Clinical trial results:
A Phase 1/2, Randomized, Single-Blind, Placebo-Controlled, Single-Ascending and Multiple-Ascending Dose, Safety, Tolerability, Pharmacokinetics, and Antiviral Efficacy Study of Subcutaneously Administered ALN-HBV in Healthy Adult Subjects and Non-cirrhotic Patients with Chronic Hepatitis B Virus (HBV) Infection

Summary

EudraCT number	2015-004360-10
Trial protocol	GB
Global end of trial date	06 October 2017

Results information

Result version number	v1 (current)
This version publication date	20 October 2018
First version publication date	20 October 2018

Trial information

Trial identification

Sponsor protocol code	ALN-HBV-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02826018
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alnylam Pharmaceuticals, Inc.
Sponsor organisation address	300 Third Street, Cambridge, MA, United States, 02142
Public contact	Investor Relations and Corporate Communications, Alnylam Pharmaceuticals, Inc., +1 866 330 0326, Investors@alnylam.com
Scientific contact	Chief Medical Officer, Alnylam Pharmaceuticals, Inc., +1 866 330 0326, medinfo@alnylam.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	06 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 October 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of single or multiple doses of ALN-HBV in healthy adult subjects and non-cirrhotic subjects with chronic hepatitis B virus (HBV) infection when administered as monotherapy or concomitantly with the anti-HBV nucleoside, entecavir, or the anti-HBV nucleotide, tenofovir.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

One clinical study site in the United Kingdom participated in this study.

Pre-assignment

Screening details:

Twenty four healthy subjects were enrolled in Part A of the study. The study was terminated before the enrollment of subjects into Parts B and C.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

A single dose of matching placebo was administered.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of matching placebo (sterile normal saline: 0.9% sodium chloride [NaCl]) was administered subcutaneously (SC) on Day 1.

Arm title	ALN-HBV 0.1 mg/kg

Arm description:

A single dose of 0.1 mg/kg ALN-HBV was administered.

Arm type	Experimental
Investigational medicinal product name	ALN-HBV
Investigational medicinal product code	
Other name	ALN-66810
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of ALN-HBV was administered SC on Day 1.

Arm title	ALN-HBV 0.3 mg/kg

Arm description:

A single dose of 0.3 mg/kg ALN-HBV was administered.

Arm type	Experimental

Investigational medicinal product name	ALN-HBV
Investigational medicinal product code	
Other name	ALN-66810
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of ALN-HBV was administered SC on Day 1.

Arm title	ALN-HBV 1.0 mg/kg

Arm description:

A single dose of 1.0 mg/kg ALN-HBV was administered.

Arm type	Experimental
Investigational medicinal product name	ALN-HBV
Investigational medicinal product code	
Other name	ALN-66810
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of ALN-HBV was administered SC on Day 1.

Arm title	ALN-HBV 3.0 mg/kg

Arm description:

A single dose of 3.0 mg/kg ALN-HBV was administered.

Arm type	Experimental
Investigational medicinal product name	ALN-HBV
Investigational medicinal product code	
Other name	ALN-66810
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of ALN-HBV was administered SC on Day 1.

Number of subjects in period 1	Placebo	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg
Started	6	3	3
Completed	6	3	3

Number of subjects in period 1	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg
Started	6	6
Completed	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
A single dose of matching placebo was administered.	
Reporting group title	ALN-HBV 0.1 mg/kg
Reporting group description:	
A single dose of 0.1 mg/kg ALN-HBV was administered.	
Reporting group title	ALN-HBV 0.3 mg/kg
Reporting group description:	
A single dose of 0.3 mg/kg ALN-HBV was administered.	
Reporting group title	ALN-HBV 1.0 mg/kg
Reporting group description:	
A single dose of 1.0 mg/kg ALN-HBV was administered.	
Reporting group title	ALN-HBV 3.0 mg/kg
Reporting group description:	
A single dose of 3.0 mg/kg ALN-HBV was administered.	

Reporting group values	Placebo	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg
Number of subjects	6	3	3
Age categorical Units: Subjects			

Age continuous			
Safety Analysis Set included all subjects, who received any amount of study drug.			
Units: years			
arithmetic mean	26.8	30.7	24.3
standard deviation	± 5.49	± 4.04	± 6.66
Gender categorical			
Safety Analysis Set included all subjects, who received any amount of study drug.			
Units: Subjects			
Female	2	1	2
Male	4	2	1

Reporting group values	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg	Total
Number of subjects	6	6	24
Age categorical Units: Subjects			

Age continuous			
Safety Analysis Set included all subjects, who received any amount of study drug.			
Units: years			
arithmetic mean	24.8	20.5	
standard deviation	± 7.17	± 0.84	-
Gender categorical			
Safety Analysis Set included all subjects, who received any amount of study drug.			
Units: Subjects			

Female	4	1	10
Male	2	5	14

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
A single dose of matching placebo was administered.	
Reporting group title	ALN-HBV 0.1 mg/kg
Reporting group description:	
A single dose of 0.1 mg/kg ALN-HBV was administered.	
Reporting group title	ALN-HBV 0.3 mg/kg
Reporting group description:	
A single dose of 0.3 mg/kg ALN-HBV was administered.	
Reporting group title	ALN-HBV 1.0 mg/kg
Reporting group description:	
A single dose of 1.0 mg/kg ALN-HBV was administered.	
Reporting group title	ALN-HBV 3.0 mg/kg
Reporting group description:	
A single dose of 3.0 mg/kg ALN-HBV was administered.	

Primary: Percentage of Subjects With Adverse Events (AEs)

End point title	Percentage of Subjects With Adverse Events (AEs)[1]

End point description:

An AE is any untoward medical occurrence in a clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Safety Analysis Set: All subjects, who received any amount of study drug.

End point type	Primary

End point timeframe:

Part A: Up to Day 29; additional laboratory tests were obtained after Day 29 at the discretion of the Investigator (or designee), incorporating input from the Sponsor and/or Safety Review committee (SRC) up to Day 151.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics were planned to be reported for this endpoint.

End point values	Placebo	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg	ALN-HBV 1.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	3	6
Units: percentage of subjects				
number (not applicable)	33.3	66.7	33.3	50.0

End point values	ALN-HBV 3.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	6			

Units: percentage of subjects				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of ALN-HBV in Plasma

End point title	Maximum Concentration (Cmax) of ALN-HBV in Plasma[2]

End point description:

Pharmacokinetic (PK) Analysis Set: All subjects who received any amount of study drug, had at least one post-dose blood sample for study drug measurement, and had sufficient data to calculate at least 1 PK parameter for ALN-HBV.

End point type	Secondary

End point timeframe:

Day 1: pre-dose, 1, 2, 4, 6, 8, 12, 24 and 48 hours, and Day 8

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: The placebo arm was not included in endpoint for pharmacokinetics.

End point values	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	6
Units: nanogram (ng)/ millllilitre (mL)				
arithmetic mean (standard deviation)	27.9 (± 4.20)	64.7 (± 23.7)	215 (± 44.6)	856 (± 197)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cmax (tmax) of ALN-HBV in Plasma

End point title	Time to Cmax (tmax) of ALN-HBV in Plasma[3]

End point description:

PK Analysis Set: All subjects who received any amount of study drug, had at least one post-dose blood sample for study drug measurement, and had sufficient data to calculate at least 1 PK parameter for ALN-HBV.

End point type	Secondary

End point timeframe:

Day 1: pre-dose, 1, 2, 4, 6, 8, 12, 24 and 48 hours, and Day 8

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: The placebo arm was not included in endpoints for pharmacokinetics.

End point values	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	6
Units: hour (hr)				
median (full range (min-max))	2.00 (2.00 to 2.00)	4.05 (2.02 to 6.00)	4.05 (2.00 to 4.07)	4.05 (2.00 to 8.03)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve from Time 0 to Time of Last Measurable Concentration (AUClast) of ALN-HBV in Plasma

End point title	Area Under the Concentration-Time Curve from Time 0 to Time of Last Measurable Concentration (AUClast) of ALN-HBV in Plasma[4]

End point description:

PK Analysis Set: All subjects who received any amount of study drug, had at least one post-dose blood sample for study drug measurement, and had sufficient data to calculate at least 1 PK parameter for ALN-HBV.

End point type	Secondary

End point timeframe:

Day 1: pre-dose, 1, 2, 4, 6, 8, 12, 24 and 48 hours, and Day 8

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: The placebo arm was not included in endpoints for pharmacokinetics.

End point values	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	6
Units: hr* microgram (ug)/mL				
arithmetic mean (standard deviation)	0.162 (± 0.0438)	0.473 (± 0.149)	1.92 (± 0.395)	8.85 (± 1.35)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve from Time 0 to Time 24 Hour (AUC0-24) of ALN-HBV in Plasma

End point title	Area Under the Concentration-Time Curve from Time 0 to Time 24 Hour (AUC0-24) of ALN-HBV in Plasma[5]

End point description:

PK Analysis Set: All subjects who received any amount of study drug, had at least one post-dose blood sample for study drug measurement, and had sufficient data to calculate at least 1 PK parameter for ALN-HBV.

End point type	Secondary

End point timeframe:

Day 1: pre-dose, 1, 2, 4, 6, 8, 12, 24 and 48 hours, and Day 8

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: The placebo arm was not included in endpoints for pharmacokinetics.

End point values	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	1[7]	5[8]	6[9]
Units: hr*ug/mL				
arithmetic mean (standard deviation)	()	0.742 (± 99999)	2.26 (± 0.416)	8.85 (± 1.35)

Notes:

[6] - No evaluable data were collected for this endpoint.

[7] - Subjects analysed is the number of subjects analysed for this endpoint.

[8] - Subjects analysed is the number of subjects analysed for this endpoint.

[9] - Subjects analysed is the number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve from Time 0 to Infinity (AUCinf) of ALN-HBV in Plasma

End point title	Area Under the Concentration-Time Curve from Time 0 to Infinity (AUCinf) of ALN-HBV in Plasma[10]

End point description:

PK Analysis Set: All subjects who received any amount of study drug, had at least one post-dose blood sample for study drug measurement, and had sufficient data to calculate at least 1 PK parameter for ALN-HBV.

End point type	Secondary

End point timeframe:

Day 1: pre-dose, 1, 2, 4, 6, 8, 12, 24 and 48 hours, and Day 8

Notes:

[10] - 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: The placebo arm was not included in endpoints for pharmacokinetics.

End point values	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[11]	1[12]	5[13]	5[14]
Units: hr*ug/mL				
arithmetic mean (standard deviation)	()	0.756 (± 99999)	2.32 (± 0.428)	9.16 (± 1.36)

Notes:

[11] - No evaluable data were collected for this endpoint.

[12] - Subjects analysed is the number of subjects analysed for this endpoint.

[13] - Subjects analysed is the number of subjects analysed for this endpoint.

[14] - Subjects analysed is the number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life (t1/2) of ALN-HBV in Plasma

End point title	Half-life (t1/2) of ALN-HBV in Plasma[15]

End point description:

PK Analysis Set: All subjects who received any amount of study drug, had at least one post-dose blood sample for study drug measurement, and had sufficient data to calculate at least 1 PK parameter for ALN-HBV.

End point type	Secondary

End point timeframe:

Day 1: pre-dose, 1, 2, 4, 6, 8, 12, 24 and 48 hours, and Day 8

Notes:

[15] - 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: The placebo arm was not included in endpoints for pharmacokinetics.

End point values	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[16]	1[17]	5[18]	5[19]
Units: hr				
arithmetic mean (standard deviation)	()	3.92 (± 99999)	4.14 (± 0.693)	4.81 (± 1.40)

Notes:

[16] - No evaluable data were collected for this endpoint.

[17] - Subjects analysed is the number of subjects analysed for this endpoint.

[18] - Subjects analysed is the number of subjects analysed for this endpoint.

[19] - Subjects analysed is the number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance (CL/F) of ALN-HBV in Plasma

End point title	Apparent Clearance (CL/F) of ALN-HBV in Plasma[20]

End point description:

PK Analysis Set: All subjects who received any amount of study drug, had at least one post-dose blood sample for study drug measurement, and had sufficient data to calculate at least 1 PK parameter for ALN-HBV.

End point type	Secondary

End point timeframe:

Day 1: pre-dose, 1, 2, 4, 6, 8, 12, 24 and 48 hours, and Day 8

Notes:

[20] - 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: The placebo arm was not included in endpoints for pharmacokinetics.

End point values	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[21]	1[22]	5[23]	5[24]
Units: Litre/hr				
arithmetic mean (standard deviation)	()	24.8 (± 99999)	27.9 (± 4.94)	20.9 (± 3.81)

Notes:

[21] - No evaluable data were collected for this endpoint.

[22] - Subjects analysed is the number of subjects analysed for this endpoint.

[23] - Subjects analysed is the number of subjects analysed for this endpoint.

[24] - Subjects analysed is the number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (Vz/F) of ALN-HBV in Plasma

End point title	Apparent Volume of Distribution (Vz/F) of ALN-HBV in

End point description:

PK Analysis Set: All subjects who received any amount of study drug, had at least one post-dose blood sample for study drug measurement, and had sufficient data to calculate at least 1 PK parameter for ALN-HBV.

End point type	Secondary

End point timeframe:

Day 1: pre-dose, 1, 2, 4, 6, 8, 12, 24 and 48 hours, and Day 8

Notes:

[25] - 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: The placebo arm was not included in endpoints for pharmacokinetics.

End point values	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[26]	1[27]	5[28]	5[29]
Units: litre(s)				
arithmetic mean (standard deviation)	()	140 (± 99999)	166 (± 40.5)	149 (± 70.9)

Notes:

[26] - No evaluable data were collected for this endpoint.

[27] - Subjects analysed is the number of subjects analysed for this endpoint.

