



Clinical trial results:

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

Summary

EudraCT number	2019-002086-35
Trial protocol	GB FR NL BE BG
Global end of trial date	19 July 2024

Results information

Result version number	v1 (current)
This version publication date	02 August 2025
First version publication date	02 August 2025

Trial information

Trial identification

Sponsor protocol code	WV41073
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04225715
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4058
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 July 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to compare the efficacy of new molecular entity (NME) combination regimens against a control arm in participants with chronic hepatitis B (CHB).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form

Background therapy:

Participants received background nucleos(t)ide (NUC) therapy in accordance with the local prescribing information.

Evidence for comparator: -

Actual start date of recruitment	05 July 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	11 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	China: 152
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Thailand: 15
Country: Number of subjects enrolled	Taiwan: 41
Worldwide total number of subjects	281
EEA total number of subjects	28

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	277
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 281 participants with CHB who had virologic suppression with NUC therapy took part in the study across 13 countries from 05 July 2020 to 19 July 2024.

Pre-assignment

Screening details:

The study consisted of a screening phase, followed by up to 48 weeks of treatment and up to 48 weeks of post-treatment follow-up. Multiple new combination therapies were compared against a common control. Combos 1, 5, 7 and 8 were prematurely terminated by the Sponsor.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	NUC Control Arm

Arm description:

Participants continued their background NUC therapy for 48 weeks. Thereafter, in line with current CHB treatment guidelines, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Arm type	Active comparator
Investigational medicinal product name	NUC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

NUC tablets, orally up to follow up Week 48.

Arm title	Combo 1: CpAM + TLR7 Agonist + NUC
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Arm description:

Participants received core protein allosteric modulator (CpAM), 600 milligrams (mg) tablets, orally, once daily (QD) for 48 weeks and toll-like receptor 7 (TLR7) agonist, 150 mg, orally, once every other day (QOD) during Weeks 1-12 and Weeks 25-36 in addition to their background NUC therapy. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Arm type	Experimental
Investigational medicinal product name	CpAM
Investigational medicinal product code	RO7049389
Other name	Linvencorvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

CpAM, 600 mg tablets, orally, QD up to Week 48.

Investigational medicinal product name	NUC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: NUC tablets, orally up to follow up Week 48.	
Investigational medicinal product name	TLR7
Investigational medicinal product code	RO7020531
Other name	Ruzotolimod
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: TLR7, 150 mg tablets, orally, QOD during Weeks 1-12 and Weeks 25-36.	
Arm title	Combo 2: siRNA (100 mg) + NUC
Arm description: Participants received short interfering ribonucleic acid (siRNA), 100 mg, as a subcutaneous (SC) injection, every 4 weeks (Q4W) in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Arm type	Experimental
Investigational medicinal product name	NUC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: NUC tablets, orally up to follow up Week 48.	
Investigational medicinal product name	siRNA
Investigational medicinal product code	RO7445482
Other name	Xalnesiran, DCR-HBVS
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: siRNA, 100 mg, as a SC injection, Q4W up to Week 48.	
Arm title	Combo 3: siRNA (200 mg) + NUC
Arm description: Participants received siRNA, 200 mg, as a SC injection, Q4W in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Arm type	Experimental
Investigational medicinal product name	NUC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: NUC tablets, orally up to follow up Week 48.	
Investigational medicinal product name	siRNA
Investigational medicinal product code	RO7445482
Other name	Xalnesiran, DCR-HBVS
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: siRNA, 200 mg, as a SC injection, Q4W up to Week 48.	
Arm title	Combo 4: siRNA + PEG-IFN + NUC

Arm description:

Participants received siRNA, 200 mg, as a SC injection, Q4W and pegylated interferon (PEG-IFN), 180 micrograms (µg), as a SC injection, every week (QW) in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Arm type	Experimental
Investigational medicinal product name	siRNA
Investigational medicinal product code	RO7445482
Other name	Xalnesiran, DCR-HBVS
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

siRNA, 200 mg, as a SC injection, Q4W up to Week 48.

Investigational medicinal product name	NUC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

NUC tablets, orally up to follow up Week 48.

Investigational medicinal product name	PEG-IFN
Investigational medicinal product code	RO0258310
Other name	Pegasys
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PEG-IFN, 180 µg, as a SC injection, QW up to Week 48.

Arm title	Combo 5: siRNA + CpAM + NUC
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Arm description:

Participants received siRNA, 200 mg, as a SC injection, Q4W and CpAM, 600 mg tablets, orally, QD in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Arm type	Experimental
Investigational medicinal product name	siRNA
Investigational medicinal product code	RO7445482
Other name	Xalnesiran, DCR-HBVS
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

siRNA, 200 mg, as a SC injection, Q4W up to Week 48.

Investigational medicinal product name	NUC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

NUC tablets, orally up to follow up Week 48.

Investigational medicinal product name	CpAM
Investigational medicinal product code	RO7049389
Other name	Linvencorvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

CpAM, 600 mg tablets, orally, QD up to Week 48.

Arm title	Combo 6: siRNA + TLR7 Agonist + NUC
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Arm description:

Participants received siRNA, 200 mg, as a SC injection, Q4W for 48 weeks and TLR7 agonist, 150 mg tablets, orally, QOD during Weeks 13-24 and Weeks 37-48 in addition to their background NUC therapy. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Arm type	Experimental
Investigational medicinal product name	siRNA
Investigational medicinal product code	RO7445482
Other name	Xalnesiran, DCR-HBVS
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

siRNA, 200 mg, as an SC injection, Q4W during Weeks 13-24 and Weeks 37-48.

Investigational medicinal product name	NUC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

NUC tablets, orally up to follow up Week 48.

Investigational medicinal product name	TLR7
Investigational medicinal product code	RO7020531
Other name	Ruzotolimod
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TLR7, 150 mg tablets, orally, QOD during Weeks 13-24 and Weeks 37-48.

Arm title	Combo 7: siRNA + PD-L1 LNA + NUC
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Arm description:

Participants received siRNA, 200 mg, as a SC injection, Q4W up to Week 24 and programmed death ligand-1 locked nucleic acid (PD-L1 LNA), 2 milligrams/kilograms (mg/kg), as a SC injection, QW during Weeks 13-24 in addition to their background NUC therapy for 24 weeks. After Week 24, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Arm type	Experimental
Investigational medicinal product name	siRNA
Investigational medicinal product code	RO7445482
Other name	Xalnesiran, DCR-HBVS
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

siRNA, 200 mg, as an SC injection, Q4W up to Week 24.

Investigational medicinal product name	NUC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

NUC tablets, orally up to follow up Week 24.

Investigational medicinal product name	PD-L1 LNA
Investigational medicinal product code	RO7191863
Other name	Cadapersen
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PD-L1 LNA, 2 mg/kg, as a SC injection, QW during Weeks 13-24.

Arm title	Combo 8: siRNA + PD-L1 LNA + NUC
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Arm description:

Participants received siRNA, 200 mg, as a SC injection, Q4W up to Week 24 and PD-L1 LNA, 2 mg/kg, as a SC injection, QW during Weeks 25-36 in addition to their background NUC therapy for 36 weeks. After Week 36, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Arm type	Experimental
Investigational medicinal product name	siRNA
Investigational medicinal product code	RO7445482
Other name	Xalnesiran, DCR-HBVS
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

siRNA, 200 mg, as an SC injection, Q4W up to Week 24.

Investigational medicinal product name	NUC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

NUC tablets, orally up to follow up Week 36.

Investigational medicinal product name	PD-L1 LNA
Investigational medicinal product code	RO7191863
Other name	Cadapersen
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PD-L1 LNA, 2 mg/kg, as a SC injection, QW during Weeks 25-36.

Number of subjects in period 1	NUC Control Arm	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC
Started	36	38	30
Completed	30	37	29
Not completed	6	1	1
Consent withdrawn by subject	4	1	1
Adverse event, non-fatal	-	-	-
Arm Terminated By Sponsor	-	-	-
Reason not Specified	1	-	-
Protocol deviation	1	-	-

Number of subjects in period 1	Combo 3: siRNA (200 mg) + NUC	Combo 4: siRNA + PEG-IFN + NUC	Combo 5: siRNA + CpAM + NUC
Started	30	30	19
Completed	30	27	9
Not completed	0	3	10
Consent withdrawn by subject	-	3	1
Adverse event, non-fatal	-	-	-
Arm Terminated By Sponsor	-	-	-
Reason not Specified	-	-	-
Protocol deviation	-	-	9

Number of subjects in period 1	Combo 6: siRNA + TLR7 Agonist + NUC	Combo 7: siRNA + PD-L1 LNA + NUC	Combo 8: siRNA + PD-L1 LNA + NUC
Started	34	33	31
Completed	33	15	12
Not completed	1	18	19
Consent withdrawn by subject	1	1	-
Adverse event, non-fatal	-	-	1
Arm Terminated By Sponsor	-	17	18
Reason not Specified	-	-	-
Protocol deviation	-	-	-

Baseline characteristics

Reporting groups

Reporting group title	NUC Control Arm
Reporting group description: Participants continued their background NUC therapy for 48 weeks. Thereafter, in line with current CHB treatment guidelines, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 1: CpAM + TLR7 Agonist + NUC
Reporting group description: Participants received core protein allosteric modulator (CpAM), 600 milligrams (mg) tablets, orally, once daily (QD) for 48 weeks and toll-like receptor 7 (TLR7) agonist, 150 mg, orally, once every other day (QOD) during Weeks 1-12 and Weeks 25-36 in addition to their background NUC therapy. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 2: siRNA (100 mg) + NUC
Reporting group description: Participants received short interfering ribonucleic acid (siRNA), 100 mg, as a subcutaneous (SC) injection, every 4 weeks (Q4W) in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 3: siRNA (200 mg) + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 4: siRNA + PEG-IFN + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W and pegylated interferon (PEG-IFN), 180 micrograms (µg), as a SC injection, every week (QW) in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 5: siRNA + CpAM + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W and CpAM, 600 mg tablets, orally, QD in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 6: siRNA + TLR7 Agonist + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W for 48 weeks and TLR7 agonist, 150 mg tablets, orally, QOD during Weeks 13-24 and Weeks 37-48 in addition to their background NUC therapy. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 7: siRNA + PD-L1 LNA + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W up to Week 24 and programmed death ligand-1 locked nucleic acid (PD-L1 LNA), 2 milligrams/kilograms (mg/kg), as a SC injection, QW during Weeks 13-24 in addition to their background NUC therapy for 24 weeks. After Week 24, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 8: siRNA + PD-L1 LNA + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W up to Week 24 and PD-L1 LNA, 2 mg/kg, as a SC injection, QW during Weeks 25-36 in addition to their background NUC therapy for 36 weeks. After Week 36, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	

Reporting group values	NUC Control Arm	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC
Number of subjects	36	38	30
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	43.64	46.03	42.83
standard deviation	± 9.2	± 9.84	± 10.69
Sex: Female, Male Units: participants			
Female	8	9	1
Male	28	29	29
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	33	34	26
Native Hawaiian or Other Pacific Islander	1	1	1
Black or African American	0	0	0
White	2	3	3
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	35	37	30
Unknown or Not Reported	0	0	0

Reporting group values	Combo 3: siRNA (200 mg) + NUC	Combo 4: siRNA + PEG-IFN + NUC	Combo 5: siRNA + CpAM + NUC
Number of subjects	30	30	19
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	39.97	38.07	38.95
standard deviation	± 11.03	± 9.54	± 9.77
Sex: Female, Male Units: participants			
Female	10	5	5
Male	20	25	14
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	29	30	19
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	1	0	0
More than one race	0	0	0

Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	30	30	19
Unknown or Not Reported	0	0	0

Reporting group values	Combo 6: siRNA + TLR7 Agonist + NUC	Combo 7: siRNA + PD-L1 LNA + NUC	Combo 8: siRNA + PD-L1 LNA + NUC
Number of subjects	34	33	31
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	42.59	49.7	48.84
standard deviation	± 8.46	± 8.87	± 8.36
Sex: Female, Male			
Units: participants			
Female	4	10	6
Male	30	23	25
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	32	22	22
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	1
White	0	9	8
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	34	33	30
Unknown or Not Reported	0	0	1

Reporting group values	Total		
Number of subjects	281		
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: participants			
Female	58		
Male	223		

Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	247		
Native Hawaiian or Other Pacific Islander	3		
Black or African American	5		
White	26		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	278		
Unknown or Not Reported	1		

