



## 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     |
| <b>Arm title</b>             | 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.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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.

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

| <b>Number of subjects in period 1</b> | 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:<br>A single dose of matching placebo was administered.  |                   |
| Reporting group title  | ALN-HBV 0.1 mg/kg |
| Reporting group description:<br>A single dose of 0.1 mg/kg ALN-HBV was administered. |                   |
| Reporting group title  | ALN-HBV 0.3 mg/kg |
| Reporting group description:<br>A single dose of 0.3 mg/kg ALN-HBV was administered. |                   |
| Reporting group title  | ALN-HBV 1.0 mg/kg |
| Reporting group description:<br>A single dose of 1.0 mg/kg ALN-HBV was administered. |                   |
| Reporting group title  | ALN-HBV 3.0 mg/kg |
| Reporting group description:<br>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 |

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## End points

### End points reporting groups

|  |                   |
|--|-------------------|
| Reporting group title  | Placebo           |
| Reporting group description:<br>A single dose of matching placebo was administered.  |                   |
| Reporting group title  | ALN-HBV 0.1 mg/kg |
| Reporting group description:<br>A single dose of 0.1 mg/kg ALN-HBV was administered. |                   |
| Reporting group title  | ALN-HBV 0.3 mg/kg |
| Reporting group description:<br>A single dose of 0.3 mg/kg ALN-HBV was administered. |                   |
| Reporting group title  | ALN-HBV 1.0 mg/kg |
| Reporting group description:<br>A single dose of 1.0 mg/kg ALN-HBV was administered. |                   |
| Reporting group title  | ALN-HBV 3.0 mg/kg |
| Reporting group description:<br>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) <sup>[1]</sup> |
| End point description:<br>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:<br>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:<br>[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.<br>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 (C<sub>max</sub>) of ALN-HBV in Plasma

|                 |   |
|-----------------|---|
| End point title | Maximum Concentration (C <sub>max</sub> ) of ALN-HBV in Plasma <sup>[2]</sup> |
|-----------------|---|

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)/ millilitre (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 C<sub>max</sub> (t<sub>max</sub>) of ALN-HBV in Plasma

|                 |  |
|-----------------|--|
| End point title | Time to C <sub>max</sub> (t <sub>max</sub> ) of ALN-HBV in Plasma <sup>[3]</sup> |
|-----------------|--|

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 <sup>[4]</sup> |
|-----------------|--|

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 <sup>[5]</sup> |
|-----------------|---|

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 <sup>[6]</sup>  | 1 <sup>[7]</sup>  | 5 <sup>[8]</sup>  | 6 <sup>[9]</sup>  |
| 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 <sup>[10]</sup> |
|-----------------|---|

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 <sup>[11]</sup> | 1 <sup>[12]</sup> | 5 <sup>[13]</sup> | 5 <sup>[14]</sup> |
| 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 (t<sub>1/2</sub>) of ALN-HBV in Plasma

|  |  |
|--|--|
| End point title  | Half-life (t <sub>1/2</sub> ) of ALN-HBV in Plasma <sup>[15]</sup> |
| End point description:<br>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:<br>Day 1: pre-dose, 1, 2, 4, 6, 8, 12, 24 and 48 hours, and Day 8   |  |
| Notes:<br>[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.<br>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 <sup>[16]</sup> | 1 <sup>[17]</sup> | 5 <sup>[18]</sup> | 5 <sup>[19]</sup> |
| 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 <sup>[20]</sup> |
| End point description:<br>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:<br>Day 1: pre-dose, 1, 2, 4, 6, 8, 12, 24 and 48 hours, and Day 8   |  |
| Notes:<br>[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.<br>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 <sup>[21]</sup> | 1 <sup>[22]</sup> | 5 <sup>[23]</sup> | 5 <sup>[24]</sup> |
| 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 (V<sub>z</sub>/F) of ALN-HBV in Plasma

|                 |   |
|-----------------|---|
| End point title | Apparent Volume of Distribution (V <sub>z</sub> /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 <sup>[26]</sup> | 1 <sup>[27]</sup> | 5 <sup>[28]</sup> | 5 <sup>[29]</sup> |
| 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 <sup>[30]</sup> |
|-----------------|--|

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 (CL<sub>r</sub>) of ALN-HBV

|  |   |
|--|---|
| End point title  | Renal Clearance (CL <sub>r</sub> ) of ALN-HBV <sup>[31]</sup> |
| 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 <sup>[32]</sup> | 1 <sup>[33]</sup> | 5 <sup>[34]</sup> | 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 %

| <b>Non-serious adverse events</b>                     | 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<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)   | 1 / 6 (16.67%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Gastroesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 6 (16.67%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 6 (16.67%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 1 / 6 (16.67%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders<br>Acne<br>subjects affected / exposed<br>occurrences (all)               | 0 / 6 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Infections and infestations<br>Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)               | 0 / 6 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Genital herpes<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |

|  |                   |                   |  |
|--|-------------------|-------------------|--|
| <b>Non-serious adverse events</b>  | ALN-HBV 1.0 mg/kg | ALN-HBV 3.0 mg/kg |  |
| Total subjects affected by non-serious adverse events<br>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<br>occurrences (all)   | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |  |
| Skin and subcutaneous tissue disorders<br>Acne<br>subjects affected / exposed<br>occurrences (all)               | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |  |
| Infections and infestations<br>Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)               | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |  |
| Genital herpes<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0 | 2 / 6 (33.33%)<br>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 $\geq 1$ 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.<br>The following additional protocol changes were made: <ul style="list-style-type: none"><li>• For Parts B and C, a normal and stable serum ALT was added as a specific inclusion criterion.</li><li>• For Part B, an additional time point for laboratory assessment was added to Day 22.</li><li>• Alcohol use during the duration of the study was updated in Exclusion Criteria for Parts A, B, and C.</li></ul> 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: