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

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STATISTICAL ANALYSIS PLAN

Roche SAP Enhanced Model Document (eMD)/Template v2.0, Revised 28 Feb 2022

STUDY 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**
STUDY NUMBER:	**WV41073**
STUDY NAME:	**PIRANGA**
VERSION NUMBER:	**1.0**
ROCHE COMPOUND(S):	**siRNA, TLR7(3), PD-L1 LNA**

STATISTICAL ANALYSIS PLAN APPROVAL

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This SAP was developed based on Roche SAP model document Roche SAP Enhanced Model Document (eMD)/Template v2.0, Revised 28 Feb 2022

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
|1|	|see electronic date stamp on title page| |day month year|	Version 7, 18 July 2022

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	Anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
CHB	chronic hepatitis b
CSR	Clinical Study Report
DAIDS	Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
EOT	End of treatment
HBCrAg	Hepatitis B core-related antigen
HBeAg	Hepatitis B early antigen
HBsAg	Hepatitis B surface antigen
IA	interim analysis
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IRF	Independent Review Facility
ISG	Interferon-stimulated genes
ISR	Injection site reactions
IxRS	interactive voice/web-based response system
LFT	Liver function tests
LLoQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
NME	New molecular entity
NUC	Nucleos(t)ide
PD	pharmacodynamic
PK	pharmacokinetic
Q4W	Every 4 weeks
QD	Once a day
QOD	Once every other day

QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
QW	Once a week
RNA	Ribonucleic acid
SAE	serious adverse events
SAP	Statistical Analysis Plan
siRNA	Short interfering RNA
SOC	Scientific Oversight Committee
TLR7	Toll-like receptor 7
TND	Target not detected
MI	Multiple Imputation
MAR	Missing at Random

1. INTRODUCTION

This is a Phase II, randomized, adaptive, open-label, multi-arm, multi-center, international, platform study designed to evaluate safety, tolerability, and efficacy of NME combination therapies 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 document contains details of the data analysis and handling rules to be used in the analysis of the clinical, pharmacodynamic (PD) and biomarker data from the study WV41073.

1.1 OBJECTIVES AND ENDPOINTS

Table 1 Primary and Secondary Objectives and Corresponding Endpoints

Primary Objective(s)	Corresponding Endpoints
• To estimate the effect of NME combination therapies on inducing a functional cure over the control arm.	• % participants with HBsAg loss (loss (i.e., HBsAg <0.05 IU/mL) at 24 weeks post-EOT.
Secondary Objective(s)[a]	**Corresponding Endpoints**
• 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.	• Change from baseline in quantitative HBsAg, anti-HBs, HBeAg, anti-HBe, 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 (included below parameters but not limited to) Area under the curve (AUC) Peak Concentration (Cmax) Volume of distribution (Vd) Clearance (CL)

	Urine PK
• To assess the safety and tolerability of NME combination therapies.	• Incidence, nature and severity of adverse events. • Incidence of laboratory abnormalities based on hematology, clinical chemistry, lipids, thyroid function tests, coagulation, urinalysis test. • ECGs. • Vital signs including blood pressure, pulse rate, respiratory rate and body temperature. • Anti-drug antibodies (ADA) (if applicable)
• 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 Objective(s)	**Corresponding Endpoints**
• 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 and quantitative anti-HBc (IgG or total).
• 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.

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.

1.2 STUDY DESIGN

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.

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, ≥ 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, ≥ 1000 IU/mL within each treatment arm, will be maintained as closely as possible to the first combination treatment and the NUC control arm (first set of enrollments).

Due to COVID-19 situation 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 a potential impact on the evaluation of the primary endpoint due to incomplete data. To preserve the viability of the study, if the COVID-19 situation continues, 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. A shorter treatment duration (12 or 24 weeks) for NME combination arms, and a 48-week response-guided therapy (RGT) arm may be added following planned interim analyses; up to four interim analyses are planned for each treatment arm. Treatment arms that achieve 30% difference, compared to NUC control arm, for HBsAg loss at EOT or at 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.

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.

Table 2 Analysis Timing

The timing of planned interim analyses and RGT below 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.

Analysis	Timing of Analysis
First interim analysis	All participants in the study have completed their 12-week visit for a treatment arm or discontinued prematurely
Second interim analysis	All participants in the study have completed their 24-week visit for a treatment arm or discontinued prematurely
Third interim analysis	All participants in the study have completed their 48-week (EOT) visit for a treatment arm or discontinued prematurely
Fourth interim analysis	All participants in the study have completed their follow-up week 12 visit or discontinued prematurely
Primary	All participants in the study have completed their follow-up week 24 visit or discontinued prematurely
Final	The end-of-study for a treatment arm is defined as the date when the last participant completes their follow-up week 48 visit or discontinued prematurely

1.2.1 Treatment Assignment and Blinding

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 < 1,000 IU/mL vs. ≥ 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. 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 ≥ 1000 IU/mL within each treatment arm will be maintained as closely as possible to the first combination treatment and the NUC control arm (first set of enrollments).

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. 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 show 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 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.

1.2.2 Independent Review Facility

No Independent Review Facility (IRF) is planned for this study.

1.2.3 Data Monitoring

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 recommendations about initiating new treatment arms based on pre-defined criterion.

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.

1.2.4 Stratification Factor

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 < 1,000 IU/mL vs. ≥ 1000 IU/mL). A minimum of 12 participants per arm with a screening HBsAg level of < 1000 IU/mL, is required.

For statistical analysis, the actual stratification will be used for analysis (that is based on screening HBsAg level). The stratification based on IxRS data and calculated based on actual data will be listed to compare if any inconsistencies.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

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

2.2 SAMPLE SIZE DETERMINATION

Approximately 30 participants will be randomized in each treatment arm. Approximately five replacement 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.

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.

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, 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 a 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 to gain additional safety data prior to Phase 3 clinical trials.

3. ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 3.

Table 3 Participant Analysis Sets

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	All 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,

4. STATISTICAL ANALYSES

This is an exploratory study for which no formal hypothesis testing will be done and thus no adjustment for multiplicity of testing will be performed.

All statistical analyses will be descriptive in nature. The statistics presented will be dependent on the variable type.

- Categorical variable - number and percentage of participants; proportion, difference in proportions along with 95% CIs
- Continuous variable – summary statistics including means, medians, ranges, and standard deviations. Absolute values and change from baseline TLGs as appropriate will be produced.

4.1 GENERAL CONSIDERATIONS

Disposition and protocol deviations listings and summaries will be based on all randomized participants. Analysis of safety will be based on the safety population. Pharmacodynamics and efficacy analysis will be based on the modified intention-to-treat (mITT) population. Pharmacokinetic analysis will be based on PK population. Immunogenicity analysis is based on the immunogenicity 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. 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.

Evaluable patients: A patient from the mITT population will be considered 'evaluable' if no more than two consecutive siRNA missing doses due to non-safety reasons (e.g., COVID-19 disruptions). This is based on the siRNA liver half-life of ~10 weeks,

estimated from ph1 data. Therefore, after two consecutive missing doses the drug left in the liver is expected to be ~40%, which was considered adequate as patients would restart dosing so up to 2 missing doses are not expected to have a major impact on the efficacy.

Evaluable patients in mITT population will be used to estimate the primary endpoint/estimand.

Any subject who does not have a virology parameter evaluation during the pre-specified window for 24-week Follow-up visit (either due to missing assessment or due to early withdrawal from the study or study treatment) will be considered as a non-responder. However, if the subject with missing evaluation is a responder both before and after the visit window, then the subject will be categorized as a responder for that visit.

Key definitions:

The following definitions will be used:

Baseline: The baseline value is defined as the last available valid (quantifiable continuous or categorical value), non-missing observation for each participant prior to first study drug administration. Repeat and unscheduled assessments will be included in the derivation of the baseline values.

HBsAg Loss: HBsAg loss refers to a negative/undetectable HBsAg level, HBsAg loss is defined HBsAg levels <0.05 IU/mL.

HBsAg Seroconversion: HBsAg seroconversion is defined as HBsAg loss (defined above) along with an anti-HBs result >= 10 IU/mL (positive)

For more granularity regarding HBsAg loss and seroconversion definitions, please refer to the table below.

Table 4 Definition HBsAg loss and seroconversion

HBsAg (quant)	HBsAg (qual)	HBsAg status	anti-HBs	Seroconversion status
Numerical value ≥ 0.05	Reactive	HBsAg present	<10 (Non-Reactive)	No
< 0.05	Reactive	HBsAg loss (present at low concentration) *	<10 (Non-Reactive)	No
< 0.05	Non-Reactive	HBsAg loss (confirmed)	<10 (Non-Reactive)	No
Numerical value ≥ 0.05	Non-Reactive	FLAG as discrepancy for review **	<10 (Non-Reactive)	No
Numerical value ≥ 0.05	Reactive	HBsAg present	≥ 10 (Reactive)	FLAG as double positive ***

< 0.05	Reactive	HBsAg loss (present at low concentration) *	≥ 10 (Reactive)	Seroconversion *
< 0.05	Non-Reactive	HBsAg loss (confirmed)	≥ 10 (Reactive)	Seroconversion
Numerical value ≥ 0.05	Non-Reactive	FLAG as discrepancy for review **	≥ 10 (Reactive)	No

* Follow longitudinal data for confirmation of HBsAg loss with the qualitative assay.
** Evaluate numerical and longitudinal data to understand the discrepancy.
*** Depending on numerical values, these may be rare cases of double positive (HBsAg and anti-HBs) usually seen from baseline. Seroconversion will need to be interpreted using longitudinal data.

These values are based on the limits of detection, limits of quantification, and thresholds for positivity defined by the assay manufacturers and may be updated if any would change.

HBeAg Loss: HBeAg loss refers to a negative/non-reactive HBeAg level ((baseline HBeAg-positive participants).

HBeAg Seroconversion: HBeAg seroconversion is defined as an HBeAg loss (defined above) along with an anti-HBe result.

4.2 PRIMARY ENDPOINTS/ESTIMANDS ANALYSES

4.2.1 Definition of Primary Endpoint(s)/Estimand(s)

Definition of Primary Endpoint:

The primary endpoint is HBsAg loss (qHBsAg <0.05 IU/mL) at week 24 post EOT.

The primary endpoint is calculated for each treatment arm as:

% participants with HBsAg loss= (Number of participants with HBsAg loss / total number of participants) *100

The percentage of participants with HBsAg loss will analyzed using evaluable patients from the mITT population.

Definition of Primary Estimand:

In line with the Estimands addendum to ICH E9, the primary efficacy estimand is defined as follows-

The difference between proportions of HBsAg loss (qHBsAg <0.05 IU/mL) at week 24 follow-up in virologically suppressed adult CHB participants on established NUC therapy, with preserved liver function and without significant fibrosis/cirrhosis, treated with

combination therapy* versus NUC, irrespective of adherence to IMP or whether prohibited medication and/or food has been taken.

*treatment and dose levels will vary depending on the combination arm and are specified in the relevant arm specific appendix.

The primary efficacy estimand is described by the following five attributes:

a) Population: Evaluable patients from the mITT population as defined in section 3. These will be CHB adult participants who are virologically suppressed for more than 6 months on established NUC therapy as defined by the inclusion and exclusion criteria listed in Protocol WV41073 section 5.

b) Primary Endpoint: % participants with HBsAg loss (qHBsAg <0.05 IU/ml) at 24 weeks post-EOT.

c) Population level summary: The difference between proportions of HBsAg loss (qHBsAg <0.05 IU/mL) between NME combination over the control arm at week 24 post-EOT

d) Treatment conditions: Treatment and dose levels will vary depending on combination arms and are specified in the relevant arm specific appendix.

e) Intercurrent Event (ICE):

Table 5 Intercurrent Events Impacting Primary Analyses:

Intercurrent Events	SDR/ NSDR	Estimand Approach
Participants with dose interruptions or switching dose/frequency	SDR	Treatment Policy
Withdrawal from study treatment due to any medical condition or AEs/laboratory abnormalities	SDR	Treatment Policy
Investigator or Sponsor determines that treatment discontinuation is in the best interest of the participant.	SDR	Treatment Policy
Withdrawal from study treatment due to participant's withdrawal of consent, pregnancy, non-compliance with study requirement, or lost to follow-up	NSDR	Treatment Policy
Participants who take prohibited medication and food and continue in the study (List of prohibited	SDR	Treatment Policy

medication and food provided in Table 4)		
COVID-19 related ICE A) Systematic disruptions: i) Discontinued study treatment due to covid19 disruptions ii) Discontinued study due to covid19 disruptions iii) Study treatment interruption due to covid19 disruptions iv) Missed dose(s) with potentially major impact on the efficacy due to covid19 B) COVID-19 infection related ICEs; i) Covid19 infection and concomitant medication ii) Use of the prohibited medicine or therapy iii) Death due to covid19	NSDR	Treatment Policy
Patients who met the NUC d/c criteria at EOT (or in the follow-up period) but did not stop NUC.	SDR	Treatment Policy

SDR- Study Drug Related, NSDR- Non study drug related

A "treatment-policy strategy" will be used accounting for each type of intercurrent event (ICE) as mentioned above. "treatment-policy strategy" where all observed values will be used regardless of the intercurrent event.

Table 6 List of prohibited medication and food

<u>List of prohibited medication-</u> 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. Arm specific prohibited medications
<u>Prohibited food:</u> For CpAM, any nutrients have been taken during study which modulate activity of CYP enzymes (e.g., grapefruit-, apple-, or Seville orange-containing products). For TLR7(3), consumption of green tea beverages during the treatment period. CHB participants who routinely take herbal medicines which may have immune-modulatory effects

4.2.2 Main Analytical Approach for Primary Endpoint(s)

The endpoint is calculated for each treatment arm as:

% participants with HBsAg loss= (Number of participants with HBsAg loss / Total number of participants) *100

The treatment difference (adjusted for baseline HBsAg stratification level, along with the associated 95% confidence interval) in the proportion of participants with HBsAg loss at 24 weeks post-EOT between the NME treatment arm and control arm will be estimated using Cochran-Mantel-Haenszel (CMH) weighting method with continuity correction [Cochran 1954; Mantel and Haenszel 1959].

The percentage of participants with HBsAg loss will be analyzed using evaluable patients from the mITT population.

4.2.3 Sensitivity Analyses

A) Following sensitivity analyses for the primary endpoint will be carried out to assess the impact of consecutive missing doses of siRNA

- Completer Analyses (only include participants who have had full siRNA dosing)
- All patients (mITT population including 'unevaluable' patients)

B) Sensitivity analysis will be performed on primary endpoint for the patients who achieve HBsAg loss at the primary endpoint but did not meet the NUC stopping criteria. A non-responder imputation will be implemented for these pts.

C) Sensitivity analysis may be performed using stratification based on IxRS data if higher number of inconsistencies are observed compare to the actual stratification.

4.2.4 Supplementary Analyses

To evaluate the impact of COVID-19, the ICE associated with the COVID-19 disruptions or other non-safety reason will be handled using a hypothetical approach for the primary endpoint, where the observed data from date of intercurrent event will be set to missing and missing data imputation using Multiple Imputation (MI) will be applied. The aim is to estimate a treatment effect "as if" the ICE had not happened.
Note that the attributes of population, variables and population level summary will remain the same as the primary estimand. The analysis methods will be the same as described for the primary estimand.

Two scenarios will be evaluated –

1) Three or more consecutive siRNA doses missing for a patient.
2) Two or more consecutive siRNA doses missing for a patient

A free-text response has been mandated in the additional observation page of eCRF if the patient missed doses due to COVID-19 or other non-safety reason. Data flag will be

creating to identify patients with ≥2 and ≥3 siRNA missing doses and observed data from date of intercurrent event will be set to missing. In a case, patients missing doses and discontinued from study at primary timepoints then it will considered as non-responder.

For the purpose of statistical analysis, it is reasonable to assume that these missing data are missing at random (MAR) and the statistical models that require MAR assumption are appropriate.

Markov Chain Monte Carlo (MCMC) will be first applied to augment data into monotonic missing pattern and PROC MI will be used to generate 30 datasets using the regression method. The variables to be included in the imputation model are: treatment group, baseline HBS stratification, Baseline, and measurements at each visit up to the end of the analysis period. The random seed for MCMC and the random seed for PROC MI are specified in Appendix 6. Subjects will be characterized as responders or non-responders based on MI imputed datasets. Using the CMH model adjusted by the stratification factor, the imputed endpoints will be analyzed using each of the 30 datasets. SAS PROC MIANALYZE will be used to generate the final inferences of the risk difference between NME treatment arm and control arm (NUC).

4.2.4.1 Subgroup Analyses for Primary Endpoint(s)

There are no subgroup analyses planned for primary endpoint.

4.3 SECONDARY ENDPOINTS ANALYSES

Secondary efficacy outcomes of response include 2 types of endpoints:

- Categorical
  - HBsAg outcomes *
    - Proportions of participants with HBsAg loss at every 12 weeks' time point
    - HBsAg seroconversion (loss of HBsAg and detection of anti-HBs antibody) over time
    - Proportions of participants with HBsAg loss (HBsAg <LLOQ) and HBV DNA <LLOQ
  - HBeAg outcomes *
    - loss of HBeAg over time
    - detection of anti-HBe antibody over time
    - HBeAg seroconversion (loss of HBeAg and detection of anti-HBe), baseline HBeAg-positive participants over time
  - Maintenance of HBV DNA levels less than lower limit of quantification (LLOQ or <20 IU/mL), <200 IU/mL and <2,000 IU/mL *)

* Time points are as (Treatment Period: 12 weeks, 24 weeks, 36 weeks and 48 weeks; Follow-up period: 12 weeks, 24 weeks, 36 weeks and 48 weeks)

- Continuous endpoints, summarized over time
    - Quantitative HBsAg value, and its change from baseline
    - Quantitative HBV DNA value, and its change from baseline
    - Quantitative HBeAg value, and its change from baseline
    - Quantitative HBcrAg value, and its change from baseline
    - Quantitative HBV RNA value, and its change from baseline
    - Quantitative anti-HBs value
    - Quantitative anti-HBc value

Summary descriptive statistics will be used to summarize these efficacy outcome measures at each of the time points by treatment group, based on the data processing rules below.

The statistical method described for the primary endpoint is applicable for the secondary categorical endpoints, i.e. to calculate the proportion by treatment group and difference in proportion along with 95% CI's.

HBeAg / HBsAg seroconversion are defined as the loss of HBeAg / HBsAg (i.e., a negative result for HBeAg / HBsAg) and the detection of anti-HBe / anti-HBs (i.e., a positive result for anti-HBe/ anti-HBs), respectively.

The proportion of HBsAg loss, HBeAg loss, HBeAg seroconversion, HBsAg seroconversion and maintenance of HBV DNA below LLOQ, 200 and 2,000 IU/mL grouped by treatment arm will be paneled by visit (EOT, 24 weeks post-EOT and 48 weeks post- EOT) in one plot. Additional bar charts will be created, one split further by HBsAg stratification level and one split by baseline HBeAg status.

The list of required outputs and output mock shell will be covered in LoPO and output specification document respectively,

Data processing rules-

- Summary graphs of continuous endpoints will include their corresponding standard deviation or 95% CIs as appropriate
- All virology parameters (absolute and change from baseline) will be reported as Log10 (unit).
- Any BLQ or ALQ result will be imputed to the corresponding BLQ or ALQ value, respectively
- Any result reported as a ">" or "<" sign with a numerical value will be imputed to the numerical value and will be used for analyses.

- Any result reported as "TND" will be imputed to the BLQ or LoD (limit of detection) value as appropriate for each parameter.

- Only participants with quantifiable baseline results will be included in any change from baseline summary statistics.

- **Treatment comparison between NME's and NUC:**

The mean change from baseline in HBsAg will be analyzed from analysis of covariance (ANCOVA) with treatment, visit, stratification, and treatment*visit interaction effect as fixed effect; different baseline covariates will be explored (baseline HBsAg, baseline body weight, age, genotype, baseline HBeAg status etc.) and the statistical significant baseline covariates will be included in the final model. Adjusted means and 95% CIs will be presented for each treatment arm. Difference in adjusted means for COMBO treatment Vs NUC control will be presented with 95% CIs.

The assumptions that are made using ANCOVA (that is normality of scores at treatment level, homogeneity of variance, homogeneity of regression slope, linear regression) will be assessed. A histogram of scores will be plotted for checking normality and a suitable transformation (e.g. log, square root) will be considered to correct non-normally distributed data. Leven's test will be used to test the assumption of homogeneity of variance supported by graphical presentation.

If the normality assumption is not met with any data transformation, then non parametric test will be used. The non-parametric test could be Wilcoxon rank sum test or van Elteren test.

- **Relationship between categorical HBsAg and baseline characteristics:**

The primary efficacy parameter is the incidence of HBsAg loss (that is <0.05 IU/ml) at 24 weeks post EOT.

HBsAg will be categorized as;

HBsAg "Y": If HBsAg loss <0.05 IU/ml

HBsAg "N": If HBsAg loss >=0.05 IU/ml

The relationship between categorized HBsAg and baseline covariates will be explored using logistic regression techniques where HBsAg category(Y/N) as response and baseline covariates- age, sex, race (or country), HBV genotyping, NME combination treatments, HBeAg status, baseline HBsAg, baseline ALT, baseline DNA as independent variable. Stepwise selection option will be used to finalized the model. The independent variable will stay in the model which are significant at P<0.1.

Covariates will be checked for collinearity. Collinearity will be examined through the Variance Inflation Factor and Tolerance. Where collinearity occurs between two variables, only one of these variables will be included in the final model.

An assessment of goodness of fit of the model will be performed using the Pearson Chi-Squared Goodness of Fit test, deviance test and visual inspection of index plots.

The odds ratio for independent variables will be reported along with the 95% confidence interval. If required, odds ratio will be reported by visit.

4.4 EXPLORATORY ENDPOINTS ANALYSES

Exploratory efficacy endpoints are:

- HBV dynamic biomarkers: quantitative anti-HBc (IgG or total), quantitative total HBsAg (post dissociation of HBsAg/HBsAb complexes)
- HBV genome sequencing: HBV RNA sequencing, HBV DNA sequencing

If available, these data will be listed at a minimum. Additionally, plots and summary statistics will be produced by treatment arm as appropriate.

Relapse Rate:

Relapse rate where HBsAg loss achieved at EOT or during follow-up period but rebounded at primary timepoint (24 weeks post-EOT), will be calculated for primary endpoint.

Subgroup Exploratory Analysis:

The association between virological outcome (HBsAg, HBeAg, HBV-DNA, HBV-RNA, HBcrAg) and baseline HBsAg stratification, baseline HBeAg status, clinical genotype (if available), gender, ethnicity will be explored graphically. Subsequent exploratory analyses may be performed at end of study or during study.

4.5 SAFETY ANALYSES

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

The safety data, including AEs, reasons for withdrawal from treatment and 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.

Key Definitions:

Modified Injection Site Reaction: A modified ISR will be defined as, an ISR for which the criteria for a 4-hour post dose injection site reaction is met.

4.5.1 Extent of Exposure

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. Tables and listings will be provided for individual participants by actual received

treatment and exposure to NME or NME combinations or NUCs. The duration of study drug administration, actual cumulative dose and percentage of actual cumulative dose in planned cumulative dose will be summarized by treatment. A patient listing of study drug administration by center/patient number will also be provided.

4.5.2 Adverse Events

Tables and listings will be presented with respect to;

- All clinical adverse events (AEs), summarized
- Serious adverse events (SAEs), and
- Adverse events of special interest (AESI)
    - 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)
    - 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.
    - ALT or aspartate aminotransferase (AST) elevations ≥ 10 x ULN
    - Grade ≥3 hematology lab abnormalities (e.g., lymphopenia, neutropenia, leukopenia)
    - Severe/serious injection site reactions and/or injection reactions
- AEs will also be summarized by grade and causal relationship to the applicable study drug(s) part of the combination, as judged by the investigator
- AEs leading to dose interruptions or study drug adjustments
- Adverse events leading to withdrawal from the study treatment/study
- Listing of participants with Grade 2 blood cell count decreases or any infections Grade 2 intensity or higher.

The original terms recorded on the eCRF by the investigator for adverse events will be standardized by the sponsor. Reported AEs will be coded to preferred terms and body

systems as defined by the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Some AEs may be summarized by gender if required.

The adverse event severity grading scale for the DAIDS (v2.1) will be used for assessing severity for adverse events. For detail of the grading scale, please refer section 3.1 of the protocol.

Glossaries of the body systems, preferred terms and verbatim terms for all AEs and subgroups of AEs of special interest will be provided.

4.5.3 Additional Safety Assessments

Pregnancies:

A listing of pregnancy test outcomes and any other information collected on CRF will be reported.

Liver Imaging Assessment:

The results of abdominal hepatic ultrasound (during treatment and follow-up) will be listed as follows:

- No. of readings taken & reading success rate (n, %)
- Median stiffness (kPa)
- Interquartile range / IQR (kPa)

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 and will be flagged for 1) AE's, 2) HBV treatment 3) other

Green tea consumption will be summarized in a separate table.

Medication Error and Overdose:

Overdose (accidental or intentional), medication error will be listed in a separate listing.

Analyses of Documenting Impact of the COVID-19:

The below tables and listing are recommended to access in case study has been impacted due to covid19.

- Listing of Major Protocol Deviations Related to COVID-19 (new listing template including new reason column)

- Summary of Major Protocol Deviations Related to COVID-19

- Summary of Reasons for Major Protocol Deviations Related to COVID-19 (new summary template with deviations categorized by reason)

Based on the above summary tables, the following relevant information can be extracted and should be described in the CSR:

- Number/% of Subjects with major pandemic-related impact on study treatment exposure

- Number/% of Subjects with major pandemic-related impact on primary endpoint assessments (and similarly for other critical study endpoints)

Premature discontinuation from treatment or study-

It is recommended that the number of subjects who prematurely withdraw from treatment or study due to COVID-19 related reasons is described in the relevant CSR sections or in CSR COVID-19 appendix.

The number of subjects with discontinuation due to direct COVID-19 impacts are available from the recommended new TLGs for the Adverse Events.

- Number/% with Suspected/Confirmed COVID-19

- Number/% with Study Treatment Discontinuation due to AEs associated with COVID-19

- Number/% with Study Discontinuation due to AEs associated with COVID-19

- Number/% with Death due to AEs associated with COVID-19

For Statistical Programming team, please refer the document (Safety Analysis Impact of COVID-19 (All Domains) v0.1) guidance for additional TLGs in case moderate to major impact on the study.

Virological Breakthrough/ Relapse:

The number of participants who had virological breakthrough and relapse will be presented by treatment arm as collected on the CRF, a listing will be provided..

4.5.3.1 Laboratory Data

All laboratory data will be reported in terms of standard ranges in System international (SI) units and will be converted from the original units as necessary.

Summary tables will detail the transformed values and change from baseline of the laboratory parameters over time by treatment group.

Absolute values and changes from baseline over time plots will be provided.

Data processing rules-

1) Unscheduled visit: If more than one visit occurred during a single visit window, then the laboratory data closest to the scheduled visit day will be used. If the two laboratory assessments were equidistant from the scheduled visit day, then the later assessment will be used.

   All unscheduled labs will be included in lab profile plots over time, and also listed by day relative to start of treatment including the clinical planned event CPE (visit) listed also.

2) Baseline visit: If the baseline value is missing, value from closest screening visit will be used. If two or more samples were collected on the day that was closest to the Baseline target day, then the earliest sample was selected; if the sample collection time was the same then the worst value was selected.

3) Values below limit of quantification will be set to limit of quantification.

4) Local laboratory results may be available. If both local and central laboratory results are available for same time point, then central lab results should be used for analyses. In cases where only the local laboratory results exist for a given timepoint, these will be normalized using the Roche document for analysis – Data Analysis Guidance: Safety Lab standardization (Please refer the output specification).

Laboratory Abnormalities:

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. For protocol-required safety laboratory assessments, please refer to protocol Appendix 4- Table 1.

Shift tables will provide shifts from DAIDS grade at baseline to DAIDS grade on treatment, where baseline is defined as the last valid, non-missing assessment prior to the first study drug administration, and percentages are based on the number of participants with valid measurement at baseline.

For all laboratory parameters included in this analysis, all the laboratory values and reference ranges will be converted into standard units if it is not in a standard unit. Laboratory values falling outside this reference range will be labeled “H” for high or “L” for low in participant listings of laboratory data. If the values fall outside of reference ranges, then “H” or “L” concatenate with the DAIDS grading and will be listed.

Abnormal Live Function Tests:

Participants with ALT increased (DAIDS grade 1 or higher) will be summarized by treatment group based on Safety population.

In addition, longitudinal participates profiles for each participant will be presented:

Liver Function test profiles: Double-axis plots including ALT, AST, ALP, Direct Bilirubin, Total Bilirubin, INR.

ALT/Virology profiles: Double-axis plots displaying ALT (as ratio over ULN), HBeAg, HBsAg, HBV DNA, HBV RNA, HBcrAg (log10)

The incidence of the following LFT abnormalities will be presented by treatment arm:

- Treatment-emergent ALT/AST > 3 x ULN and >3 x BSL, in combination with total bilirubin > 2 x ULN.
- Treatment-emergent ALT or AST > 3 x ULN and >3 x BSL, in combination with clinical jaundice.

In addition, an eDISH plot (Evaluation of Drug-Induced Serious Hepatotoxicity) will be created

4.5.3.2 Vital Signs

Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities (Roche Standard- refer output specification). In addition, absolute values and changes from baseline for vital signs data will be summarized. Absolute values and Changes from baseline over time plots will be provided.

Vital signs will include measurements of blood pressure (BP- systolic and diastolic), pulse rate, respiratory rate and body temperature (oral or tympanic).

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.

4.5.3.3 ECGs

- Summary descriptive statistics for the actual values and changes from baseline will be tabulated by nominal time for HR, QRS duration, PR, QT, QTc interval, QTcF (Fridericia's correction) and RR. Actual values and changes from baseline over time plots will be created for the above ECG parameters.
- For multiple measurements taken at a nominal time point, the average of these measurements will be used as the value at that nominal time point in all summaries.
- In addition, QTcF will be categorized at each time point as ≤450 ms, >450 – 480 ms, >480 – 500 ms and >500 ms and summarized.
- Similarly, a summary will be provided of the QTcF increase from baseline at each time point categorized as < 30 ms, 30 – 60 ms, and > 60 ms.
- Changes of the overall ECG interpretation, T-wave and U-wave morphology will be summarized.
- Listing of clinically significant ECG abnormalities will be provided
- Abnormal T and U wave will be summarized.

4.6 OTHER ANALYSES

4.6.1 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 by treatment. Major protocol deviations will be summarized and listed by each treatment arm. Separate listing will be provided for the patients who have met the NUC discontinuation criteria at EOT or follow-up but have not stopped NUC (reluctant to do).

For each participant assessment, the baseline value will be the latest non-missing assessment prior to the first dose administration, this being study Day 1 pre-dose. In the absence of data on study Day 1, the latest non-missing value collected during screening will be used, if such data are not available then the assessment baseline value will be missing for that participant.

4.6.2 Summaries of Treatment Group Comparability/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 (including incidence of Peg-IFN), and length of time on NUCs.

For NUC treatment duration calculation, if there is a break of treatment of less than 6 months then the duration will be cumulative, if break of treatment is more than 6 months, then the last continuous course of treatment with any nucleos(t)ide products prior to baseline (categorized as <3 years, >=3 to <5 years, >=5 years to <10 years, and >=10 years) will be counted. The effect of this duration covariate will be examined with respect to efficacy, immunogenicity, and antiviral endpoints in separate analyses.

4.6.3 Pharmacokinetic Analyses

The analysis of PK variables will be conducted by Clinical Pharmacology and reported in the CSR.

4.6.4 Immunogenicity Analyses

The analyses will be carried out on the immunogenicity analysis population

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).

4.7 INTERIM ANALYSES

4.7.1 Planned 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, 24, and EOT respectively after the start of therapy (or have discontinued from the study). The fourth interim analysis will be performed when all participants within a treatment arm have completed the follow-up Week 12 visit (or have discontinued 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 pharmacodynamics data and may commence a new treatment arm of sample size of approximately 30 participants with 12-weeks' treatment duration.

- 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 pharmacodynamics data and may commence a new treatment arm of sample size of approximately 30 participants with 24-weeks treatment duration.

- 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.

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

The following endpoint will be assessed as part of the interim analysis:

Efficacy endpoint:

1) HBsAg loss
2) Change in HBsAg and anti-HBs over time
3) HBsAg seroconversion (loss of HBsAg and presence of anti-HBs antibody)
4) Changes in HBeAg and anti-HBe status
5) HBeAg loss and seroconversion
6) HBC DNA

Safety Endpoint:

1) All clinical adverse events (AEs)
2) Serious Adverse events
3) Adverse events of special interest (AESI)
4) Liver/ Renal/ Urine Analysis Function Test and some important Lab parameters
5) Laboratory abnormalities

The estimated treatment difference adjusted for baseline HBsAg level, along with the associated 95% confidence interval in the proportion of participants with HBsAg loss for each interim analysis between the experimental and associated control arm will be provided.

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

Summary descriptive statistics will be used to summarize these efficacy and safety outcome measures at each of the time points by treatment group. In addition, graphical displays will be produced of mean and individual participant data as appropriate. Means and change from baseline for efficacy and safety endpoints will be provided. Mean (95% Cis) and individual HBsAg maximum decrease from baseline will be provided. ALT increase plots will be provided.

5. SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 ANALYSIS DETAILS SPECIFIC TO NUC CONTROL ARM

An overview of the nucleos(t)ide (NUC) control treatment arm is shown in appendix 7 in protocol.

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.

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.

The NUC control arm is a continuous recruiting arm and the number of patients in this arm will depend on new enrolling NME. For any major reporting event, the number patients who completed study will be included in the corresponding reporting event.

5.2 APPENDIX 2 ANALYSIS DETAILS SPECIFIC TO TLR7 TREATMENT COMBINATION

TLR7 treatment combination arm specific analysis are listed in this appendix.

Immune Pharmacodynamics Biomarker Analysis: Markers of Humoral and Cellular Response

PD biomarker variables measured are listed in Table 7 below.

Table 7 List of Immune PD biomarker variables

Type	Variable	Label	Unit
Transcriptional	TLR7	TLR7	delta Ct*
Transcriptional	OAS-1	OAS1	delta Ct*
Transcriptional	MX1	MX1	delta Ct*
Transcriptional	ISG-15	ISG15	delta Ct*
Serum soluble protein (cytokine)	IFN-α	IFN-alpha	ng/L
Serum soluble protein (cytokine)	IFN-γ	IFN-Gamma	ng/L
Serum soluble protein (cytokine)	IP-10	IP-10	ng/L
Serum soluble protein (cytokine)	TNF-α	TNF-alpha	ng/L
Serum soluble protein (cytokine)	IL-6	IL-6	ng/L
Serum soluble protein (cytokine)	IL-1	IL-1	ng/mL
Serum soluble protein (cytokine)	IL-10	IL-10	ng/L

* delta Ct will be provided by the lab performing the analysis.

For each PD variable, descriptive statistics will be presented separately by treatment arm, appropriate TLGs will be produced as listed below.

1) Descriptive Statistics- N, Mean, SEM, SD, Median, Min, Max

2) Geometric Mean and Change from baseline (baseline for the period) for each time point- tables and plots

3) Plot of Absolute Values over Time

4) Fold Change (FC) from BL for each time point – tables and plots

Cytokine and Neopterin Variables:

- Log10 for each variable at each time point
- Fold change from baseline for each time point based upon raw data
- Log10 fold change from baseline for each time point

Interferon-alpha:

- Systemic Interferon post dose is defined as interferon-alpha post dose > LLOQ pg/mL

Transcriptional Variables:

- Fold change from baseline for each time point calculated as 2**(Change from BL), eg, If change from BL=3 then fold change from baseline = 2**(3) =8.

PD data processing rules-

- Values below limit of quantification set to limit of quantification for cytokine and neopterin derived variables ('<' stripped from string).
- Raw value as transmitted to Roche for cytokine and neopterin variables
- Raw value is negative of original value as transmitted to Roche for transcriptional variables

Relationship between categorical HBsAg and PD Biomarkers:

The primary efficacy parameter is the incidence of HBsAg loss (that is <0.05IU/ml) at 24 weeks post EOT.

HBsAg will be categorized as;

HBsAg "Y": If HBsAg loss <0.05 IU/ml

HBsAg "N": If HBsAg loss >=0.05 IU/ml

The relationship between categorized HBsAg and PD biomarkers will be explored using logistic regression techniques where HBsAg category(Y/N) as response and PD biomarkers (IFN-alpha, IFN-Gamma, IP-10, TNF-alpha, IL6, IL10, IL1, Neopterin, TLR7, OAS1, MX1 and ISG15) and baseline quantitative HBsAg as independent variable. Stepwise selection option will be used to finalize the model. The independent variable will stay in the model which are significant at P<0.1.

The mathematical form of the model is as;

Response (Y/N) = IFN-alpha+ IFN-Gamma+ IP-10+ TNF-alpha+ IL6+ IL10+ IL1+ Neopterin+ TLR7+ OAS+, MX1+ ISG15+ BASE_HBsAg

Covariates will be checked for collinearity. Where collinearity occurs between two variables, only one of these variables will be included in the final model.

An assessment of the goodness of fit of the model will be performed using the Pearson Chi-Squared Goodness of fit test, deviance test and visual inspection of index plots.

The odds ratio for PD biomarkers will be reported along with the 95% confidence interval. If required odds ratio will be reported by visit.

Estimand for TLR7 Treatment Combination:

The difference between proportions of HBsAg loss (qHBsAg <0.05 IU/mL) at week 24 follow-up in virologically suppressed adult CHB participants on established NUC therapy, with preserved liver function and without significant fibrosis/cirrhosis, treated with combination therapy [CpAM (600mg QD) +TLR7 (150mg QOD, 100mg QOD, 100mg QW) + NUC] versus NUC irrespective of adherence to IMP or whether prohibited medication and/or food has been taken.

5.3 APPENDIX 3 ANALYSIS DETAILS SPECIFIC TO SIRNA TREATMENT COMBINATION ARM

Effects of ADA on NMEs and/or IMP:

Relationship between ADA status, PK,safety, PD, and efficacy will be explored. The analysis detail will be given in final version of the statistical analysis plan.

Characterization of Injection Site 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)''

All injection site reaction or injection reaction information will be listed.
Injection Site Reactions (ISR) are usually immunological with delayed onset. ISR of onset 4 hours or more hours post dose called as modified ISR.

Grading of pre-defined ISR signs and symptoms (pain, erythema swelling and pruritus) should be based on DAIDS

The listing and summary table will be created for the ISR or IR and modified ISR. Summary table will include the number of participants (%) experiencing an event and the number of events.

Summaries are as follow:

1) Number of Injection site reaction/ injection reactions
2) Number of patients with modified ISR
3) ISR/IR with DAIDS grade >=3

Estimand for siRNA Treatment Combination:

The difference between proportions of HBsAg loss (qHBsAg <0.05 IU/mL) at week 24 follow-up in virologically suppressed adult CHB participants on established NUC therapy, with preserved liver function and without significant fibrosis/cirrhosis, treated with combination therapies;

1) siRNA (100 or 200mg Q4W)+ NUC,
2) siRNA (200mg Q4W) + PEG-IFN (180ug QW)+ NUC,
3) siRNA (200mg Q4W) +CpAM (600mg QOD) +NUC,
4) siRNA (200mg Q4W) + TLR7 (150mg QOD, 100mg QOD, 100mg QW) + NUC

versus NUC, irrespective of adherence to IMP or whether prohibited medication and/or food has been taken.

5.4 APPENDIX 4 ANALYSIS DETAILS SPECIFIC TO PD-L1 LNA TREATMENT COMBINATION ARM

PD-L1 LNA treatment combination arm specific analysis are listed in this appendix.

The PD-L1 LNA treatment combination arms as follow:

1) One treatment arm will evaluate a 24-week treatment duration where siRNA (200 mg Q4W) will be given during Weeks 1-24 and PDL1-LNA [redacted] will be given during Weeks 13-24.

2) A second treatment arm will evaluate a 36-week treatment duration where siRNA (200 mg Q4W) will be given during Weeks 1-24 and PDL1-LNA [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

The detail analysis of the PBMC and FNA data will be cover in the next version of the statistical analysis plan.

Estimand for PDL1-LNA Treatment Combination:

The difference between proportions of HBsAg loss (qHBsAg <0.05 IU/mL) at week 24 follow-up in virologically suppressed adult CHB participants on established NUC therapy, with preserved liver function and without significant fibrosis/cirrhosis, treated with combination therapies

1) siRNA (200mg Q4W)+ PDL1-LNA [redacted] + NUC, with 24 weeks treatment duration

2) siRNA (200mg Q4W)+ PDL1-LNA [redacted] + NUC, with 36 weeks treatment duration

versus NUC, irrespective of adherence to IMP or whether prohibited medication and/or food has been taken.

The detail analysis of the PBMC and FNA data will be cover in the final version of the statistical analysis plan.

5.5 APPENDIX 5 PLANNED TREATMENT ARMS

An overview of the planned treatment arms is shown below.

Table 8 Planned Treatment Arms

Group	Treatment Arm	Arm Status	Number of Participants
1	NUC control	Ongoing	30[b]
2	CpAM (600 mg) (RO7049389) + TLR7 (150 mg) (RO7020531) + NUC	Terminated[c]	~30
3	siRNA (100 mg) (RO7445482) + NUC	Ongoing	~30
4	siRNA (200 mg) (RO7445482) + NUC	Ongoing	~30
5	siRNA (200 mg) (RO7445482) + PEG-IFN (180 µg)+ NUC	Ongoing	~30
6	siRNA (200 mg) (RO7445482) + CpAM (600 mg) (RO7049389) + NUC	Terminated[c]	~30
7	siRNA (200 mg) (RO7445482) + TLR7 (150 mg) (RO7020531) + NUC	Ongoing	~30
8	siRNA (200 mg) (RO7445482) + PDL1-LNA [redacted] (*RO7191863*) + NUC (24 weeks treatment duration)	Ongoing	~30
9	siRNA (200 mg) (RO7445482) + PDL1-LNA [redacted] (RO7191863) + NUC (36 weeks treatment duration)	Ongoing	~30
TBD[a]	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.

5.6 APPENDIX 6 MULTIPLE IMPUTATION TO HANDLE MISSING DATA DUE TO COVID-19 PANDEMIC OR DUE TO HYPOTHETICAL STRATEGY

Random Seed:

Random seed for MCMC procedure will be 21614 and MI procedure will be 22040. In case of non-convergence, the random seed will be updated by adding 18751 at each attempt until convergence of model happens.

Multiple Imputation (MI) and MAR Assumption:

When a categorical variable is derived from a continuous scale, for example, (SLOSS when HBSAG<0.05), HBSAG value will be log10 transformed to achieve normality, and then log10 transformed values will be imputed using MI method. To get the original scale, the imputed values will be back transformed. Then the categorical variable will be derived from the back transformed imputed value. Since the "<0.05" value is set to 0.05 for continuous scale in the database, as a conservative approach if the back transformed imputed value "<0.05" is categorized as the responder.

The MI procedure assumes that the data are missing at random (MAR). That is, for an outcome variable Y, the probability that an observation is missing depends only on the observed values of other variables, not on the unobserved values of the outcome variable Y. Statistical inference from the MI procedure is valid under the MAR assumption.

Imputation Algorithm:

It is reasonable to assume the missing values of the longitudinal data for an outcome variable follows a monotone missing pattern. In practice, the missing data of the outcome variable might have an arbitrary (non-monotone) missing data pattern. An extra step may be added to augment data into a monotone missing pattern.
For the outcome variable (e.g., HBSAG at each visit), K 'complete' datasets can be generated in two steps: augmentation step and imputation step. K, the number of repetitions, is determined below.

Augmentation Step

For datasets with non-monotone missing data patterns the augmentation step will first impute enough values to augment the data into a monotonic missing pattern:

Markov Chain Monte Carlo (MCMC) will be applied to augment the data using PROC MI with the MCMC IMPUTE=monotone statement, assuming a multivariate normal distribution. The augmented data will be used in the subsequent imputation step to generate 'complete' datasets. Covariates included in the model are treatment, stratification factors, Baseline, and all post-baseline visits of the outcome variable according to the pre-specified order. Of note, categorical variables are included using the form of dummy variables.

Repeat the imputation process K=30 times using the procedure described above to form K=30 monotone missing datasets, where K is determined as described in "Repetition of

imputations (K)."

Imputation Step

For missing data with monotone missing patterns, the choice of multiple imputation using a parametric regression model that assumes multivariate normality is appropriate.

The imputation step is described below:

- The imputation model for the missing data is a regression model, which controls for treatment, stratification factors,, Baseline, and all post-baseline visits of the outcome variable. The covariates included in the model and the order of these variables are consistent with the augmentation step.

- For each monotone missing dataset, using SAS PROC MI with MONOTONE REG model statement, the outcome variable at each post-baseline visit with missing values will be imputed sequentially with covariates constructed from their corresponding sets of preceding variables.

- A 'complete' dataset with imputed values for the missing data is generated after the augmentation and imputation steps are completed

Repetition of Imputations (K)

Repetition of imputations, K, must be determined in advance. In the usual clinical settings expecting less than 30% missing information, K=30 repetitions are deemed sufficient. When missingness exceeds 30%, depending on the power falloff tolerance level, number of repetitions may need to be increased. It is suggested that the number of repetitions (K) should be at least equal to the percentage of missing.

Derivation of Response Status and Non-Responder Imputation.

For each 'complete' dataset, the imputed post-baseline values will be back transformed to the original scale of the same precision as the observed data. Response status will be determined accordingly.

The imputed response status for missing due to reasons other than COVID-19 will be overridden by non-responder imputation to ensure that multiple imputation is only applied to missing due to COVID-19 and due to hypothetical strategy.

The only exception is that a subject will be categorized as a responder for the visit if the subject is a responder both before and after the specified visit window.

Analysis:

The statistical analysis will use the Cochran-Mantel-Haenszel (CMH) test adjusted by the stratification factors.

Also, binomial proportion and exact confidence interval for a proportion will be calculated for each treatment arm.

Analysis of Each Dataset

For each of the K 'complete' datasets, the CMH test will be used to estimate the NME difference versus control and the corresponding standard error.

Also, for each of the K 'complete' datasets, binomial proportion and exact confidence interval for proportions will be calculated for each NME and control arm and the corresponding standard error.

Synthesis of Results for Statistical Inference

The results from the K 'complete' datasets will be synthesized using the SAS procedure PROC MIANALYZE, following Rubin's formula to derive the MI estimator of the treatment difference and proportions for the final inferences.

6. REFERENCES

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