End points

End points reporting groups

Reporting group title	NUC Control Arm
Reporting group description: Participants continued their background NUC therapy for 48 weeks. Thereafter, in line with current CHB treatment guidelines, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 1: CpAM + TLR7 Agonist + NUC
Reporting group description: Participants received core protein allosteric modulator (CpAM), 600 milligrams (mg) tablets, orally, once daily (QD) for 48 weeks and toll-like receptor 7 (TLR7) agonist, 150 mg, orally, once every other day (QOD) during Weeks 1-12 and Weeks 25-36 in addition to their background NUC therapy. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 2: siRNA (100 mg) + NUC
Reporting group description: Participants received short interfering ribonucleic acid (siRNA), 100 mg, as a subcutaneous (SC) injection, every 4 weeks (Q4W) in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 3: siRNA (200 mg) + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 4: siRNA + PEG-IFN + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W and pegylated interferon (PEG-IFN), 180 micrograms (µg), as a SC injection, every week (QW) in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 5: siRNA + CpAM + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W and CpAM, 600 mg tablets, orally, QD in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 6: siRNA + TLR7 Agonist + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W for 48 weeks and TLR7 agonist, 150 mg tablets, orally, QOD during Weeks 13-24 and Weeks 37-48 in addition to their background NUC therapy. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 7: siRNA + PD-L1 LNA + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W up to Week 24 and programmed death ligand-1 locked nucleic acid (PD-L1 LNA), 2 milligrams/kilograms (mg/kg), as a SC injection, QW during Weeks 13-24 in addition to their background NUC therapy for 24 weeks. After Week 24, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Reporting group title	Combo 8: siRNA + PD-L1 LNA + NUC
Reporting group description: Participants received siRNA, 200 mg, as a SC injection, Q4W up to Week 24 and PD-L1 LNA, 2 mg/kg, as a SC injection, QW during Weeks 25-36 in addition to their background NUC therapy for 36 weeks. After Week 36, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	
Subject analysis set title	Combo 7 and 8: siRNA + PD-L1 LNA + NUC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received siRNA, 200 mg, as a SC injection, Q4W up to Week 24 and PD-L1 LNA, 2 mg/kg, as a SC injection, QW during Weeks 13-24 (Combo 7)/ Weeks 25-36 (Combo 8) in addition to their background NUC therapy for 24 weeks (Combo 7)/ 36 weeks (Combo 8). After Week 24/36, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Primary: Percentage of Participants with Hepatitis B Surface Antigen (HBsAg) Loss at 24 Weeks Post-End of Treatment (EOT)

End point title	Percentage of Participants with Hepatitis B Surface Antigen (HBsAg) Loss at 24 Weeks Post-End of Treatment (EOT)
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End point description:

HBsAg loss was defined as quantitative HBsAg <0.05 international units/milliliters (IU/mL). The percentage of participants with HBsAg loss was calculated as number of participants with HBsAg loss / total number of participants *100. 95% confidence interval (CI) was calculated using the Clopper-Pearson method. Modified Intent to Treat (mITT) population included participants who were randomized and received at least one dose of each drug for their assigned treatment regimen. Percentages have been rounded off.

End point type	Primary
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End point timeframe:

Follow-up Week (FUW) 24

End point values	NUC Control Arm	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	35	30	30
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 10)	0 (0 to 0)	6.7 (0.8 to 22.1)	3.3 (0.1 to 17.2)

End point values	Combo 4: siRNA + PEG-IFN + NUC	Combo 5: siRNA + CpAM + NUC	Combo 6: siRNA + TLR7 Agonist + NUC	Combo 7: siRNA + PD-L1 LNA + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	9	34	33
Units: percentage of participants				
number (confidence interval 95%)	23.3 (9.9 to 42.3)	0 (0 to 0)	11.8 (3.3 to 27.5)	0 (0 to 10.6)

End point values	Combo 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage of participants				
number (confidence interval 95%)	6.7 (0.8 to 22.1)			

Statistical analyses

Statistical analysis title	NUC vs Combo 2
Statistical analysis description: 95% CI for difference of two proportions was calculated using Cochran-Mantel-Haenszel (CMH) method.	
Comparison groups	NUC Control Arm v Combo 2: siRNA (100 mg) + NUC
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	16.4

Statistical analysis title	NUC vs Combo 8
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	
Comparison groups	NUC Control Arm v Combo 8: siRNA + PD-L1 LNA + NUC
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	15.7

Statistical analysis title	NUC vs Combo 6
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	
Comparison groups	NUC Control Arm v Combo 6: siRNA + TLR7 Agonist + NUC

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	12.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	23.3

Statistical analysis title	NUC vs Combo 5
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	
Comparison groups	NUC Control Arm v Combo 7: siRNA + PD-L1 LNA + NUC
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	NUC vs Combo 3
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	
Comparison groups	NUC Control Arm v Combo 3: siRNA (200 mg) + NUC
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	10

Statistical analysis title	NUC vs Combo 4
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	

Comparison groups	NUC Control Arm v Combo 4: siRNA + PEG-IFN + NUC
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	24.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	9
upper limit	39.5

Secondary: Percentage of Participants With HBsAg loss

End point title	Percentage of Participants With HBsAg loss
End point description:	
HBsAg loss was defined as quantitative HBsAg <0.05 IU/mL. The percentage of participants with HBsAg loss was calculated as number of participants with HBsAg loss / total number of participants *100. 95% CI was calculated using the Clopper-Pearson method. Percentages have been rounded off. mITT population included participants who were randomized and received at least one dose of each drug for their assigned treatment regimen. n = participants with data available for analysis at that specified timepoint. 9999= No participants were analyzed for this timepoint.	
End point type	Secondary
End point timeframe:	
Combos 2, 3, 4, 6 and NUC Arm: Week 48 and FUW 48; Combo 7: Week 24; Combo 8: Week 36	

End point values	NUC Control Arm	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	36	30	30
Units: percentage of participants				
number (confidence interval 95%)				
Week 24 (n=0,36,0,0,0,4,0,33,0)	9999 (9999 to 9999)	0 (0 to 0)	9999 (9999 to 9999)	9999 (9999 to 9999)
Week 36 (n=0,23,0,0,0,1,0,0,30)	9999 (9999 to 9999)	0 (0 to 0)	9999 (9999 to 9999)	9999 (9999 to 9999)
Week 48 (n=35,20,30,30,30,4,30,0,0)	0 (0 to 10)	0 (0 to 0)	6.7 (0.8 to 22.1)	3.3 (0.1 to 17.2)
FUW 48 (n=35,28,30,30,30,1,34,0,0)	2.9 (0.1 to 14.9)	0 (0 to 0)	10 (2.1 to 26.5)	0 (0 to 11.6)

End point values	Combo 4: siRNA + PEG-IFN + NUC	Combo 5: siRNA + CpAM + NUC	Combo 6: siRNA + TLR7 Agonist + NUC	Combo 7: siRNA + PD-L1 LNA + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	4	34	33
Units: percentage of participants				

number (confidence interval 95%)				
Week 24 (n=0,36,0,0,0,4,0,33,0)	9999 (9999 to 9999)	0 (0 to 0)	9999 (9999 to 9999)	6.1 (0.7 to 20.2)
Week 36 (n=0,23,0,0,0,1,0,0,30)	9999 (9999 to 9999)	0 (0 to 0)	9999 (9999 to 9999)	9999 (9999 to 9999)
Week 48 (n=35,20,30,30,30,4,30,0,0)	30 (14.7 to 49.4)	0 (0 to 0)	17.6 (6.8 to 34.5)	9999 (9999 to 9999)
FUW 48 (n=35,28,30,30,30,1,34,0,0)	16.7 (5.6 to 34.7)	0 (0 to 0)	11.8 (3.3 to 27.5)	9999 (9999 to 9999)

End point values	Combo 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage of participants				
number (confidence interval 95%)				
Week 24 (n=0,36,0,0,0,4,0,33,0)	9999 (9999 to 9999)			
Week 36 (n=0,23,0,0,0,1,0,0,30)	13.3 (3.8 to 30.7)			
Week 48 (n=35,20,30,30,30,4,30,0,0)	9999 (9999 to 9999)			
FUW 48 (n=35,28,30,30,30,1,34,0,0)	9999 (9999 to 9999)			

Statistical analyses

Statistical analysis title	NUC vs Combo 7: Week 24
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	
Comparison groups	NUC Control Arm v Combo 7: siRNA + PD-L1 LNA + NUC
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	6.2
Point estimate	6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	14.5

Statistical analysis title	NUC vs Combo 8: Week 36
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	
Comparison groups	NUC Control Arm v Combo 8: siRNA + PD-L1 LNA + NUC

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	13.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	25.6

Statistical analysis title	Combo 2: Week 48
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	
Comparison groups	NUC Control Arm v Combo 2: siRNA (100 mg) + NUC
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	16.4

Statistical analysis title	NUC vs Combo 3: Week 48
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	
Comparison groups	NUC Control Arm v Combo 3: siRNA (200 mg) + NUC
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	10

Statistical analysis title	NUC vs Combo 4: Week 48
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	

Comparison groups	NUC Control Arm v Combo 4: siRNA + PEG-IFN + NUC
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	31.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.7
upper limit	47.6

Statistical analysis title	NUC vs Combo 3: FUW 48
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	
Comparison groups	NUC Control Arm v Combo 3: siRNA (200 mg) + NUC
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	2.7

Statistical analysis title	NUC vs Combo 6: Week 48
Statistical analysis description: 95% CI for difference of two proportions was calculated using CMH method.	
Comparison groups	NUC Control Arm v Combo 6: siRNA + TLR7 Agonist + NUC
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	18.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	31.4

Statistical analysis title	NUC vs Combo 2: FUW 48
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Statistical analysis description:

95% CI for difference of two proportions was calculated using CMH method.

Comparison groups	NUC Control Arm v Combo 2: siRNA (100 mg) + NUC
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	20.1

Statistical analysis title

NUC vs Combo 4: FUW 48

Statistical analysis description:

95% CI for difference of two proportions was calculated using CMH method.

Comparison groups	NUC Control Arm v Combo 4: siRNA + PEG-IFN + NUC
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	28.8

Statistical analysis title

NUC vs Combo 6: FUW 48

Statistical analysis description:

95% CI for difference of two proportions was calculated using CMH method.

Comparison groups	NUC Control Arm v Combo 6: siRNA + TLR7 Agonist + NUC
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Response Rate
Point estimate	9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	21.5

Secondary: Percentage of Participants With HBsAg Seroconversion

End point title	Percentage of Participants With HBsAg Seroconversion
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End point description:

HBsAg seroconversion was defined as a quantitative HBsAg < 0.05 IU/mL and a positive anti-HBs antibody (defined as per assay reactive threshold anti-HBs ≥10 IU/L). 95% CI was calculated using the Clopper-Pearson method. Percentages have been rounded off. mITT population included participants who were randomized and received at least one dose of each drug for their assigned treatment regimen. Number analyzed included participants with data available for analysis at that specified timepoint. n = participants with data available for analysis at that specified timepoint. 9999= No participants were analyzed for this timepoint.

End point type	Secondary
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End point timeframe:

Combos 2, 3, 4, 6 and NUC Arm: Week 48, FUW 24 and FUW 48; Combo 7: Week 24 and FUW 24; Combo 8: Week 36 and FUW 24

End point values	NUC Control Arm	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	36	30	30
Units: percentage of participants				
number (confidence interval 95%)				
Week 24 (n=0,36,0,0,0,9,0,33,0)	9999 (9999 to 9999)	0 (0 to 0)	9999 (9999 to 9999)	9999 (9999 to 9999)
Week 36 (n=0,23,0,0,0,1,0,0,30)	9999 (9999 to 9999)	0 (0 to 0)	9999 (9999 to 9999)	9999 (9999 to 9999)
Week 48 (n=35,20,30,30,30,4,34,0,0)	0 (0 to 10)	0 (0 to 0)	3.3 (0.1 to 17.2)	0 (0 to 11.6)
FUW 24 (n=35,35,30,30,30,9,34,33,30)	0 (0 to 10)	0 (0 to 0)	3.3 (0.1 to 17.2)	0 (0 to 11.6)
FUW 48 (n=35,28,30,30,30,1,34,0,0)	2.9 (0.1 to 14.9)	0 (0 to 0)	3.3 (0.1 to 17.2)	0 (0 to 11.6)

End point values	Combo 4: siRNA + PEG-IFN + NUC	Combo 5: siRNA + CpAM + NUC	Combo 6: siRNA + TLR7 Agonist + NUC	Combo 7: siRNA + PD-L1 LNA + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	9	34	33
Units: percentage of participants				
number (confidence interval 95%)				
Week 24 (n=0,36,0,0,0,9,0,33,0)	9999 (9999 to 9999)	0 (0 to 0)	9999 (9999 to 9999)	0 (0 to 10.6)
Week 36 (n=0,23,0,0,0,1,0,0,30)	9999 (9999 to 9999)	0 (0 to 0)	9999 (9999 to 9999)	9999 (9999 to 9999)
Week 48 (n=35,20,30,30,30,4,34,0,0)	23.3 (9.9 to 42.3)	0 (0 to 0)	0 (0 to 10.3)	9999 (9999 to 9999)
FUW 24 (n=35,35,30,30,30,9,34,33,30)	20 (7.7 to 38.6)	0 (0 to 0)	3.1 (0.1 to 16.2)	0 (0 to 10.9)
FUW 48 (n=35,28,30,30,30,1,34,0,0)	16.7 (5.6 to 34.7)	0 (0 to 0)	5.9 (0.7 to 19.7)	9999 (9999 to 9999)

End point values	Combo 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage of participants				
number (confidence interval 95%)				
Week 24 (n=0,36,0,0,0,9,0,33,0)	9999 (9999 to 9999)			
Week 36 (n=0,23,0,0,0,1,0,0,30)	0 (0 to 11.9)			
Week 48 (n=35,20,30,30,30,4,34,0,0)	9999 (9999 to 9999)			
FUW 24 (n=35,35,30,30,30,9,34,33,30)	0 (0 to 11.6)			
FUW 48 (n=35,28,30,30,30,1,34,0,0)	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Hepatitis B Early Antigen (HBeAg) Loss in Baseline HBeAg-positive Participants

End point title	Percentage of Participants With Hepatitis B Early Antigen (HBeAg) Loss in Baseline HBeAg-positive Participants
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End point description:

HBeAg loss was defined as negative /non-reactive HBeAg level. Percentages have been rounded off. mITT population included participants who were randomized and received at least one dose of each drug for their assigned treatment regimen. Number analyzed included participants from the mITT population who were positive for HBeAg at baseline. n = participants with data available for analysis at that specified timepoint. 9999= No participants were analyzed for this timepoint.

End point type	Secondary
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End point timeframe:

Weeks 12, 24, 36, and 48; FUW 12, 24, 36, and 48

End point values	NUC Control Arm	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	9	8
Units: percentage of participants				
number (not applicable)				
Week 12 (n=8,8,9,8,12,7,10,9,5)	0	0	22.2	50
Week 24 (n=7,8,8,8,12,2,7,9,5)	0	0	37.5	50
Week 36 (n=7,5,9,4,9,0,10,0,5)	14.3	0	44.4	25
Week 48 (n=8,5,9,8,11,2,10,0,0)	12.5	20	44.4	62.5
FUW 12 (n=6,8,7,8,11,3,9,9,5)	16.7	0	42.9	62.5
FUW 24 (n=7,8,8,8,11,3,9,9,5)	14.3	0	12.5	50

FUW 36 (n=8,8,8,8,11,0,9,6,3)	12.5	0	12.5	50
FUW 48 (n=7,8,9,8,11,0,9,5,0)	14.3	25	33.3	50

End point values	Combo 4: siRNA + PEG- IFN + NUC	Combo 5: siRNA + CpAM + NUC	Combo 6: siRNA + TLR7 Agonist + NUC	Combo 7: siRNA + PD-L1 LNA + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	7	10	9
Units: percentage of participants				
number (not applicable)				
Week 12 (n=8,8,9,8,12,7,10,9,5)	33.3	28.6	30	11.1
Week 24 (n=7,8,8,8,12,2,7,9,5)	41.7	50	28.6	11.1
Week 36 (n=7,5,9,4,9,0,10,0,5)	55.6	9999	50	9999
Week 48 (n=8,5,9,8,11,2,10,0,0)	54.5	50	50	9999
FUW 12 (n=6,8,7,8,11,3,9,9,5)	54.5	33.3	44.4	11.1
FUW 24 (n=7,8,8,8,11,3,9,9,5)	36.4	66.7	44.4	11.1
FUW 36 (n=8,8,8,8,11,0,9,6,3)	27.3	9999	33.3	0
FUW 48 (n=7,8,9,8,11,0,9,5,0)	27.3	9999	44.4	0

End point values	Combo 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percentage of participants				
number (not applicable)				
Week 12 (n=8,8,9,8,12,7,10,9,5)	40			
Week 24 (n=7,8,8,8,12,2,7,9,5)	40			
Week 36 (n=7,5,9,4,9,0,10,0,5)	40			
Week 48 (n=8,5,9,8,11,2,10,0,0)	9999			
FUW 12 (n=6,8,7,8,11,3,9,9,5)	20			
FUW 24 (n=7,8,8,8,11,3,9,9,5)	60			
FUW 36 (n=8,8,8,8,11,0,9,6,3)	66.7			
FUW 48 (n=7,8,9,8,11,0,9,5,0)	9999			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBeAg Seroconversion in Baseline HBeAg-positive Participants

End point title	Percentage of Participants With HBeAg Seroconversion in Baseline HBeAg-positive Participants
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End point description:

HBeAg seroconversion was defined as a negative /non-reactive HBeAg level and a positive anti-HBe antibody. Percentages have been rounded off. Number analyzed included participants from the mITT

population who were positive for HBeAg at baseline. n = participants with data available for analysis at that specified timepoint. 9999= No participants were analyzed for this timepoint.

End point type	Secondary
End point timeframe:	
Weeks 12, 24, 36, and 48; FUW 12, 24, 36, and 48	

End point values	NUC Control Arm	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	9	8
Units: percentage of participants				
number (not applicable)				
Week 12 (n=8,8,9,8,12,7,10,9,5)	0	0	11.1	0
Week 24 (n=7,8,8,8,12,2,7,9,5)	0	0	0	12.5
Week 36 (n=7,5,9,4,9,0,10,0,5)	0	0	11.1	0
Week 48 (n=8,5,9,8,11,2,10,0,0)	0	0	11.1	12.5
FUW 12 (n=6,8,7,8,11,3,9,9,5)	16.7	0	14.3	12.5
FUW 24 (n=7,8,8,8,11,3,9,9,5)	14.3	0	0	25
FUW 36 (n=8,8,8,8,11,0,9,6,3)	12.5	0	0	25
FUW 48 (n=7,8,9,8,11,0,9,5,0)	14.3	25	11.1	37.5

End point values	Combo 4: siRNA + PEG-IFN + NUC	Combo 5: siRNA + CpAM + NUC	Combo 6: siRNA + TLR7 Agonist + NUC	Combo 7: siRNA + PD-L1 LNA + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	7	10	9
Units: percentage of participants				
number (not applicable)				
Week 12 (n=8,8,9,8,12,7,10,9,5)	8.3	14.3	0	0
Week 24 (n=7,8,8,8,12,2,7,9,5)	8.3	0	0	0
Week 36 (n=7,5,9,4,9,0,10,0,5)	11.1	9999	10	9999
Week 48 (n=8,5,9,8,11,2,10,0,0)	18.2	0	10	9999
FUW 12 (n=6,8,7,8,11,3,9,9,5)	18.2	0	11.1	0
FUW 24 (n=7,8,8,8,11,3,9,9,5)	9.1	33.3	11.1	0
FUW 36 (n=8,8,8,8,11,0,9,6,3)	9.1	9999	11.1	0
FUW 48 (n=7,8,9,8,11,0,9,5,0)	9.1	9999	33.3	0

End point values	Combo 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percentage of participants				
number (not applicable)				
Week 12 (n=8,8,9,8,12,7,10,9,5)	0			

Week 24 (n=7,8,8,8,12,2,7,9,5)	0			
Week 36 (n=7,5,9,4,9,0,10,0,5)	0			
Week 48 (n=8,5,9,8,11,2,10,0,0)	9999			
FUW 12 (n=6,8,7,8,11,3,9,9,5)	0			
FUW 24 (n=7,8,8,8,11,3,9,9,5)	0			
FUW 36 (n=8,8,8,8,11,0,9,6,3)	0			
FUW 48 (n=7,8,9,8,11,0,9,5,0)	9999			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Hepatitis B Virus Deoxyribonucleic Acid (HBV DNA) < Lower Limit of Quantification (LLOQ), <200 IU/mL, and <2,000 IU/mL

End point title	Number of Participants With Hepatitis B Virus Deoxyribonucleic Acid (HBV DNA) < Lower Limit of Quantification (LLOQ), <200 IU/mL, and <2,000 IU/mL
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End point description:

Chronic HBV infection is characterized by high levels of circulating HBV DNA. Therefore, HBV levels are indicative of virological response. At screening participants were on NUC therapy and had circulating HBV DNA levels below the assay LLOQ or below 20 IU/mL for at least 6 months. The emergence of a virological breakthrough (HBV DNA >100 IU/mL or >1 log increase from nadir) while on NUC therapy, or the emergence of a virological relapse (>2,000 IU/mL) in participants taken off NME combination and NUC therapy during follow-up, was monitored through the quantification of HBV DNA in plasma. mITT population included participants who were randomized and received at least one dose of each drug for their assigned treatment regimen. n = participants with data available for analysis at that specified timepoint. Different participants may have contributed data for each timepoint. 9999= No participants were analyzed for this timepoint.

End point type	Secondary
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End point timeframe:

FUW 12, 24, 36, and 48

End point values	NUC Control Arm	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	35	30	30
Units: participants				
FUW12: OFFNUC(<LLOQ;n=1,0,5,6,5,0,10,3,5)	0	9999	3	4
FUW12: OFFNUC(≥LLOQ-<20IU/mL;n=1,0,0,0,0,0,3,5)	1	9999	9999	9999
FUW12: OFFNUC(≥20 - <200IU/mL;n=1,0,0,0,0,0,3,5)	0	9999	9999	9999
FUW12:OFFNUC(≥LLOQ-<200IU/mL;n=1,0,5,6,5,0,10,0,0)	0	9999	1	1
FUW12:OFFNUC(≥200-<2000IU/mL;n=1,0,5,6,5,0,10,3,5)	0	9999	1	1
FUW12: OFFNUC(≥2000IU/mL;n=1,0,5,6,5,0,10,3,5)	0	9999	0	0
FUW12: ON NUC(<LLOQ;n=28,32,19,23,21,8,20,30,	28	32	19	23

FUW12:ONNUC(≥LLOQ- <20IU/mL;n=28,32,0,0,0,0,8,30,25	0	0	9999	9999
FUW12:ONNUC(≥20- <200IU/mL;n=28,32,0,0,0,0,8,30,25	0	0	9999	9999
FUW12:ONNUC(≥LLOQ- <200IU/mL;n=28,0,0,0,0,0,0,30,25	0	9999	0	0
FW12:ONNUC(≥200- 2000;n=28,32,19,23,21,8,20,30,25	0	0	0	0
FUW12:ONNUC(≥2000IU/mL;n=28,32,1 9,23,21,8,20,30,25	0	0	0	0
FUW24:OFFNUC(<LLOQ;n=2,0,4,5,7,0, 12,8,9)	0	9999	2	3
FUW24:OFFNUC(≥LLOQ- <20IU/mL;n=2,0,0,0,0,0,0,8,9)	0	9999	9999	9999
FUW24:OFFNUC(≥20- <200IU/mL;n=2,0,0,0,0,0,0,8,9)	1	9999	9999	9999
FUW24:OFFNUC(≥LLOQ- <200IU/mL;n=2,0,4,5,7,0,12,0,0)	0	9999	2	0
FUW24:OFFNUC(≥200- <2000IU/mL;n=2,0,4,5,7,0,12,8,9)	0	9999	0	2
FUW24:OFFNUC(≥2000IU/mL;n=2,0,4, 5,7,0,12,8,9)	1	9999	0	0
FUW24:ON NUC(<LLOQ;n=27,35,24,24,20,9,21,24,	27	35	22	24
FUW24:ONNUC(≥LLOQ- <20IU/mL;n=27,35,0,0,0,9,0,24,21	0	0	9999	9999
FUW24:ONNUC(≥20- <200IU/mL;n=27,35,0,0,0,9,0,24,21	0	0	9999	9999
FUW24:ONNUC(≥LLOQ- <200;n=27,0,24,24,20,0,21,0,0	0	9999	1	0
FUW24:ONNUC(≥200- <2000;n=27,35,24,24,20,9,21,24,21	0	0	0	0
FUW24:ONNUC(≥2000IU/mL;n=27,35,2 4,24,20,9,21,24,21	0	0	1	0
FUW36:OFFNUC(<LLOQ)(n=1,0,3,5,6,0, 9,5,6)	0	9999	1	3
FUW36:OFFNUC(≥LLOQ- <20IU/mL;n=1,0,0,0,0,0,0,5,6)	0	9999	9999	9999
FUW36:OFFNUC(≥20- <200IU/mL;n=1,0,0,0,0,0,0,5,6)	0	9999	9999	9999
FUW36:OFFNUC(≥LLOQ - <200IU/mL;n=1,0,3,5,6,0,9,0,0)	0	9999	1	0
FUW36:OFFNUC(≥200- <2000IU/mL;n=1,0,3,5,6,0,9,5,6)	1	9999	0	2
FUW36:OFFNUC(≥2000IU/mL;n=1,0,3, 5,6,0,9,5,6)	0	9999	1	0
FUW36:ON NUC(<LLOQ;n=29,31,25,25,21,1,24,17,	29	31	24	25
FUW36:ONNUC(≥LLOQ- <20IU/mL;n=29,31,0,0,0,1,0,17,13	0	0	9999	9999
FUW36:ONNUC(≥20- <200IU/mL;n=29,31,0,0,0,1,0,17,13)	0	0	9999	9999
FUW36:ONNUC(≥LLOQ- <200;n=29,0,25,25,21,0,24,0,0	0	9999	1	0
FUW36:ONNUC(≥200- <2000;n=29,31,25,25,21,1,24,17,13	0	0	0	0
FUW36:ONNUC(≥2000IU/mL;n=29,31,2 5,25,21,1,24,17,13	0	0	0	0
FUW48:OFFNUC(<LLOQ)(n=0,0,2,7,6,0, 9,5,4)	9999	9999	0	5
FUW48:OFFNUC(≥LLOQ - <20IU/mL;n=0,0,0,0,0,0,0,5,4)	9999	9999	9999	9999

FUW48:OFFNUC(≥20- <200IU/mL;n=0,0,0,0,0,0,5,4)	9999	9999	9999	9999
FUW48:OFFNUC(≥LLOQ- <200IU/mL;n=0,0,2,7,6,0,9,5,4)	9999	9999	1	0
FUW48:OFFNUC(≥200- <2000IU/mL;n=0,0,2,7,6,0,9,5,4)	9999	9999	1	2
FUW48:OFFNUC(≥2000IU/mL;n=0,0,2, 7,6,0,9,5,4)	9999	9999	0	0
FUW48:ON NUC(<LLOQ;n=30,28,27,23,21,1,23,10,	30	28	27	23
FUW48:ON NUC(≥LLOQ - <20;n=30,28,0,0,0,1,0,10,8	0	0	9999	9999
FUW48:ONNUC(≥20- <200IU/mL;n=30,28,0,0,0,1,0,10,8	0	0	9999	9999
FUW48:ON NUC(≥LLOQ- <200;n=30,0,27,23,21,0,23,0,0	0	9999	0	0
FUW48:ONNUC(≥200-< 2000;n=30,28,27,23,21,1,23,10,8	0	0	0	0
FUW48:ON NUC(≥2000IU/mL;n=30,28,27,23,21,1,	0	0	0	0

End point values	Combo 4: siRNA + PEG- IFN + NUC	Combo 5: siRNA + CpAM + NUC	Combo 6: siRNA + TLR7 Agonist + NUC	Combo 7: siRNA + PD-L1 LNA + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	9	34	33
Units: participants				
FUW12: OFFNUC(<LLOQ;n=1,0,5,6,5,0,10,3,5)	4	9999	7	2
FUW12: OFFNUC(≥LLOQ- <20IU/mL;n=1,0,0,0,0,0,0,3,5)	9999	9999	9999	1
FUW12: OFFNUC(≥20 - <200IU/mL;n=1,0,0,0,0,0,0,3,5)	9999	9999	9999	0
FUW12:OFFNUC(≥LLOQ- <200IU/mL;n=1,0,5,6,5,0,10,0,0)	0	9999	2	9999
FUW12:OFFNUC(≥200- <2000IU/mL;n=1,0,5,6,5,0,10,3,5)	1	9999	1	0
FUW12: OFFNUC(≥2000IU/mL;n=1,0,5,6,5,0,10	0	9999	0	0
FUW12: ON NUC(<LLOQ;n=28,32,19,23,21,8,20,30,	21	8	20	30
FUW12:ONNUC(≥LLOQ- <20IU/mL;n=28,32,0,0,0,0,8,30,25	9999	0	9999	0
FUW12:ONNUC(≥20- <200IU/mL;n=28,32,0,0,0,0,8,30,25	9999	0	9999	0
FUW12:ONNUC(≥LLOQ- <200IU/mL;n=28,0,0,0,0,0,0,30,25	0	9999	0	9999
FW12:ONNUC(≥200-< 2000;n=28,32,19,23,21,8,20,30,25	0	0	0	0
FUW12:ONNUC(≥2000IU/mL;n=28,32,1 9,23,21,8,20,30,25	0	0	0	0
FUW24:OFFNUC(<LLOQ;n=2,0,4,5,7,0, 12,8,9)	6	9999	5	5
FUW24:OFFNUC(≥LLOQ- <20IU/mL;n=2,0,0,0,0,0,0,8,9)	9999	9999	9999	0
FUW24:OFFNUC(≥20- <200IU/mL;n=2,0,0,0,0,0,0,8,9)	9999	9999	9999	2

FUW24:OFFNUC(\geq LLOQ- <200IU/mL;n=2,0,4,5,7,0,12,0,0)	0	9999	5	9999
FUW24:OFFNUC(\geq 200- <2000IU/mL;n=2,0,4,5,7,0,12,8,9)	1	9999	2	1
FUW24:OFFNUC(\geq 2000IU/mL;n=2,0,4, 5,7,0,12,8,9)	0	9999	0	0
FUW24:ON NUC(<LLOQ;n=27,35,24,24,20,9,21,24,	20	9	21	24
FUW24:ONNUC(\geq LLOQ- <20IU/mL;n=27,35,0,0,0,9,0,24,21	9999	0	9999	0
FUW24:ONNUC(\geq 20- <200IU/mL;n=27,35,0,0,0,9,0,24,21	9999	0	9999	0
FUW24:ONNUC(\geq LLOQ- <200;n=27,0,24,24,20,0,21,0,0	0	9999	0	9999
FUW24:ONNUC(\geq 200- <2000;n=27,35,24,24,20,9,21,24,21	0	0	0	0
FUW24:ONNUC(\geq 2000IU/mL;n=27,35,2, 4,24,20,9,21,24,21	0	0	0	0
FUW36:OFFNUC(<LLOQ)(n=1,0,3,5,6,0, 9,5,6)	6	9999	1	5
FUW36:OFFNUC(\geq LLOQ- <20IU/mL;n=1,0,0,0,0,0,0,5,6)	9999	9999	9999	0
FUW36:OFFNUC(\geq 20- <200IU/mL;n=1,0,0,0,0,0,0,5,6)	9999	9999	9999	0
FUW36:OFFNUC(\geq LLOQ - <200IU/mL;n=1,0,3,5,6,0,9,0,0)	0	9999	3	9999
FUW36:OFFNUC(\geq 200- <2000IU/mL;n=1,0,3,5,6,0,9,5,6)	0	9999	5	0
FUW36:OFFNUC(\geq 2000IU/mL;n=1,0,3, 5,6,0,9,5,6)	0	9999	0	0
FUW36:ON NUC(<LLOQ;n=29,31,25,25,21,1,24,17,	21	1	22	16
FUW36:ONNUC(\geq LLOQ- <20IU/mL;n=29,31,0,0,0,1,0,17,13	9999	0	9999	0
FUW36:ONNUC(\geq 20- <200IU/mL;n=29,31,0,0,0,1,0,17,13)	9999	0	9999	1
FUW36:ONNUC(\geq LLOQ- <200;n=29,0,25,25,21,0,24,0,0	0	9999	2	9999
FUW36:ONNUC(\geq 200- <2000;n=29,31,25,25,21,1,24,17,13	0	0	0	0
FUW36:ONNUC(\geq 2000IU/mL;n=29,31,2, 5,25,21,1,24,17,13	0	0	0	0
FUW48:OFFNUC(<LLOQ)(n=0,0,2,7,6,0, 9,5,4)	3	9999	3	4
FUW48:OFFNUC(\geq LLOQ - <20IU/mL;n=0,0,0,0,0,0,0,5,4)	9999	9999	9999	0
FUW48:OFFNUC(\geq 20- <200IU/mL;n=0,0,0,0,0,0,0,5,4)	9999	9999	9999	1
FUW48:OFFNUC(\geq LLOQ- <200IU/mL;n=0,0,2,7,6,0,9,5,4)	3	9999	4	9999
FUW48:OFFNUC(\geq 200- <2000IU/mL;n=0,0,2,7,6,0,9,5,4)	0	9999	2	0
FUW48:OFFNUC(\geq 2000IU/mL;n=0,0,2, 7,6,0,9,5,4)	0	9999	0	0
FUW48:ON NUC(<LLOQ;n=30,28,27,23,21,1,23,10,	21	1	23	10
FUW48:ON NUC(\geq LLOQ - <20;n=30,28,0,0,0,1,0,10,8	9999	0	0	0
FUW48:ONNUC(\geq 20- <200IU/mL;n=30,28,0,0,0,1,0,10,8	9999	0	9999	0
FUW48:ON NUC(\geq LLOQ- <200;n=30,0,27,23,21,0,23,0,0	0	9999	0	9999

FUW48:ONNUC(≥ 200 -<2000;n=30,28,27,23,21,1,23,10,8	0	0	0	0
FUW48:ONNUC(≥ 2000 IU/mL;n=30,28,27,23,21,1,	0	0	0	0

End point values	Combo 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: participants				
FUW12: OFFNUC(<LLOQ;n=1,0,5,6,5,0,10,3,5)	4			
FUW12: OFFNUC(\geq LLOQ-<20IU/mL;n=1,0,0,0,0,0,3,5)	0			
FUW12: OFFNUC(≥ 20 -<200IU/mL;n=1,0,0,0,0,0,3,5)	1			
FUW12:OFFNUC(\geq LLOQ-<200IU/mL;n=1,0,5,6,5,0,10,0,0)	9999			
FUW12:OFFNUC(≥ 200 -<2000IU/mL;n=1,0,5,6,5,0,10,3,5)	0			
FUW12: OFFNUC(≥ 2000 IU/mL;n=1,0,5,6,5,0,10	0			
FUW12: ON NUC(<LLOQ;n=28,32,19,23,21,8,20,30,	24			
FUW12:ONNUC(\geq LLOQ-<20IU/mL;n=28,32,0,0,0,0,8,30,25	0			
FUW12:ONNUC(≥ 20 -<200IU/mL;n=28,32,0,0,0,0,8,30,25	0			
FUW12:ONNUC(\geq LLOQ-<200IU/mL;n=28,0,0,0,0,0,30,25	9999			
FW12:ONNUC(≥ 200 -<2000;n=28,32,19,23,21,8,20,30,25	1			
FUW12:ONNUC(≥ 2000 IU/mL;n=28,32,19,23,21,8,20,30,25	0			
FUW24:OFFNUC(<LLOQ;n=2,0,4,5,7,0,12,8,9)	6			
FUW24:OFFNUC(\geq LLOQ-<20IU/mL;n=2,0,0,0,0,0,0,8,9)	0			
FUW24:OFFNUC(≥ 20 -<200IU/mL;n=2,0,0,0,0,0,0,8,9)	1			
FUW24:OFFNUC(\geq LLOQ-<200IU/mL;n=2,0,4,5,7,0,12,0,0)	9999			
FUW24:OFFNUC(≥ 200 -<2000IU/mL;n=2,0,4,5,7,0,12,8,9)	1			
FUW24:OFFNUC(≥ 2000 IU/mL;n=2,0,4,5,7,0,12,8,9)	1			
FUW24:ON NUC(<LLOQ;n=27,35,24,24,20,9,21,24,	21			
FUW24:ONNUC(\geq LLOQ-<20IU/mL;n=27,35,0,0,0,9,0,24,21	0			
FUW24:ONNUC(≥ 20 -<200IU/mL;n=27,35,0,0,0,9,0,24,21	0			
FUW24:ONNUC(\geq LLOQ-<200;n=27,0,24,24,20,0,21,0,0	9999			
FUW24:ONNUC(≥ 200 -<2000;n=27,35,24,24,20,9,21,24,21	0			

FUW24:ONNUC(≥ 2000 IU/mL;n=27,35,24,24,20,9,21,24,21	0			
FUW36:OFFNUC($< \text{LLOQ}$)(n=1,0,3,5,6,0,9,5,6)	3			
FUW36:OFFNUC($\geq \text{LLOQ}$ - < 20 IU/mL;n=1,0,0,0,0,0,0,5,6)	0			
FUW36:OFFNUC(≥ 20 - < 200 IU/mL;n=1,0,0,0,0,0,0,5,6)	2			
FUW36:OFFNUC($\geq \text{LLOQ}$ - < 200 IU/mL;n=1,0,3,5,6,0,9,0,0)	9999			
FUW36:OFFNUC(≥ 200 - < 2000 IU/mL;n=1,0,3,5,6,0,9,5,6)	0			
FUW36:OFFNUC(≥ 2000 IU/mL;n=1,0,3,5,6,0,9,5,6)	1			
FUW36:ONNUC($< \text{LLOQ}$;n=29,31,25,25,21,1,24,17,13	13			
FUW36:ONNUC($\geq \text{LLOQ}$ - < 20 IU/mL;n=29,31,0,0,0,1,0,17,13	0			
FUW36:ONNUC(≥ 20 - < 200 IU/mL;n=29,31,0,0,0,1,0,17,13)	0			
FUW36:ONNUC($\geq \text{LLOQ}$ - < 200 ;n=29,0,25,25,21,0,24,0,0	9999			
FUW36:ONNUC(≥ 200 - < 2000 ;n=29,31,25,25,21,1,24,17,13	0			
FUW36:ONNUC(≥ 2000 IU/mL;n=29,31,25,25,21,1,24,17,13	0			
FUW48:OFFNUC($< \text{LLOQ}$)(n=0,0,2,7,6,0,9,5,4)	1			
FUW48:OFFNUC($\geq \text{LLOQ}$ - < 20 IU/mL;n=0,0,0,0,0,0,0,5,4)	1			
FUW48:OFFNUC(≥ 20 - < 200 IU/mL;n=0,0,0,0,0,0,0,5,4)	0			
FUW48:OFFNUC($\geq \text{LLOQ}$ - < 200 IU/mL;n=0,0,2,7,6,0,9,5,4)	9999			
FUW48:OFFNUC(≥ 200 - < 2000 IU/mL;n=0,0,2,7,6,0,9,5,4)	1			
FUW48:OFFNUC(≥ 2000 IU/mL;n=0,0,2,7,6,0,9,5,4)	1			
FUW48:ONNUC($< \text{LLOQ}$;n=30,28,27,23,21,1,23,10,8	7			
FUW48:ONNUC($\geq \text{LLOQ}$ - < 20 ;n=30,28,0,0,0,1,0,10,8	1			
FUW48:ONNUC(≥ 20 - < 200 IU/mL;n=30,28,0,0,0,1,0,10,8	0			
FUW48:ONNUC($\geq \text{LLOQ}$ - < 200 ;n=30,0,27,23,21,0,23,0,0	9999			
FUW48:ONNUC(≥ 200 - < 2000 ;n=30,28,27,23,21,1,23,10,8	0			
FUW48:ONNUC(≥ 2000 IU/mL;n=30,28,27,23,21,1,23,10,8	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HBsAg, Anti-HBs, HBeAg, HBV Ribonucleic Acid (RNA) and HBV DNA Levels Over Time

End point title	Change From Baseline in HBsAg, Anti-HBs, HBeAg, HBV
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End point description:

The serological markers of HBV infection include viral antigens (HBsAg & HBeAg) and antibody (anti-HBs). Changes in serological markers and efficacy biomarkers (HBV DNA & HBV RNA) from baseline are reported. mITT population included participants who were randomized and received at least one dose of each drug for their assigned treatment regimen. n = participants with data available for analysis at that specified timepoint. 999=Since only 1 participant was analyzed, standard deviation (SD) could not be calculated. 9999= No participants were analyzed for this timepoint. 99999= Mean and SD were not estimable due to majority of samples being below LLOQ.

End point type	Secondary
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End point timeframe:

Combo 2, 3, 4, 6 and NUC arm: Weeks 24, 36, 48, FUW 24 and FUW 48; Combo 7: Week 24, FUW 24 and FUW 48; Combo 8: Weeks 24, 36, FUW 24 and FUW 48

End point values	NUC Control Arm	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	36	30	30
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
HBsAg: Week 24(n=34,36,28,29,28,4,18,33,30)	-0.08 (± 0.16)	-0.11 (± 0.26)	-1.49 (± 0.56)	-1.78 (± 0.59)
HBsAg: Week 36(n=33,23,24,19,22,1,34,0,30)	-0.08 (± 0.13)	-0.13 (± 0.23)	-1.52 (± 0.67)	-1.93 (± 0.47)
HBsAg: Week 48(n=34,20,29,30,28,4,34,0,0)	-0.2 (± 0.52)	-0.09 (± 0.12)	-1.58 (± 0.63)	-1.93 (± 0.6)
HBsAg: FUW 24(n=29,35,28,30,27,9,31,32,30)	-0.19 (± 0.35)	-0.18 (± 0.31)	-1.19 (± 0.76)	-1.71 (± 0.75)
HBsAg: FUW 48(n=30,28,29,30,27,1,32,15,12)	-0.25 (± 0.43)	-0.25 (± 0.36)	-0.89 (± 0.76)	-1.2 (± 0.84)
Anti-HBs: Week 24(n=34,36,28,29,28,4,18,33,30)	-0.01 (± 0.04)	-0.01 (± 0.08)	0.06 (± 0.32)	0 (± 0)
Anti-HBs: Week 36(n=34,23,24,19,22,1,34,0,30)	-0.01 (± 0.02)	-0.02 (± 0.09)	0.06 (± 0.34)	0 (± 0)
Anti-HBs: Week 48(n=34,20,29,30,28,4,34,0,0)	0 (± 0.01)	-0.04 (± 0.11)	0.06 (± 0.35)	0 (± 0)
Anti-HBs: FUW 24(n=29,35,28,30,27,9,31,32,25)	-0.02 (± 0.08)	-0.01 (± 0.06)	0.05 (± 0.31)	0.01 (± 0.05)
Anti-HBs: FUW 48(n=30,28,29,30,27,1,32,9,9)	0.04 (± 0.33)	-0.01 (± 0.04)	0.01 (± 0.28)	0.02 (± 0.12)
HBeAg: Week 24(n=7,8,8,8,12,2,7,9,5)	-0.08 (± 0.1)	-0.04 (± 0.13)	-0.39 (± 0.16)	-0.4 (± 0.21)
HBeAg: Week 36(n=7,5,9,4,9,0,10,0,5)	-0.08 (± 0.14)	-0.05 (± 0.04)	-0.45 (± 0.2)	-0.53 (± 0.15)
HBeAg: Week 48(n=8,5,9,8,11,2,10,0,0)	-0.06 (± 0.15)	-0.06 (± 0.06)	-0.48 (± 0.18)	-0.48 (± 0.2)
HBeAg: FUW 24(n=7,8,8,8,11,3,9,9,5)	-0.19 (± 0.15)	-0.09 (± 0.12)	-0.02 (± 1.37)	-0.42 (± 0.22)
HBeAg: FUW 48(n=7,8,9,8,11,0,9,5,0)	-0.36 (± 0.31)	-0.22 (± 0.11)	-0.14 (± 1.06)	-0.38 (± 0.19)
HBV RNA: Week 24(n=9,11,10,14,14,2,10,33,6)	0.09 (± 0.43)	-1.19 (± 1.19)	-0.7 (± 0.34)	-0.95 (± 0.6)
HBV RNA: Week 36(n=9,6,9,9,9,0,15,0,6)	0.05 (± 0.3)	-1.66 (± 1.4)	-0.74 (± 0.41)	-0.73 (± 0.57)
HBV RNA: Week 48(n=10,6,11,15,14,2,15,0,0)	-0.04 (± 0.32)	-1.66 (± 1.4)	-0.8 (± 0.48)	-0.94 (± 0.6)
HBV RNA: FUW 24(n=9,11,11,15,14,4,13,10,6)	-0.25 (± 0.28)	-0.13 (± 0.12)	-0.68 (± 0.49)	-0.87 (± 0.59)
HBV RNA: FUW 48(n=8,8,11,15,14,0,14,4,2)	-0.43 (± 0.6)	-0.11 (± 0.19)	-0.6 (± 0.48)	-0.78 (± 0.55)

HBV DNA: Week 24 (n=0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 9999)	99999 (± 9999)	9999 (± 9999)
HBV DNA: Week 36 (n=0,0,0,0,0,0,0,0)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)
HBV DNA: Week 48 (n=0,0,0,0,0,0,0,0)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)
HBV DNA: FUW 24 (n=27,35,24,24,20,9,21,24,21)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
HBV DNA: FUW 48(n=30,28,2,7,6,1,9,10,8)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Combo 4: siRNA + PEG- IFN + NUC	Combo 5: siRNA + CpAM + NUC	Combo 6: siRNA + TLR7 Agonist + NUC	Combo 7: siRNA + PD-L1 LNA + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	9	34	33
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
HBsAg: Week 24(n=34,36,28,29,28,4,18,33,30)	-1.89 (± 1.05)	-1.38 (± 0.41)	-1.74 (± 0.62)	-2.12 (± 0.73)
HBsAg: Week 36(n=33,23,24,19,22,1,34,0,30)	-2.14 (± 1.27)	-1.51 (± 999)	-1.71 (± 0.69)	9999 (± 9999)
HBsAg: Week 48(n=34,20,29,30,28,4,34,0,0)	-2.22 (± 1.16)	-1.3 (± 0.45)	-2.18 (± 0.86)	9999 (± 9999)
HBsAg: FUW 24(n=29,35,28,30,27,9,31,32,30)	-1.71 (± 1.24)	-1.5 (± 0.89)	-1.47 (± 0.81)	-1.3 (± 0.7)
HBsAg: FUW 48(n=30,28,29,30,27,1,32,15,12)	-1.28 (± 1.12)	-2.02 (± 999)	-1.01 (± 0.8)	-0.91 (± 0.69)
Anti-HBs: Week 24(n=34,36,28,29,28,4,18,33,30)	0.03 (± 0.2)	0.06 (± 0.13)	-0.01 (± 0.04)	0.01 (± 0.12)
Anti-HBs: Week 36(n=34,23,24,19,22,1,34,0,30)	0.3 (± 0.69)	0 (± 999)	-0.07 (± 0.27)	9999 (± 9999)
Anti-HBs: Week 48(n=34,20,29,30,28,4,34,0,0)	0.55 (± 0.96)	0.01 (± 0.02)	-0.05 (± 0.27)	9999 (± 9999)
Anti-HBs: FUW 24(n=29,35,28,30,27,9,31,32,25)	0.63 (± 1.04)	0.09 (± 0.2)	-0.02 (± 0.41)	0.01 (± 0.1)
Anti-HBs: FUW 48(n=30,28,29,30,27,1,32,9,9)	0.41 (± 0.93)	0 (± 999)	0.04 (± 0.49)	0.09 (± 0.26)
HBeAg: Week 24(n=7,8,8,8,12,2,7,9,5)	-0.37 (± 0.19)	-0.19 (± 0.32)	-0.53 (± 0.3)	-0.47 (± 0.32)
HBeAg: Week 36(n=7,5,9,4,9,0,10,0,5)	-0.43 (± 0.2)	9999 (± 9999)	-0.65 (± 0.44)	9999 (± 9999)
HBeAg: Week 48(n=8,5,9,8,11,2,10,0,0)	-0.44 (± 0.19)	-0.28 (± 0.42)	-0.69 (± 0.44)	9999 (± 9999)
HBeAg: FUW 24(n=7,8,8,8,11,3,9,9,5)	-0.33 (± 0.19)	-0.68 (± 0.73)	-0.56 (± 0.33)	-0.4 (± 0.37)
HBeAg: FUW 48(n=7,8,9,8,11,0,9,5,0)	-0.3 (± 0.16)	9999 (± 9999)	-0.5 (± 0.38)	-0.42 (± 0.47)
HBV RNA: Week 24(n=9,11,10,14,14,2,10,33,6)	-1.43 (± 0.89)	-1.34 (± 0.65)	-0.92 (± 0.92)	-1.17 (± 1.26)
HBV RNA: Week 36(n=9,6,9,9,9,0,15,0,6)	-1.67 (± 0.9)	9999 (± 9999)	-0.76 (± 0.76)	9999 (± 9999)
HBV RNA: Week 48(n=10,6,11,15,14,2,15,0,0)	-1.43 (± 0.95)	-1.32 (± 0.68)	-0.9 (± 0.81)	9999 (± 9999)
HBV RNA: FUW 24(n=9,11,11,15,14,4,13,10,6)	-0.64 (± 0.82)	-1.04 (± 0.63)	-0.51 (± 0.63)	-0.82 (± 0.75)
HBV RNA: FUW 48(n=8,8,11,15,14,0,14,4,2)	-0.85 (± 0.75)	9999 (± 9999)	-0.37 (± 0.52)	-0.98 (± 0.8)
HBV DNA: Week 24 (n=0,0,0,0,0,0,0,0,0)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)

HBV DNA: Week 36 (n=0,0,0,0,0,0,0,0)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)
HBV DNA: Week 48 (n=0,0,0,0,0,0,0,0)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)
HBV DNA: FUW 24 (n=27,35,24,24,20,9,21,24,21)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
HBV DNA: FUW 48(n=30,28,2,7,6,1,9,10,8)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Combo 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
HBsAg: Week 24(n=34,36,28,29,28,4,18,33,30)	-1.8 (± 0.49)			
HBsAg: Week 36(n=33,23,24,19,22,1,34,0,30)	-2.08 (± 0.63)			
HBsAg: Week 48(n=34,20,29,30,28,4,34,0,0)	9999 (± 9999)			
HBsAg: FUW 24(n=29,35,28,30,27,9,31,32,30)	-1.46 (± 0.74)			
HBsAg: FUW 48(n=30,28,29,30,27,1,32,15,12)	-1.14 (± 0.83)			
Anti-HBs: Week 24(n=34,36,28,29,28,4,18,33,30)	-0.03 (± 0.1)			
Anti-HBs: Week 36(n=34,23,24,19,22,1,34,0,30)	-0.03 (± 0.11)			
Anti-HBs: Week 48(n=34,20,29,30,28,4,34,0,0)	9999 (± 9999)			
Anti-HBs: FUW 24(n=29,35,28,30,27,9,31,32,25)	-0.06 (± 0.2)			
Anti-HBs: FUW 48(n=30,28,29,30,27,1,32,9,9)	0.02 (± 0.07)			
HBeAg: Week 24(n=7,8,8,8,12,2,7,9,5)	-0.46 (± 0.15)			
HBeAg: Week 36(n=7,5,9,4,9,0,10,0,5)	-0.46 (± 0.26)			
HBeAg: Week 48(n=8,5,9,8,11,2,10,0,0)	9999 (± 9999)			
HBeAg: FUW 24(n=7,8,8,8,11,3,9,9,5)	-0.51 (± 0.31)			
HBeAg: FUW 48(n=7,8,9,8,11,0,9,5,0)	9999 (± 9999)			
HBV RNA: Week 24(n=9,11,10,14,14,2,10,33,6)	-0.81 (± 0.55)			
HBV RNA: Week 36(n=9,6,9,9,9,0,15,0,6)	-0.76 (± 0.56)			
HBV RNA: Week 48(n=10,6,11,15,14,2,15,0,0)	9999 (± 9999)			
HBV RNA: FUW 24(n=9,11,11,15,14,4,13,10,6)	-0.81 (± 0.55)			
HBV RNA: FUW 48(n=8,8,11,15,14,0,14,4,2)	-0.49 (± 0.57)			
HBV DNA: Week 24 (n=0,0,0,0,0,0,0,0,0)	9999 (± 9999)			
HBV DNA: Week 36 (n=0,0,0,0,0,0,0,0,0)	9999 (± 9999)			

HBV DNA: Week 48 (n=0,0,0,0,0,0,0,0)	9999 (± 9999)			
HBV DNA: FUW 24 (n=27,35,24,24,20,9,21,24,21)	99999 (± 99999)			
HBV DNA: FUW 48(n=30,28,2,7,6,1,9,10,8)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 7 and 8: Maximum Plasma Concentration (Cmax) at Week 1 (Cmax1-0-168h) of PD-L1 LNA

End point title	Combos 7 and 8: Maximum Plasma Concentration (Cmax) at Week 1 (Cmax1-0-168h) of PD-L1 LNA
End point description: The Cmax was predicted and summarized by modelling & simulation via the PopPK method based on pre and post dose samples. As per planned analysis data was collected and reported in a pooled manner for Combos 7 and 8. PK population included participants who received at least one dose of the PD-L1 LNA and had at least one evaluable post-baseline PK sample.	
End point type	Secondary
End point timeframe: Predose on Day 1 and up to 168 hours post dose (Week 1)	

End point values	Combo 7 and 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Subject analysis set			
Number of subjects analysed	63			
Units: nanomoles/liters (nmol/L)				
arithmetic mean (standard deviation)	163 (± 60.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 7 and 8: Area Under the Plasma Concentration-time Curve Over the Dosing Interval at Week 1 (AUC1-0-168h) of PD-L1 LNA

End point title	Combos 7 and 8: Area Under the Plasma Concentration-time Curve Over the Dosing Interval at Week 1 (AUC1-0-168h) of PD-L1 LNA
End point description: The AUC was predicted and summarized by modelling & simulation via the population pharmacokinetics (PopPK) method based on pre and post dose samples. As per planned analysis data was collected and reported in a pooled manner for Combos 7 and 8. PK population included participants who received at least one dose of the PD-L1 LNA and had at least one evaluable post-baseline PK sample.	
End point type	Secondary

End point timeframe:

Predose on Day 1 and up to 168 hours post dose (Week 1)

End point values	Combo 7 and 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Subject analysis set			
Number of subjects analysed	63			
Units: hours*nanomoles/liters (hr*nmol/L)				
arithmetic mean (standard deviation)	1047 (± 273)			

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 7 and 8: AUC Over the Dosing Interval at Week 12 (AUC12-0-168h) of PD-L1 LNA

End point title	Combos 7 and 8: AUC Over the Dosing Interval at Week 12 (AUC12-0-168h) of PD-L1 LNA
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End point description:

The AUC was predicted and summarized by modelling & simulation via the PopPK method based on pre and post dose samples. As per planned analysis data was collected and reported in a pooled manner for Combos 7 and 8. PK population included participants who received at least one dose of the PD-L1 LNA and had at least one evaluable post-baseline PK sample.

End point type	Secondary
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End point timeframe:

Predose on Day 1 of Week 12 up to 168 hours post dose (Week 12)

End point values	Combo 7 and 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Subject analysis set			
Number of subjects analysed	63			
Units: hr*nmol/L				
arithmetic mean (standard deviation)	1143 (± 286)			

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 7 and 8: Cmax at Week 12 (Cmax12-0-168h) of PD-L1 LNA

End point title	Combos 7 and 8: Cmax at Week 12 (Cmax12-0-168h) of PD-L1 LNA
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End point description:

The C_{max} was predicted and summarized by modelling & simulation via the PopPK method based on pre and post dose samples. As per planned analysis data was collected and reported in a pooled manner for Combos 7 and 8. PK population included participants who received at least one dose of the PD-L1 LNA and had at least one evaluable post-baseline PK sample.

End point type Secondary

End point timeframe:

Predose on Day 1 of Week 12 up to 168 hours post dose (Week 12)

End point values	Combo 7 and 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Subject analysis set			
Number of subjects analysed	63			
Units: nmol/L				
arithmetic mean (standard deviation)	165 (± 60.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 2, 3, 4, 6, 7 and 8: Area Under the Plasma Concentration Time Curve (AUC) Over Days 1-28 of siRNA

End point title Combos 2, 3, 4, 6, 7 and 8: Area Under the Plasma Concentration Time Curve (AUC) Over Days 1-28 of siRNA^[1]

End point description:

The AUC was predicted and summarized by modelling & simulation via the PopPK method based on pre and post dose samples. PK population included participants who received at least one dose of the siRNA and had at least one evaluable post-baseline PK sample.

End point type Secondary

End point timeframe:

Predose on Day 1 and 1-3 and 4-6 hours post dose each day, up to Day 28

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is assessing PK parameter for Combos 2, 3, 4, 6, 7 and 8 only.

End point values	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC	Combo 4: siRNA + PEG-IFN + NUC	Combo 6: siRNA + TLR7 Agonist + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	30	30	34
Units: hours*nanograms/millilitres (hr*ng/mL)				
arithmetic mean (standard deviation)	4670 (± 1112)	11098 (± 2499)	11073 (± 2272)	9831 (± 2215)

End point values	Combo 7:	Combo 8:		
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	siRNA + PD-L1 LNA + NUC	siRNA + PD-L1 LNA + NUC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: hours*nanograms/millilitres (hr*ng/mL)				
arithmetic mean (standard deviation)	9780 (± 1942)	9110 (± 1418)		

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 2, 3, 4, 6, 7 and 8: Cmax Over Days 1-28 of siRNA

End point title	Combos 2, 3, 4, 6, 7 and 8: Cmax Over Days 1-28 of siRNA ^[2]
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End point description:

The Cmax was predicted and summarized by modelling & simulation via the PopPK method based on pre and post dose samples. PK population included participants who received at least one dose of the siRNA and had at least one evaluable post-baseline PK sample.

End point type	Secondary
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End point timeframe:

Predose on Day 1 and 1-3 and 4-6 hours post dose each day, up to Day 28

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is assessing PK parameter for Combos 2, 3, 4, 6, 7 and 8 only.

End point values	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC	Combo 4: siRNA + PEG-IFN + NUC	Combo 6: siRNA + TLR7 Agonist + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	30	30	34
Units: nanograms/millilitres (ng/mL)				
arithmetic mean (standard deviation)	190 (± 116)	463 (± 203)	450 (± 168)	408 (± 168)

End point values	Combo 7: siRNA + PD-L1 LNA + NUC	Combo 8: siRNA + PD-L1 LNA + NUC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: nanograms/millilitres (ng/mL)				
arithmetic mean (standard deviation)	373 (± 149)	311 (± 97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 2, 3, 4, 6, 7 and 8: Area Under the Plasma Concentration Time

Curve During the Dosing Interval (AUC Tau) Over Days 29-56 of siRNA

End point title	Combos 2, 3, 4, 6, 7 and 8: Area Under the Plasma Concentration Time Curve During the Dosing Interval (AUC Tau) Over Days 29-56 of siRNA ^[3]
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End point description:

The AUC tau was predicted and summarized by modelling & simulation via the PopPK method based on pre and post dose samples. PK population included participants who received at least one dose of the siRNA and had at least one evaluable post-baseline PK sample.

End point type	Secondary
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End point timeframe:

From predose on Day 29 and multiple timepoints post dose up to Day 56

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is assessing PK parameter for Combos 2, 3, 4, 6, 7 and 8 only.

End point values	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC	Combo 4: siRNA + PEG-IFN + NUC	Combo 6: siRNA + TLR7 Agonist + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	30	30	34
Units: hr*ng/mL				
arithmetic mean (standard deviation)	5401 (± 1245)	12591 (± 2659)	12623 (± 2428)	11207 (± 2371)

End point values	Combo 7: siRNA + PD-L1 LNA + NUC	Combo 8: siRNA + PD-L1 LNA + NUC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: hr*ng/mL				
arithmetic mean (standard deviation)	11216 (± 2068)	10513 (± 1511)		

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 2, 3, 4, 6, 7 and 8: Cmax Over Days 29-56 of siRNA

End point title	Combos 2, 3, 4, 6, 7 and 8: Cmax Over Days 29-56 of siRNA ^[4]
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End point description:

The Cmax was predicted and summarized by modelling & simulation via the PopPK method based on pre and post dose samples. PK population included participants who received at least one dose of the siRNA and had at least one evaluable post-baseline PK sample.

End point type	Secondary
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End point timeframe:

From predose on Day 29 and multiple timepoints post dose up to Day 56

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is assessing PK parameter for Combos 2, 3, 4, 6, 7 and 8 only.

End point values	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC	Combo 4: siRNA + PEG-IFN + NUC	Combo 6: siRNA + TLR7 Agonist + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	30	30	34
Units: ng/mL				
arithmetic mean (standard deviation)	192 (\pm 116)	468 (\pm 204)	454 (\pm 169)	411 (\pm 169)

End point values	Combo 7: siRNA + PD-L1 LNA + NUC	Combo 8: siRNA + PD-L1 LNA + NUC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: ng/mL				
arithmetic mean (standard deviation)	376 (\pm 150)	315 (\pm 98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 1 and 6: AUC of TLR7

End point title	Combos 1 and 6: AUC of TLR7 ^[5]
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End point description:

The AUC was predicted and summarized by modelling & simulation via the PopPK method based on pre and post dose samples. PK population included participants who received at least one dose of the TLR7 and had at least one evaluable post-baseline PK sample.

End point type	Secondary
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End point timeframe:

Predose and 1-3 and 4-6 hours post-dose on Days 1, 3, 5 on Weeks 12 and 36

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is assessing PK parameter for Combos 1 and 6 only.

End point values	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 6: siRNA + TLR7 Agonist + NUC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	34		
Units: ng*hr/mL				
arithmetic mean (standard deviation)	3139 (\pm 938.8)	2813 (\pm 75.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)
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End point description:

An AE was any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory values or abnormal clinical test results), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Safety population included 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.

End point type	Secondary
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End point timeframe:

From Day 1 up to end of 48 weeks of follow up (up to approximately 1.8 years)

End point values	NUC Control Arm	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	38	30	30
Units: participants	27	34	30	29

End point values	Combo 4: siRNA + PEG-IFN + NUC	Combo 5: siRNA + CpAM + NUC	Combo 6: siRNA + TLR7 Agonist + NUC	Combo 7: siRNA + PD-L1 LNA + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	19	34	33
Units: participants	30	18	33	26

End point values	Combo 8: siRNA + PD-L1 LNA + NUC			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: participants	27			

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 1 and 6: Cmax of TLR7

End point title	Combos 1 and 6: Cmax of TLR7 ^[6]
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End point description:

The C_{max} was predicted and summarized by modelling & simulation via the PopPK method based on pre and post dose samples. PK population included participants who received at least one dose of the TLR7 and had at least one evaluable post-baseline PK sample.

End point type	Secondary
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End point timeframe:

Predose and 1-3 and 4-6 hours post-dose on Days 1, 3, 5 on Weeks 12 and 36

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is assessing PK parameter for Combos 1 and 6 only.

End point values	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 6: siRNA + TLR7 Agonist + NUC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	34		
Units: ng/mL				
arithmetic mean (standard deviation)	1548 (± 419.7)	1491 (± 334.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 2, 3, 4, 5, 6, 7 and 8: Number of Participants with Anti-siRNA Antibodies

End point title	Combos 2, 3, 4, 5, 6, 7 and 8: Number of Participants with Anti-siRNA Antibodies ^[7]
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End point description:

Treatment-emergent anti drug antibody (ADA) was defined as participants who seroconverted or experienced a boost in preexisting ADA during the study. Participants were considered to be ADA positive if they were ADA negative or had missing data at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they were ADA positive at baseline and the titer of one or more post-baseline samples were greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment-enhanced ADA response). Immunogenicity population included participants who had at least one pre-dose (baseline) or at least one post-dose assessment will be included and analyzed according to the treatment they actually received or were allocated to receive.

End point type	Secondary
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End point timeframe:

From Day 1 up to end of follow up (up to approximately 4 years)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is assessing PK parameter for Combos 2, 3, 4, 6, 7 and 8 only.

End point values	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC	Combo 4: siRNA + PEG- IFN + NUC	Combo 5: siRNA + CpAM + NUC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	30	30	19
Units: participants	3	2	12	1

End point values	Combo 6: siRNA + TLR7 Agonist + NUC	Combo 7: siRNA + PD-L1 LNA + NUC	Combo 8: siRNA + PD-L1 LNA + NUC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	33	31	
Units: participants	3	10	14	

Statistical analyses

No statistical analyses for this end point

Secondary: Combos 7 and 8: Number of Participants with Anti-PD-L1 Antibodies

End point title	Combos 7 and 8: Number of Participants with Anti-PD-L1 Antibodies ^[8]
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End point description:

Treatment-emergent ADA was defined as participants who seroconverted or experienced a boost in preexisting ADA during the study. Participants were considered to be ADA positive if they were ADA negative or had missing data at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they were ADA positive at baseline and the titer of one or more post-baseline samples were greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment-enhanced ADA response). Immunogenicity population included participants who had at least one pre-dose (baseline) or at least one post-dose assessment will be included and analyzed according to the treatment they actually received or were allocated to receive.

End point type	Secondary
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End point timeframe:

From Day 1 for Combo 7 and 8 up to end of follow up (Up to approximately 2 years)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is assessing PK parameter for Combos 7 and 8 only.

End point values	Combo 7: siRNA + PD-L1 LNA + NUC	Combo 8: siRNA + PD-L1 LNA + NUC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: participants	16	15		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to end of 48 week follow up (up to approximately 1.8 years)

Adverse event reporting additional description:

Safety population included 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.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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Reporting groups

Reporting group title	Combo 1: CpAM + TLR7 Agonist + NUC
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Reporting group description:

Participants received CpAM, 600 mg tablets, orally, QD for 48 weeks and TLR7 agonist, 150 mg, orally, QOD during Weeks 1-12 and Weeks 25-36 in addition to their background NUC therapy. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Reporting group title	Combo 2: siRNA (100 mg) + NUC
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Reporting group description:

Participants received siRNA, 100 mg, as a SC injection, Q4W in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Reporting group title	Combo 3: siRNA (200 mg) + NUC
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Reporting group description:

Participants received siRNA, 200 mg, as a SC injection, Q4W in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Reporting group title	Combo 4: siRNA + PEG-IFN + NUC
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Reporting group description:

Participants received siRNA, 200 mg, as a SC injection, Q4W and PEG-IFN, 180 µg, as a SC injection, QW in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Reporting group title	Combo 5: siRNA + CpAM + NUC
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Reporting group description:

Participants received siRNA, 200 mg, as a SC injection, Q4W and CpAM, 600 mg tablets, orally, QD in addition to their background NUC therapy for 48 weeks. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Reporting group title	Combo 6: siRNA + TLR7 Agonist + NUC
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Reporting group description:

Participants received siRNA, 200 mg, as a SC injection, Q4W for 48 weeks and TLR7 agonist, 150 mg tablets, orally, QOD during Weeks 13-24 and Weeks 37-48 in addition to their background NUC therapy. After Week 48, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Reporting group title	Combo 7: siRNA + PD-L1 LNA + NUC
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Reporting group description:

Participants received siRNA, 200 mg, as a SC injection, Q4W up to Week 24 and PD-L1 LNA, 2 mg/kg, as a SC injection, QW during Weeks 13-24 in addition to their background NUC therapy for 24 weeks. After Week 24, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

Reporting group title	Combo 8: siRNA + PD-L1 LNA + NUC
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Reporting group description:

Participants received siRNA, 200 mg, as a SC injection, Q4W up to Week 24 and PD-L1 LNA, 2 mg/kg, as a SC injection, QW during Weeks 25-36 in addition to their background NUC therapy for 36 weeks. After Week 36, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.

were met.

Reporting group title	NUC Control Arm
Reporting group description:	
Participants continued their background NUC therapy for 48 weeks. Thereafter, in line with current CHB treatment guidelines, participants continued NUC treatment during follow-up unless the NUC discontinuation criteria were met.	

Serious adverse events	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 38 (7.89%)	3 / 30 (10.00%)	4 / 30 (13.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic neuroendocrine tumour			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign hepatic neoplasm			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			

subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestine polyp			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Panic reaction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Vertebral osteophyte			
subjects affected / exposed	0 / 38 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Fascioliasis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 38 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Combo 4: siRNA + PEG-IFN + NUC	Combo 5: siRNA + CpAM + NUC	Combo 6: siRNA + TLR7 Agonist + NUC
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	2 / 34 (5.88%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic neuroendocrine tumour			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign hepatic neoplasm			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Femoral neck fracture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestine polyp			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			

subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Panic reaction			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Vertebral osteophyte			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Fascioliasis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Combo 7: siRNA + PD-L1 LNA + NUC	Combo 8: siRNA + PD-L1 LNA + NUC	NUC Control Arm
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 35 (2.86%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic neuroendocrine tumour			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign hepatic neoplasm			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Diplopia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestine polyp			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Panic reaction			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Vertebral osteophyte			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Fascioliasis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Combo 1: CpAM + TLR7 Agonist + NUC	Combo 2: siRNA (100 mg) + NUC	Combo 3: siRNA (200 mg) + NUC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 38 (86.84%)	27 / 30 (90.00%)	29 / 30 (96.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	0 / 38 (0.00%)	2 / 30 (6.67%)	1 / 30 (3.33%)
occurrences (all)	0	2	1
Skin papilloma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 30 (3.33%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Asthenia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1

Vessel puncture site bruise subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 30 (6.67%) 2	0 / 30 (0.00%) 0
Injection site reaction subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 30 (6.67%) 2	9 / 30 (30.00%) 16
Fatigue subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 5	1 / 30 (3.33%) 1	2 / 30 (6.67%) 2
Pyrexia subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 9	0 / 30 (0.00%) 0	3 / 30 (10.00%) 3
Chest pain subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 30 (3.33%) 1	2 / 30 (6.67%) 2
Influenza like illness subjects affected / exposed occurrences (all)	14 / 38 (36.84%) 62	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Thirst subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Sensation of foreign body subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Reproductive system and breast disorders Prostatic calcification subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	3 / 30 (10.00%) 3
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	4 / 30 (13.33%) 5	1 / 30 (3.33%) 1
Epistaxis subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Depression subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Investigations			
Neutrophil count decreased subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 4	1 / 30 (3.33%) 2	1 / 30 (3.33%) 3
Thyroxine free decreased subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Blood uric acid increased subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Blood triglycerides increased subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 4	6 / 30 (20.00%) 11	10 / 30 (33.33%) 17
Amylase increased subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	5 / 30 (16.67%) 6	5 / 30 (16.67%) 5
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
White blood cell count decreased			
subjects affected / exposed	4 / 38 (10.53%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	4	2	4
Electrocardiogram PR shortened			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Cystatin C increased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Lipase increased			
subjects affected / exposed	0 / 38 (0.00%)	3 / 30 (10.00%)	3 / 30 (10.00%)
occurrences (all)	0	4	5
Blood bilirubin increased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 30 (3.33%)	3 / 30 (10.00%)
occurrences (all)	1	5	4
Weight decreased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Alanine aminotransferase increased			
subjects affected / exposed	4 / 38 (10.53%)	13 / 30 (43.33%)	13 / 30 (43.33%)
occurrences (all)	5	22	21
Blood phosphorus decreased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Glutamate dehydrogenase increased			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	3 / 30 (10.00%)
occurrences (all)	1	0	3
Platelet count decreased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Protein urine present			

subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Injury, poisoning and procedural complications			
Product dose omission issue subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 3	13 / 30 (43.33%) 14	14 / 30 (46.67%) 14
Overdose subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Muscle strain subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Accidental overdose subjects affected / exposed occurrences (all)	8 / 38 (21.05%) 10	5 / 30 (16.67%) 5	6 / 30 (20.00%) 6
Cardiac disorders			
Atrioventricular block first degree subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Ventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 30 (3.33%) 1	2 / 30 (6.67%) 5
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1
Sinus arrhythmia subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 30 (6.67%) 3	3 / 30 (10.00%) 4
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 4	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Headache subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 24	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Hypoaesthesia			

subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Monocytopenia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Ear discomfort			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 38 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Chronic gastritis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	1	1	1
Gingival bleeding			
subjects affected / exposed	2 / 38 (5.26%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Abdominal discomfort			

subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Periodontal disease			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 38 (0.00%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	0	2	2
Dental caries			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 38 (5.26%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	1 / 38 (2.63%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	1 / 38 (2.63%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences (all)	1	3	0
Flatulence			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	2 / 38 (5.26%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Hepatobiliary disorders			

Bile duct stone subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 30 (6.67%) 2	0 / 30 (0.00%) 0
Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	7 / 30 (23.33%) 8	3 / 30 (10.00%) 3
Cholelithiasis subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Hepatic cyst subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	2 / 30 (6.67%) 2	1 / 30 (3.33%) 1
Liver disorder subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Hepatic mass subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 30 (0.00%) 0	2 / 30 (6.67%) 2
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1
Alopecia subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 30 (6.67%) 2	1 / 30 (3.33%) 1
Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Ecchymosis subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Musculoskeletal and connective tissue disorders			

Rotator cuff syndrome			
subjects affected / exposed	2 / 38 (5.26%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Back pain			
subjects affected / exposed	2 / 38 (5.26%)	1 / 30 (3.33%)	3 / 30 (10.00%)
occurrences (all)	2	2	3
Pain in extremity			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	3
Arthralgia			
subjects affected / exposed	2 / 38 (5.26%)	3 / 30 (10.00%)	3 / 30 (10.00%)
occurrences (all)	2	3	4
Intervertebral disc protrusion			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Myalgia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Herpes virus infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	6 / 38 (15.79%)	10 / 30 (33.33%)	16 / 30 (53.33%)
occurrences (all)	6	10	17
Hepatitis B reactivation			
subjects affected / exposed	0 / 38 (0.00%)	6 / 30 (20.00%)	1 / 30 (3.33%)
occurrences (all)	0	6	1
Gingivitis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 30 (6.67%)	1 / 30 (3.33%)
occurrences (all)	0	3	1
Pharyngitis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Conjunctivitis			

subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	4 / 30 (13.33%)
occurrences (all)	1	0	5
Gastroenteritis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 38 (10.53%)	14 / 30 (46.67%)	11 / 30 (36.67%)
occurrences (all)	5	24	16
Nasopharyngitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Sinusitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	1 / 38 (2.63%)	6 / 30 (20.00%)	6 / 30 (20.00%)
occurrences (all)	1	9	9
Hypertriglyceridaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	0	2	4
Hyperphosphataemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Dyslipidaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Hyperlipidaemia			
subjects affected / exposed	0 / 38 (0.00%)	6 / 30 (20.00%)	7 / 30 (23.33%)
occurrences (all)	0	10	15
Hypocalcaemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0

Diabetes mellitus inadequate control subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 30 (6.67%) 3	1 / 30 (3.33%) 2
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Non-serious adverse events	Combo 4: siRNA + PEG-IFN + NUC	Combo 5: siRNA + CpAM + NUC	Combo 6: siRNA + TLR7 Agonist + NUC
Total subjects affected by non-serious adverse events subjects affected / exposed	29 / 30 (96.67%)	18 / 19 (94.74%)	33 / 34 (97.06%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Haemangioma of liver subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 19 (0.00%) 0	0 / 34 (0.00%) 0
Skin papilloma subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 19 (0.00%) 0	1 / 34 (2.94%) 1
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 19 (0.00%) 0	0 / 34 (0.00%) 0
General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 19 (5.26%) 1	2 / 34 (5.88%) 2
Asthenia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 19 (5.26%) 1	0 / 34 (0.00%) 0
Pain subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 19 (0.00%) 0	2 / 34 (5.88%) 3
Vessel puncture site bruise subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 19 (5.26%) 1	0 / 34 (0.00%) 0
Injection site reaction subjects affected / exposed occurrences (all)	15 / 30 (50.00%) 39	3 / 19 (15.79%) 4	7 / 34 (20.59%) 10
Fatigue			

subjects affected / exposed occurrences (all)	7 / 30 (23.33%) 12	1 / 19 (5.26%) 1	3 / 34 (8.82%) 3
Pyrexia subjects affected / exposed occurrences (all)	7 / 30 (23.33%) 7	4 / 19 (21.05%) 4	7 / 34 (20.59%) 10
Chest pain subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 19 (0.00%) 0	0 / 34 (0.00%) 0
Influenza like illness subjects affected / exposed occurrences (all)	8 / 30 (26.67%) 12	1 / 19 (5.26%) 1	16 / 34 (47.06%) 38
Thirst subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	0 / 19 (0.00%) 0	0 / 34 (0.00%) 0
Sensation of foreign body subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 19 (5.26%) 1	0 / 34 (0.00%) 0
Reproductive system and breast disorders Prostatic calcification subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 19 (0.00%) 0	2 / 34 (5.88%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 5	0 / 19 (0.00%) 0	3 / 34 (8.82%) 3
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 19 (0.00%) 0	0 / 34 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	3 / 19 (15.79%) 3	1 / 34 (2.94%) 1
Epistaxis subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 6	0 / 19 (0.00%) 0	0 / 34 (0.00%) 0
Psychiatric disorders			

Insomnia			
subjects affected / exposed	3 / 30 (10.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	3	0	0
Depression			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	1 / 34 (2.94%)
occurrences (all)	1	1	1
Investigations			
Neutrophil count decreased			
subjects affected / exposed	12 / 30 (40.00%)	0 / 19 (0.00%)	6 / 34 (17.65%)
occurrences (all)	24	0	11
Thyroxine free decreased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Blood uric acid increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 30 (23.33%)	1 / 19 (5.26%)	1 / 34 (2.94%)
occurrences (all)	9	1	1
Blood triglycerides increased			
subjects affected / exposed	3 / 30 (10.00%)	0 / 19 (0.00%)	1 / 34 (2.94%)
occurrences (all)	8	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 30 (70.00%)	7 / 19 (36.84%)	11 / 34 (32.35%)
occurrences (all)	32	7	21
Amylase increased			
subjects affected / exposed	6 / 30 (20.00%)	1 / 19 (5.26%)	5 / 34 (14.71%)
occurrences (all)	14	1	6
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 30 (16.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	7	0	0
White blood cell count decreased			
subjects affected / exposed	8 / 30 (26.67%)	0 / 19 (0.00%)	5 / 34 (14.71%)
occurrences (all)	14	0	11
Electrocardiogram PR shortened			

subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Cystatin C increased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Lymphocyte count decreased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	1 / 34 (2.94%)
occurrences (all)	5	0	1
Lipase increased			
subjects affected / exposed	2 / 30 (6.67%)	3 / 19 (15.79%)	2 / 34 (5.88%)
occurrences (all)	4	5	4
Blood bilirubin increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	3 / 30 (10.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	3	0	0
Alanine aminotransferase increased			
subjects affected / exposed	25 / 30 (83.33%)	10 / 19 (52.63%)	15 / 34 (44.12%)
occurrences (all)	39	16	25
Blood phosphorus decreased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Glutamate dehydrogenase increased			
subjects affected / exposed	5 / 30 (16.67%)	1 / 19 (5.26%)	2 / 34 (5.88%)
occurrences (all)	12	1	2
Platelet count decreased			
subjects affected / exposed	17 / 30 (56.67%)	1 / 19 (5.26%)	3 / 34 (8.82%)
occurrences (all)	26	1	3
Protein urine present			
subjects affected / exposed	8 / 30 (26.67%)	2 / 19 (10.53%)	1 / 34 (2.94%)
occurrences (all)	12	2	1
Injury, poisoning and procedural complications			
Product dose omission issue			