[28] - Subjects analysed is the number of subjects analysed for this endpoint.

[29] - Subjects analysed is the number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Fraction Excreted from Time 0 to Time 24 Hour (Fe0-24) of ALN-HBV in Urine

End point title	Fraction Excreted from Time 0 to Time 24 Hour (Fe0-24) of ALN-HBV in Urine[30]

End point description:

PK Analysis Set: All subjects who received any amount of study drug, had at least one post-dose blood sample for study drug measurement, and had sufficient data to calculate at least 1 PK parameter for ALN-HBV.

End point type	Secondary

End point timeframe:

Day 1: pre-dose, >6 hours, >12 hours, >24 hours

Notes:

[30] - 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: The placebo arm was not included in endpoints for pharmacokinetics.

End point values	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	6
Units: percent				
arithmetic mean (standard deviation)	12.0 (± 1.88)	7.95 (± 5.90)	10.3 (± 7.09)	17.3 (± 5.90)

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Clearance (CLr) of ALN-HBV

End point title	Renal Clearance (CLr) of ALN-HBV[31]

End point description:

PK Analysis Set: All subjects who received any amount of study drug, had at least one post-dose blood sample for study drug measurement, and had sufficient data to calculate at least 1 PK parameter for ALN-HBV.

End point type	Secondary

End point timeframe:

Day 1: pre-dose, >6 hours, >12 hours, >24 hours, Day 3, Day 8

Notes:

[31] - 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: The placebo arm was not included in endpoints for pharmacokinetics.

End point values	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[32]	1[33]	5[34]	6
Units: Litre/hr				
arithmetic mean (standard deviation)	()	3.72 (± 99999)	4.05 (± 0.802)	3.77 (± 1.02)

Notes:

[32] - No evaluable data were collected for this endpoint.

[33] - Subjects analysed is the number of subjects analysed for this endpoint.

[34] - Subjects analysed is the number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 29; additional laboratory tests were obtained after Day 29 at the discretion of the Investigator (or designee), incorporating input from the Sponsor and/or Safety Review committee (SRC) up to Day 151.

Adverse event reporting additional description:

Safety Analysis Set: All subjects, who received any amount of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

A single dose of matching placebo was administered.

Reporting group title	ALN-HBV 0.1 mg/kg

Reporting group description:

A single dose of 0.1 mg/kg ALN-HBV was administered.

Reporting group title	ALN-HBV 0.3 mg/kg

Reporting group description:

A single dose of 0.3 mg/kg ALN-HBV was administered.

Reporting group title	ALN-HBV 1.0 mg/kg

Reporting group description:

A single dose of 1.0 mg/kg ALN-HBV was administered.

Reporting group title	ALN-HBV 3.0 mg/kg

Reporting group description:

A single dose of 3.0 mg/kg ALN-HBV was administered.

Serious adverse events	Placebo	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	ALN-HBV 0.1 mg/kg	ALN-HBV 0.3 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	2 / 3 (66.67%)	1 / 3 (33.33%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Injection site reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Medical device site reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Genital herpes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	ALN-HBV 1.0 mg/kg	ALN-HBV 3.0 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	6 / 6 (100.00%)	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	4	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	5	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Muscle strain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site reaction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Medical device site reaction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Genital herpes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2016	Removed Part D multiple dosing in subjects who are anti-HBV treatment-naïve, clarified that the maximum possible dose in Part C is 3.0 mg/kg, amended the stopping rules for Part C to state that dosing will be discontinued if >/=1 subject experiences a serious adverse event (SAE) considered to be possibly or definitely related to study drug, and clarified reasons leading to dosing discontinuation.
26 January 2017	Included specific alanine transaminase (ALT) inclusion criteria and increased liver function test monitoring. Also, each subsequent dose escalation after 0.1 mg/kg ALN-HBV was to be preceded by protocol-specified Safety Review Committee (SRC) review of safety data. The following additional protocol changes were made: • For Parts B and C, a normal and stable serum ALT was added as a specific inclusion criterion. • For Part B, an additional time point for laboratory assessment was added to Day 22. • Alcohol use during the duration of the study was updated in Exclusion Criteria for Parts A, B, and C. Additionally, clarified that the use of herbal supplements was prohibited during the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 October 2017	The study was terminated as part of a business decision to advance a new HBV development candidate and not due to any safety concerns. At the time of study termination all healthy volunteers had completed Part A, and postdosing safety monitoring was considered complete per the SRC.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Only Part A of the study was completed. No subjects were enrolled in Parts B and C, which were to include subjects with HBV infection. Therefore, the efficacy endpoint of hepatitis B surface antigen (HBsAg) levels could not be assessed.

Notes: