; HBV = hepatitis B virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; NUC = nucleos(t)ide analogue; PD-L1 = programmed death ligand-1; PK = pharmacokinetics; RBR = Research Biosample Repository; RNA = ribonucleic acid; siRNA= short interfering ribonucleic acid; Total HBsAg = post-dissociation of HBsAg/HBsAb complexes/components of HBsAg; VB/VR = virological breakthrough/relapse; UV = unscheduled visit.

Note: If participants discontinue NUC later in the follow-up, additional visits should be scheduled with a frequency of every 2 weeks for the first three months and every 4 weeks up to week 48 of follow-up period.

[a] Full physical exam at screening and at the end-of-treatment. Limited symptom-directed physical exam at other visits and as clinically indicated.

[b] Blood pressure, pulse rate, respiratory rate, and body temperature obtained at least 5 minutes after participant has been in supine/sitting position.

[c] Alcohol and drugs of abuse screen to be conducted according to local procedures.

[d] Pregnancy testing for females of childbearing potential only; serum test at screening, urine test at other visits. If urine test is positive, it must be confirmed by a serum test.

[e] Total HBsAg refers to HBsAg measured post-dissociation of HBsAg/HBsAb/components of HBsAg.

[f] No plasma PK samples are collected during the follow-up period. During the PK assessment for VB/BR visits, only one pre-dose sample is required for collection.

[g] RBR samples collected only from RBR-consenting participants.

[h] Cytokine panel (e.g., INF-α, IP-10, IL-1, IL-6, IL-10, IFN-γ, and TNF-α).

[i] PBMC at selected sites only, *two collections: Follow-up Days 84 and 168. The exact days of collection may be adjusted by the Sponsor based on emerging data.*

[j] Optional sub-study FNA at selected sites only.

[k] Participants who discontinue study treatment prematurely will be required to attend an unscheduled/early termination visit.

Appendix 13-*Table 9* Schedule of Activities for siRNA + PD-L1 LNA + NUC Treatment Arm – 24 and 36 Week (Follow-up Period) (cont.)

[l] *Visit window may be extended to +6 weeks in extreme circumstances such as pandemic, natural disasters, supply chain disruption, outbreak of hostilities.*

[m] *Participants with HBV DNA > 2,000 IU/mL during the follow-up period will undergo weekly monitoring. Participants with HBV DNA >20 IU/mL but < 2,000 IU/mL, should undergo monitoring every two weeks. Participants, who have discontinued NUC therapy, should have monthly visits from follow up Week 24 to Week 48, instead of the 3 monthly follow up visits shown in the SoA, which are relevant for participants on NUC therapy, to enable early detection and appropriate management of HBV DNA rebound. At these additional unscheduled monitoring visits, the following laboratory assessments should be performed using the unscheduled lab kit: hematology, chemistry, coagulation, GLDH, urinalysis, HBV serology, HBV DNA quantitative, total HBsAg, HBcrAg, and HBV RNA quantitative.*

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