subjects affected / exposed occurrences (all)	19 / 30 (63.33%) 23	2 / 19 (10.53%) 7	15 / 34 (44.12%) 33
Overdose subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	3 / 19 (15.79%) 3	1 / 34 (2.94%) 1
Muscle strain subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 19 (0.00%) 0	0 / 34 (0.00%) 0
Accidental overdose subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 19 (5.26%) 1	4 / 34 (11.76%) 6
Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 19 (5.26%) 1	0 / 34 (0.00%) 0
Ventricular extrasystoles subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 19 (0.00%) 0	0 / 34 (0.00%) 0
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 19 (5.26%) 1	0 / 34 (0.00%) 0
Sinus arrhythmia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	2 / 19 (10.53%) 2	0 / 34 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	0 / 19 (0.00%) 0	5 / 34 (14.71%) 12
Headache subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 19 (5.26%) 1	3 / 34 (8.82%) 6
Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 2	0 / 19 (0.00%) 0	2 / 34 (5.88%) 2
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 19 (10.53%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Thrombocytopenia			
subjects affected / exposed	4 / 30 (13.33%)	0 / 19 (0.00%)	1 / 34 (2.94%)
occurrences (all)	6	0	1
Lymphopenia			
subjects affected / exposed	3 / 30 (10.00%)	0 / 19 (0.00%)	1 / 34 (2.94%)
occurrences (all)	3	0	1
Monocytopenia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 19 (10.53%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Neutropenia			
subjects affected / exposed	5 / 30 (16.67%)	2 / 19 (10.53%)	2 / 34 (5.88%)
occurrences (all)	5	2	2
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Ear discomfort			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 30 (6.67%)	1 / 19 (5.26%)	0 / 34 (0.00%)
occurrences (all)	2	1	0
Gastrointestinal disorders			
Chronic gastritis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	3 / 34 (8.82%)
occurrences (all)	0	0	3
Gingival bleeding			
subjects affected / exposed	3 / 30 (10.00%)	0 / 19 (0.00%)	1 / 34 (2.94%)
occurrences (all)	3	0	1
Abdominal discomfort			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Abdominal pain			

subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	1
Periodontal disease			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Abdominal distension			
subjects affected / exposed	4 / 30 (13.33%)	0 / 19 (0.00%)	1 / 34 (2.94%)
occurrences (all)	6	0	1
Dental caries			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	3 / 34 (8.82%)
occurrences (all)	1	0	4
Nausea			
subjects affected / exposed	2 / 30 (6.67%)	1 / 19 (5.26%)	1 / 34 (2.94%)
occurrences (all)	2	1	3
Abdominal pain upper			
subjects affected / exposed	2 / 30 (6.67%)	4 / 19 (21.05%)	4 / 34 (11.76%)
occurrences (all)	4	5	4
Dyspepsia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 30 (3.33%)	2 / 19 (10.53%)	2 / 34 (5.88%)
occurrences (all)	1	2	2
Flatulence			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	1 / 30 (3.33%)	2 / 19 (10.53%)	2 / 34 (5.88%)
occurrences (all)	1	2	2
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0

Hepatic steatosis			
subjects affected / exposed	6 / 30 (20.00%)	1 / 19 (5.26%)	2 / 34 (5.88%)
occurrences (all)	6	1	2
Cholelithiasis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Hepatic cyst			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	1
Liver disorder			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Hepatic mass			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	5 / 30 (16.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	5	0	0
Hyperhidrosis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	3 / 30 (10.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	3	0	0
Ecchymosis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Back pain			

subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	1 / 34 (2.94%)
occurrences (all)	4	0	1
Arthralgia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	3
Intervertebral disc protrusion			
subjects affected / exposed	0 / 30 (0.00%)	2 / 19 (10.53%)	0 / 34 (0.00%)
occurrences (all)	0	3	0
Myalgia			
subjects affected / exposed	3 / 30 (10.00%)	1 / 19 (5.26%)	3 / 34 (8.82%)
occurrences (all)	4	1	4
Infections and infestations			
Herpes virus infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
COVID-19			
subjects affected / exposed	17 / 30 (56.67%)	3 / 19 (15.79%)	17 / 34 (50.00%)
occurrences (all)	17	3	18
Hepatitis B reactivation			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	10 / 34 (29.41%)
occurrences (all)	2	0	10
Gingivitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Conjunctivitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Gastroenteritis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0

Upper respiratory tract infection subjects affected / exposed occurrences (all)	13 / 30 (43.33%) 16	5 / 19 (26.32%) 6	4 / 34 (11.76%) 6
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 19 (0.00%) 0	0 / 34 (0.00%) 0
Sinusitis subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	0 / 19 (0.00%) 0	0 / 34 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	2 / 19 (10.53%) 2	0 / 34 (0.00%) 0
Hyperuricaemia subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 5	1 / 19 (5.26%) 1	2 / 34 (5.88%) 3
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3	0 / 19 (0.00%) 0	0 / 34 (0.00%) 0
Hyperphosphataemia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 19 (5.26%) 1	0 / 34 (0.00%) 0
Dyslipidaemia subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3	1 / 19 (5.26%) 1	0 / 34 (0.00%) 0
Hyperlipidaemia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 19 (0.00%) 0	4 / 34 (11.76%) 11
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 19 (5.26%) 1	0 / 34 (0.00%) 0
Diabetes mellitus inadequate control subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 19 (0.00%) 0	1 / 34 (2.94%) 1

Non-serious adverse events	Combo 7: siRNA + PD-L1 LNA + NUC	Combo 8: siRNA + PD-L1 LNA + NUC	NUC Control Arm
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Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 33 (69.70%)	25 / 31 (80.65%)	25 / 35 (71.43%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Skin papilloma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 33 (3.03%)	2 / 31 (6.45%)	0 / 35 (0.00%)
occurrences (all)	1	2	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
Vessel puncture site bruise			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	5 / 33 (15.15%)	7 / 31 (22.58%)	1 / 35 (2.86%)
occurrences (all)	9	37	1
Fatigue			
subjects affected / exposed	3 / 33 (9.09%)	3 / 31 (9.68%)	0 / 35 (0.00%)
occurrences (all)	8	3	0
Pyrexia			
subjects affected / exposed	1 / 33 (3.03%)	2 / 31 (6.45%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Chest pain			

subjects affected / exposed	1 / 33 (3.03%)	2 / 31 (6.45%)	0 / 35 (0.00%)
occurrences (all)	2	2	0
Influenza like illness			
subjects affected / exposed	0 / 33 (0.00%)	4 / 31 (12.90%)	0 / 35 (0.00%)
occurrences (all)	0	6	0
Thirst			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Sensation of foreign body			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Prostatic calcification			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 33 (3.03%)	4 / 31 (12.90%)	1 / 35 (2.86%)
occurrences (all)	1	4	1
Rhinorrhoea			
subjects affected / exposed	3 / 33 (9.09%)	1 / 31 (3.23%)	1 / 35 (2.86%)
occurrences (all)	3	1	1
Oropharyngeal pain			
subjects affected / exposed	2 / 33 (6.06%)	1 / 31 (3.23%)	1 / 35 (2.86%)
occurrences (all)	2	1	1
Epistaxis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 31 (3.23%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Depression			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Investigations			

Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	1 / 35 (2.86%) 1
Thyroxine free decreased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Blood uric acid increased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	2 / 35 (5.71%) 3
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Blood triglycerides increased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	1 / 35 (2.86%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	2 / 31 (6.45%) 3	1 / 35 (2.86%) 1
Amylase increased subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	1 / 31 (3.23%) 1	1 / 35 (2.86%) 1
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 31 (6.45%) 2	0 / 35 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	1 / 35 (2.86%) 1
Electrocardiogram PR shortened subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Cystatin C increased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Lymphocyte count decreased			

subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Lipase increased subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	1 / 31 (3.23%) 1	0 / 35 (0.00%) 0
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	2 / 35 (5.71%) 2
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 6	6 / 31 (19.35%) 8	3 / 35 (8.57%) 3
Blood phosphorus decreased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Glutamate dehydrogenase increased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 31 (3.23%) 1	1 / 35 (2.86%) 1
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	1 / 35 (2.86%) 1
Protein urine present subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Injury, poisoning and procedural complications			
Product dose omission issue subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	13 / 35 (37.14%) 13
Overdose subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	1 / 31 (3.23%) 1	1 / 35 (2.86%) 1
Muscle strain			

subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Accidental overdose			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
Sinus arrhythmia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 33 (3.03%)	1 / 31 (3.23%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	2 / 33 (6.06%)	3 / 31 (9.68%)	0 / 35 (0.00%)
occurrences (all)	3	4	0
Hypoaesthesia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			

subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Monocytopenia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	2 / 33 (6.06%)	2 / 31 (6.45%)	0 / 35 (0.00%)
occurrences (all)	2	2	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Chronic gastritis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	1 / 33 (3.03%)	3 / 31 (9.68%)	0 / 35 (0.00%)
occurrences (all)	2	4	0
Periodontal disease			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			

subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	2 / 33 (6.06%)	1 / 31 (3.23%)	1 / 35 (2.86%)
occurrences (all)	8	1	1
Abdominal pain upper			
subjects affected / exposed	1 / 33 (3.03%)	1 / 31 (3.23%)	1 / 35 (2.86%)
occurrences (all)	2	1	1
Dyspepsia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Flatulence			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Hepatic steatosis			
subjects affected / exposed	3 / 33 (9.09%)	0 / 31 (0.00%)	4 / 35 (11.43%)
occurrences (all)	3	0	4
Cholelithiasis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0

Hepatic cyst subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	1 / 35 (2.86%) 1
Liver disorder subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Hepatic mass subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Alopecia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	1 / 31 (3.23%) 2	0 / 35 (0.00%) 0
Ecchymosis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 31 (9.68%) 3	0 / 35 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 31 (3.23%) 1	1 / 35 (2.86%) 2
Arthralgia			

subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 31 (6.45%) 3	1 / 35 (2.86%) 1
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	1 / 35 (2.86%) 1
Myalgia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 31 (6.45%) 2	0 / 35 (0.00%) 0
Infections and infestations			
Herpes virus infection subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	4 / 31 (12.90%) 4	8 / 35 (22.86%) 8
Hepatitis B reactivation subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	7 / 31 (22.58%) 7	3 / 35 (8.57%) 3
Gingivitis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	1 / 35 (2.86%) 1
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 31 (0.00%) 0	0 / 35 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 31 (6.45%) 4	4 / 35 (11.43%) 4
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	4 / 31 (12.90%) 5	0 / 35 (0.00%) 0

Sinusitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Dyslipidaemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Hypocalcaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2019	<ul style="list-style-type: none"> - Enhance the safety monitoring for flu-like symptoms. - NUC analogue stopping criteria were introduced which applied to all arms to increase participants' safety and reduce the chances of Alanine aminotransferase (ALT) flares after discontinuation. - The follow-up period was extended from 24 to 48 weeks, to comply with American Association for the Study of Liver Diseases (AASLD) guidelines that recommend monitoring for recurrent viremia, ALT flares, seroconversion, and clinical decompensation up to 48 weeks. - History of orthostatic hypotension was added in the exclusion criteria for the CpAM (RO7049389) + TLR7 (RO7020531) + NUC arm as a precautionary measure and to be able to distinguish any potential study drug driven hypotension from pre-existing propensity for hypotension.
20 July 2020	<ul style="list-style-type: none"> - Introduction of an option for RO7020531 dose reduction to 100 mg once every other day (QOD) and to a dosing regimen of 100 mg QW for participants who experience recurrent/repetitive flu-like symptoms to improve tolerability. - Updated the inclusion criteria for women of childbearing potential (WOCBP) to "Have a negative pregnancy test at screening (Day -14 to -7)". - An event that leads to hospitalization for administrative reasons, e.g., participant lives far away and is kept in the clinic/hospital for participant and/or site convenience was updated to not considered as serious adverse event (SAE).
14 October 2020	Five additional combination treatment arms were added. These new combination treatment arms included a direct-acting antiviral (DAA), which was a siRNA that targets HBV RNA transcripts, thus inhibiting HBV gene expression. These 5 treatment arms were: siRNA + NUC (2 treatment arms), siRNA + PEG-IFN + NUC, siRNA + CpAM + NUC, and siRNA + TLR7 + NUC.
25 August 2021	<ul style="list-style-type: none"> - NUC stopping criteria had been amended - Minor clarifications and updates on the general study exclusion criteria - Addition of tables to summarize existing information on dose interruption, modification, and discontinuation - Exclusion criterion related to systemic use of anti-neoplastic, immunosuppressive, immune modulator, and systemic steroids has been added. - Exclusion criterion related to prohibited medications and prohibited foods has been added.
16 December 2021	<ul style="list-style-type: none"> - Two additional treatment arms had been added with the same treatment combinations siRNA (RO7445482) + PD-L1 LNA (RO7191863) + NUC but with different treatment durations. - 2D-shear wave elastography [2D-SWE] was added as an acceptable procedure to assess significant liver fibrosis, cirrhosis, or decompensated liver disease. - Hypersensitivity to study drug excipients was added as an exclusion criterion.
18 July 2022	<ul style="list-style-type: none"> - NUC re-starting criteria was amended to enable early detection and prompt management of virological relapse to prevent participants potentially developing liver decompensation. NUC discontinuation criteria was amended to take into account participants with very low HBsAg levels at baseline. - Appendix 13 has been updated to confirm dose selected and provide dose justification for 2.0 mg/kg once a week (QW), including preliminary pre-clinical AAV-HBV data supporting the rationale for combining PD-L1 LNA and siRNA; PD-L1 LNA dosing regimens that are no longer applicable removed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported