



Clinical trial results:

A Phase 1b/2, Open Label, Randomized, Repeat-Dose, Dose-Escalation Study to Evaluate the Safety, Tolerability, Biological Activity, and Pharmacokinetics of ND-L02-s0201 Injection, a Vitamin A-Coupled Lipid Nanoparticle Containing siRNA Against HSP47, in Subjects with Moderate to Extensive Hepatic Fibrosis (METAVIR F3-4)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-004882-26 |
| Trial protocol | BG |
| Global end of trial date | 10 May 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 21 February 2018 |
| First version publication date | 21 February 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | ND-L02-s0201-002 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02227459 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com |
| Scientific contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.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 | 10 May 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 May 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety and tolerability of once or twice a week ND-L02-s0201 Injection(ND-L02-s0201) administered as intravenous (IV) infusions for 5 consecutive weeks to subjects with moderate to extensive hepatic fibrosis (METAVIR fibrosis stage 3-4 [F3-4]).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 01 October 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Bulgaria: 5 |
| Country: Number of subjects enrolled | United States: 20 |
| Worldwide total number of subjects | 25 |
| EEA total number of subjects | 5 |

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) | 21 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 25 subjects were enrolled, randomized to a treatment group, and received at least 1 dose of study drug.

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 | Cohort 1 (0.2 mg/kg/wk) |

Arm description:

ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ND-L02-s0201 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

ND-L02-s0201 0.2 mg/kg/week administered by IV infusion either once weekly or twice weekly in 2 divided doses

| | |
|------------------|-------------------------|
| Arm title | Cohort 2 (0.4 mg/kg/wk) |
|------------------|-------------------------|

Arm description:

ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ND-L02-s0201 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

ND-L02-s0201 0.4 mg/kg/week administered by IV infusion either once weekly or twice weekly in 2 divided doses

| | |
|------------------|-------------------------|
| Arm title | Cohort 3 (0.6 mg/kg/wk) |
|------------------|-------------------------|

Arm description:

ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-----------------------|
| Investigational medicinal product name | ND-L02-s0201 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

ND-L02-s0201 0.6 mg/kg/week administered by IV infusion either once weekly or twice weekly in 2 divided doses

| Number of subjects in period 1 | Cohort 1 (0.2 mg/kg/wk) | Cohort 2 (0.4 mg/kg/wk) | Cohort 3 (0.6 mg/kg/wk) |
|---------------------------------------|-------------------------|-------------------------|-------------------------|
| Started | 8 | 8 | 9 |
| Completed | 7 | 7 | 8 |
| Not completed | 1 | 1 | 1 |
| Consent withdrawn by subject | 1 | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|--|-------------------------|
| Reporting group title | Cohort 1 (0.2 mg/kg/wk) |
| Reporting group description: ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks | |
| Reporting group title | Cohort 2 (0.4 mg/kg/wk) |
| Reporting group description: ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks | |
| Reporting group title | Cohort 3 (0.6 mg/kg/wk) |
| Reporting group description: ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks | |

| Reporting group values | Cohort 1 (0.2 mg/kg/wk) | Cohort 2 (0.4 mg/kg/wk) | Cohort 3 (0.6 mg/kg/wk) |
|---|-------------------------|-------------------------|-------------------------|
| Number of subjects | 8 | 8 | 9 |
| Age Categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 7 | 6 | 8 |
| From 65-84 years | 1 | 2 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 56.0 | 60.0 | 55.2 |
| standard deviation | ± 10.35 | ± 5.93 | ± 7.98 |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 2 | 4 | 5 |
| Male | 6 | 4 | 4 |
| Assessment of Liver Stiffness by FibroScan | | | |
| FibroScans were performed to assess liver stiffness and the results were recorded as a specific score in kilopascals (kPa). | | | |
| Units: kPa | | | |
| arithmetic mean | 21.06 | 21.56 | 18.39 |
| standard deviation | ± 13.90 | ± 10.89 | ± 9.39 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 25 | | |

| | | | |
|---|----|--|--|
| Age Categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 21 | | |
| From 65-84 years | 4 | | |
| 85 years and over | 0 | | |
| Age Continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender Categorical Units: Subjects | | | |
| Female | 11 | | |
| Male | 14 | | |
| Assessment of Liver Stiffness by FibroScan | | | |
| FibroScans were performed to assess liver stiffness and the results were recorded as a specific score in kilopascals (kPa). | | | |
| Units: kPa | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

Subject analysis sets

| | |
|---|------------------------------|
| Subject analysis set title | Cohort 1 - Dose Once Weekly |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Cohort 1 subjects receiving 0.2 mg/kg once weekly | |
| Subject analysis set title | Cohort 1 - Dose Twice Weekly |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Cohort 1 subjects receiving 0.1 mg/kg twice weekly | |
| Subject analysis set title | Cohort 2 - Dose Once Weekly |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Cohort 2 subjects receiving 0.4 mg/kg once weekly | |
| Subject analysis set title | Cohort 2 - Dose Twice Weekly |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Cohort 2 subjects receiving 0.2 mg/kg twice weekly | |
| Subject analysis set title | Cohort 3 - Dose Once Weekly |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Cohort 3 subjects receiving 0.6 mg/kg once weekly | |
| Subject analysis set title | Cohort 3 - Dose Twice Weekly |
| Subject analysis set type | Intention-to-treat |

| Reporting group values | Cohort 1 - Dose Once Weekly | Cohort 1 - Dose Twice Weekly | Cohort 2 - Dose Once Weekly |
|---|-----------------------------|------------------------------|-----------------------------|
| Number of subjects | 4 | 4 | 4 |
| Age Categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age Continuous Units: years | | | |
| arithmetic mean | 54.0 | 58.0 | 59.0 |
| standard deviation | ± 15.25 | ± 2.58 | ± 7.35 |
| Gender Categorical Units: Subjects | | | |
| Female | 1 | 1 | 2 |
| Male | 3 | 3 | 2 |
| Assessment of Liver Stiffness by FibroScan | | | |
| FibroScans were performed to assess liver stiffness and the results were recorded as a specific score in kilopascals (kPa). | | | |
| Units: kPa | | | |
| arithmetic mean | 17.18 | 24.95 | 12.63 |
| standard deviation | ± 12.04 | ± 16.30 | ± 4.04 |

| Reporting group values | Cohort 2 - Dose Twice Weekly | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly |
|---|------------------------------|-----------------------------|------------------------------|
| Number of subjects | 4 | 5 | 4 |
| Age Categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age Continuous Units: years | | | |
| arithmetic mean | 61.0 | 55.4 | 55.0 |
| standard deviation | ± 5.03 | ± 9.29 | ± 7.39 |

| | | | |
|---|--------|--------|---------|
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 2 | 2 | 3 |
| Male | 2 | 3 | 1 |
| Assessment of Liver Stiffness by FibroScan | | | |
| FibroScans were performed to assess liver stiffness and the results were recorded as a specific score in kilopascals (kPa). | | | |
| Units: kPa | | | |
| arithmetic mean | 30.50 | 19.70 | 16.75 |
| standard deviation | ± 6.87 | ± 9.56 | ± 10.33 |

End points

End points reporting groups

| | |
|--|------------------------------|
| Reporting group title | Cohort 1 (0.2 mg/kg/wk) |
| Reporting group description: ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks | |
| Reporting group title | Cohort 2 (0.4 mg/kg/wk) |
| Reporting group description: ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks | |
| Reporting group title | Cohort 3 (0.6 mg/kg/wk) |
| Reporting group description: ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks | |
| Subject analysis set title | Cohort 1 - Dose Once Weekly |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Cohort 1 subjects receiving 0.2 mg/kg once weekly | |
| Subject analysis set title | Cohort 1 - Dose Twice Weekly |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Cohort 1 subjects receiving 0.1 mg/kg twice weekly | |
| Subject analysis set title | Cohort 2 - Dose Once Weekly |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Cohort 2 subjects receiving 0.4 mg/kg once weekly | |
| Subject analysis set title | Cohort 2 - Dose Twice Weekly |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Cohort 2 subjects receiving 0.2 mg/kg twice weekly | |
| Subject analysis set title | Cohort 3 - Dose Once Weekly |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Cohort 3 subjects receiving 0.6 mg/kg once weekly | |
| Subject analysis set title | Cohort 3 - Dose Twice Weekly |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Cohort 3 subjects receiving 0.3 mg/kg twice weekly | |

Primary: Number of subjects with serious and non-serious adverse events

| | |
|---|---|
| End point title | Number of subjects with serious and non-serious adverse events ^[1] |
| End point description: AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Treatment-related=having certain, probable, possible, or missing relationship to study drug. Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4= Potentially Life-threatening or disabling. | |
| End point type | Primary |
| End point timeframe: After treatment for 5 consecutive weeks and follow-up through week 24 | |

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 specified for this endpoint.

| End point values | Cohort 1 (0.2 mg/kg/wk) | Cohort 2 (0.4 mg/kg/wk) | Cohort 3 (0.6 mg/kg/wk) | Cohort 1 - Dose Once Weekly |
|---|-------------------------|-------------------------|-------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 9 | 4 |
| Units: subjects | | | | |
| Subjects with any AE | 5 | 6 | 3 | 4 |
| Subjects with study drug-related AEs | 4 | 3 | 1 | 3 |
| Subjects with premedication-related AEs | 0 | 0 | 0 | 0 |
| Subjects with severe/life-threatening AEs | 3 | 2 | 1 | 2 |
| Subjects who died due to an AE | 0 | 0 | 0 | 0 |
| Subjects who discontinued study drug due to an AE | 0 | 0 | 0 | 0 |
| Subjects with a serious AE | 0 | 2 | 1 | 0 |

| End point values | Cohort 1 - Dose Twice Weekly | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly | Cohort 3 - Dose Once Weekly |
|---|------------------------------|-----------------------------|------------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 4 | 4 | 5 |
| Units: subjects | | | | |
| Subjects with any AE | 1 | 3 | 3 | 1 |
| Subjects with study drug-related AEs | 1 | 1 | 2 | 0 |
| Subjects with premedication-related AEs | 0 | 0 | 0 | 0 |
| Subjects with severe/life-threatening AEs | 1 | 1 | 1 | 0 |
| Subjects who died due to an AE | 0 | 0 | 0 | 0 |
| Subjects who discontinued study drug due to an AE | 0 | 0 | 0 | 0 |
| Subjects with a serious AE | 0 | 1 | 1 | 0 |

| End point values | Cohort 3 - Dose Twice Weekly | | | |
|---|------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 4 | | | |
| Units: subjects | | | | |
| Subjects with any AE | 2 | | | |
| Subjects with study drug-related AEs | 1 | | | |
| Subjects with premedication-related AEs | 0 | | | |
| Subjects with severe/life-threatening AEs | 1 | | | |
| Subjects who died due to an AE | 0 | | | |
| Subjects who discontinued study drug due to an AE | 0 | | | |

| | | | | |
|----------------------------|---|--|--|--|
| Subjects with a serious AE | 1 | | | |
|----------------------------|---|--|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Mean percent change from baseline of HSP47 qRT-PCR values at week 6

| | |
|-----------------|--|
| End point title | Mean percent change from baseline of HSP47 qRT-PCR values at week 6 ^[2] |
|-----------------|--|

End point description:

Percentage change from baseline at Week 6 for Heat Shock Protein 47 (HSP47) Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and mitochondrial ribosomal protein L19 (MRPL19) in Cohorts 2 and 3 are presented for all subjects with samples available at baseline and week 6. No screening biopsies were conducted for Cohort 1 subjects.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

6 weeks

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: Not all arms were specified in this endpoint.

| End point values | Cohort 2 (0.4 mg/kg/wk) | Cohort 3 (0.6 mg/kg/wk) | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly |
|--------------------------------------|-------------------------|-------------------------|-----------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 4 | 4 |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| HSP47 qRT-PCR normalized to GAPDH | 68.83 (± 63.33) | 16.77 (± 57.77) | 39.87 (± 44.13) | 107.45 (± 72.08) |
| HSP47 qRT-PCR normalized to MRPL19 | 17.88 (± 45.62) | -6.43 (± 28.46) | 15.21 (± 54.62) | 23.23 (± 37.00) |

| End point values | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | | |
|--------------------------------------|-----------------------------|------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 5 | 4 | | |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| HSP47 qRT-PCR normalized to GAPDH | 56.55 (± 52.14) | -23.01 (± 29.11) | | |
| HSP47 qRT-PCR normalized to MRPL19 | 12.07 (± 24.47) | -24.92 (± 19.47) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean absolute change from baseline for collagen type IV

| | |
|-----------------|---|
| End point title | Mean absolute change from baseline for collagen type IV |
|-----------------|---|

End point description:

A summary of absolute change from baseline values for collagen type IV at the first assessed follow-up visit (Week 8), and the final follow-up visit (Week 24) are presented for each cohort.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 8, and 24 weeks

| End point values | Cohort 1 (0.2 mg/kg/wk) | Cohort 2 (0.4 mg/kg/wk) | Cohort 3 (0.6 mg/kg/wk) | Cohort 1 - Dose Once Weekly |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 9 | 4 |
| Units: micrograms per liter (ug/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8 | 25.2 (± 104.92) | 13.4 (± 92.24) | 5.8 (± 42.44) | 52.0 (± 45.3) |
| Week 24 | -8.1 (± 48.78) | 52.3 (± 99.08) | -12.5 (± 63.79) | -13.0 (± 40.52) |

| End point values | Cohort 1 - Dose Twice Weekly | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly | Cohort 3 - Dose Once Weekly |
|--------------------------------------|------------------------------|-----------------------------|------------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 4 | 4 | 5 |
| Units: micrograms per liter (ug/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8 | -1.7 (± 152.67) | 14.3 (± 59.05) | 12.3 (± 142.44) | -6.5 (± 60.29) |
| Week 24 | -1.7 (± 67.57) | 69.0 (± 37.55) | 30.0 (± 161.34) | -45.3 (± 72.82) |

| End point values | Cohort 3 - Dose Twice Weekly | | | |
|------------------|------------------------------|--|--|--|
|------------------|------------------------------|--|--|--|

| | | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 4 | | | |
| Units: micrograms per liter (ug/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8 | 18.0 (± 12.96) | | | |
| Week 24 | 20.3 (± 36.47) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in FibroScan results

| | |
|-----------------|--|
| End point title | Mean change from baseline in FibroScan results |
|-----------------|--|

End point description:

FibroScans were performed to assess liver stiffness and the results were recorded as a specific score in kilopascals (kPa). The mean absolute change from baseline FibroScan result was reported for each cohort.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 5, 12, and 24 weeks

| End point values | Cohort 1 (0.2 mg/kg/wk) | Cohort 2 (0.4 mg/kg/wk) | Cohort 3 (0.6 mg/kg/wk) | Cohort 1 - Dose Once Weekly |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 9 | 4 |
| Units: kilopascal (kPa) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 5 | -2.44 (± 3.68) | -3.77 (± 3.70) | -0.06 (± 3.37) | -1.75 (± 4.11) |
| Week 12 | 99999 (± 99999) | 99999 (± 99999) | -0.75 (± 4.63) | 99999 (± 99999) |
| Week 24 | -3.51 (± 4.18) | -5.29 (± 5.52) | -0.70 (± 3.61) | -1.65 (± 3.44) |

| End point values | Cohort 1 - Dose Twice Weekly | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly | Cohort 3 - Dose Once Weekly |
|--------------------------------------|------------------------------|-----------------------------|------------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 4 | 4 | 5 |
| Units: kilopascal (kPa) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 5 | -3.13 (± 3.67) | -1.60 (± 3.45) | -6.67 (± 1.06) | 1.78 (± 2.82) |
| Week 12 | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 1.65 (± 4.42) |
| Week 24 | -6.00 (± 4.29) | -2.23 (± 4.06) | -9.37 (± 4.80) | -0.45 (± 5.21) |

| End point values | Cohort 3 - Dose Twice Weekly | | | |
|--------------------------------------|------------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 4 | | | |
| Units: kilopascal (kPa) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 5 | -1.90 (± 3.09) | | | |
| Week 12 | -3.15 (± 3.89) | | | |
| Week 24 | -0.95 (± 1.73) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with categorical results of liver fibrosis marker M2BPGi by visit

| | |
|-----------------|---|
| End point title | Number of subjects with categorical results of liver fibrosis marker M2BPGi by visit ^[3] |
|-----------------|---|

End point description:

The number of subjects achieving a categorical shift in Mac-2 binding protein glycosylation isomer (M2BPGi) are reported by visit. The categorical results shown correspond to the following M2BPGi cut-off index ranges: Negative = Less than 1.00; 1+ = 1.00 to 2.99; 2+ = 3.00 and above. M2BPGi was assessed for subjects in cohort 3 only.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 5, 12, and 24 weeks

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: Not all arms were specified in this endpoint.

| End point values | Cohort 3 (0.6 mg/kg/wk) | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | |
|---------------------------------------|----------------------------|-----------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: subjects | | | | |
| Week 5: Negative shift from baseline | 7 | 0 | 0 | |
| Week 5: 1+ shift from baseline | 1 | 4 | 3 | |
| Week 5: 2+ shift from baseline | 8 | 0 | 1 | |
| Week 12: Negative shift from baseline | 6 | 0 | 0 | |
| Week 12: 1+ shift from baseline | 2 | 3 | 3 | |
| Week 12: 2+ shift from baseline | 8 | 1 | 1 | |
| Week 24: Negative shift from baseline | 1 | 1 | 0 | |
| Week 24: 1+ shift from baseline | 5 | 2 | 3 | |
| Week 24: 2+ shift from baseline | 2 | 1 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: METAVIR Fibrosis Score Change from Baseline at week 6

| | |
|-----------------|--|
| End point title | METAVIR Fibrosis Score Change from Baseline at week 6 ^[4] |
|-----------------|--|

End point description:

Fibrosis stage and activity grade of liver biopsies were evaluated by a local pathologist using meta-analysis of histological data in viral hepatitis (METAVIR) fibrosis staging and activity grading. The number of subjects that achieved a change in METAVIR score at week 6 is reported for each arm for all subjects with scores available at Baseline and Week 6. A decrease in score represents an improvement in METAVIR fibrosis stage (METAVIR Fibrosis score: 0 = no fibrosis; 1 = portal fibrosis with rare septa; 3 = numerous septa without cirrhosis; 4 = cirrhosis)

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 6

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: Not all arms were specified in this endpoint.

| End point values | Cohort 2 (0.4 mg/kg/wk) | Cohort 3 (0.6 mg/kg/wk) | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly |
|--|-------------------------|-------------------------|-----------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 9 | 4 | 4 |
| Units: subjects | | | | |
| METAVIR fibrosis score change from baseline = -2 | 0 | 1 | 0 | 0 |
| METAVIR fibrosis score change from baseline = -1 | 1 | 2 | 1 | 0 |
| METAVIR fibrosis score change from baseline = 0 | 6 | 5 | 3 | 3 |

| End point values | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | | |
|--|-----------------------------|------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 5 | 4 | | |
| Units: subjects | | | | |
| METAVIR fibrosis score change from baseline = -2 | 0 | 1 | | |
| METAVIR fibrosis score change from baseline = -1 | 0 | 2 | | |
| METAVIR fibrosis score change from baseline = 0 | 4 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean maximum plasma concentration (C_{max}) of NDT-05-0038

| | |
|-----------------|--|
| End point title | Mean maximum plasma concentration (C _{max}) of NDT-05-0038 |
|-----------------|--|

End point description:

Blood samples were drawn at weeks 1, 3 and 5 to analyze the pharmacokinetics of siRNA ingredient NDT-05-0038. Arithmetic means and standard deviations of maximum plasma concentration (C_{max}) are reported in nanograms per milliliter (ng/mL) for all subjects in each dosing regimen with evaluable PK samples. Primary parameters were fit to the data using a 2 compartment model. Secondary parameters were estimated from the primary parameters.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

5 weeks

| End point values | Cohort 1 - Dose Once Weekly | Cohort 1 - Dose Twice Weekly | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly |
|--------------------------------------|-----------------------------------|------------------------------------|-----------------------------------|------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 4 | 4 | 3 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 240 (± 67.2) | 168 (± 60.7) | 570 (± 200) | 387 (± 257) |

| End point values | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | | |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2 | 3 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 1148 (± 616) | 720 (± 280) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean maximum plasma concentration (C_{max}) of DiVA (1 compartment model)

| | |
|-----------------|---|
| End point title | Mean maximum plasma concentration (C _{max}) of DiVA (1 compartment model) |
|-----------------|---|

End point description:

Blood samples were drawn at weeks 1, 3 and 5 to analyze the pharmacokinetics of vitamin A-conjugated targeting agent (DiVA). Arithmetic means and standard deviations of maximum plasma concentration (C_{max}) are reported in nanograms per milliliter (ng/mL) for all subjects in each dosing regimen with evaluable PK samples. Primary parameters were fit to the data using a 1 compartment model. Secondary parameters were estimated from the primary parameters.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

5 weeks

| End point values | Cohort 1 - Dose Once Weekly | Cohort 1 - Dose Twice Weekly | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly |
|--------------------------------------|-----------------------------------|------------------------------------|-----------------------------------|------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 4 | 4 | 4 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 1430 (± 163) | 579 (± 144) | 1814 (± 352) | 962 (± 225) |

| End point values | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | | |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 5 | 4 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 3873 (± 871) | 2033 (± 297) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean maximum plasma concentration (C_{max}) of NDT-05-0038 (1 compartment model)

| | |
|-----------------|--|
| End point title | Mean maximum plasma concentration (C _{max}) of NDT-05-0038 (1 compartment model) |
|-----------------|--|

End point description:

Blood samples were drawn at weeks 1, 3 and 5 to analyze the pharmacokinetics of siRNA ingredient NDT-05-0038. Arithmetic means and standard deviations of maximum plasma concentration (C_{max}) are reported in nanograms per milliliter (ng/mL) for all subjects in each dosing regimen with evaluable PK samples. Primary parameters were fit to the data using a 1 compartment model. Secondary parameters were estimated from the primary parameters.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

5 weeks

| End point values | Cohort 2 - Dose Twice Weekly | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | |
|--------------------------------------|------------------------------------|-----------------------------------|------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 1 | 3 | 1 | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 195 (± 99999) | 930 (± 36.6) | 508 (± 99999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean area under the curve (AUC) of NDT-05-0038

| | |
|-----------------|--|
| End point title | Mean area under the curve (AUC) of NDT-05-0038 |
|-----------------|--|

End point description:

Blood samples were drawn at weeks 1, 3 and 5 to analyze the pharmacokinetics of siRNA ingredient NDT-05-0038. Arithmetic means and standard deviations of area under the curve (AUC) are reported in hours*nanograms/milliliter (hr*ng/mL) for all subjects in each dosing regimen with evaluable PK samples. Primary parameters were fit to the data using a 2 compartment model. Secondary parameters were estimated from the primary parameters.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

5 weeks

| End point values | Cohort 1 - Dose Once Weekly | Cohort 1 - Dose Twice Weekly | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly |
|--------------------------------------|-----------------------------------|------------------------------------|-----------------------------------|------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 4 | 4 | 3 |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 5863 (± 4186) | 2592 (± 1222) | 16772 (± 10506) | 12676 (± 16786) |

| End point values | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | | |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2 | 3 | | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 26023 (± 26505) | 12801 (± 3400) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean area under the curve (AUC) of DiVA (1 compartment model)

| | |
|-----------------|---|
| End point title | Mean area under the curve (AUC) of DiVA (1 compartment model) |
|-----------------|---|

End point description:

Blood samples were drawn at weeks 1, 3 and 5 to analyze the pharmacokinetics of DiVA. Arithmetic means and standard deviations of area under the curve (AUC) are reported in hours*nanograms/milliliter (hr*ng/mL) for all subjects in each dosing regimen with evaluable PK samples. Primary parameters were fit to the data using a 1 compartment model. Secondary parameters were estimated from the primary parameters.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

5 weeks

| End point values | Cohort 1 - Dose Once Weekly | Cohort 1 - Dose Twice Weekly | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly |
|--------------------------------------|-----------------------------------|------------------------------------|-----------------------------------|------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 4 | 4 | 4 |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 119059 (± 28431) | 36060 (± 7388) | 141222 (± 12646) | 91878 (± 52016) |

| End point values | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | | |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 5 | 4 | | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 370818 (± 100854) | 154341 (± 27357) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean area under the curve (AUC) of NDT-05-0038 (1 compartment model)

| | |
|-----------------|--|
| End point title | Mean area under the curve (AUC) of NDT-05-0038 (1 compartment model) |
|-----------------|--|

End point description:

Blood samples were drawn at weeks 1, 3 and 5 to analyze the pharmacokinetics of siRNA ingredient NDT-05-0038. Arithmetic means and standard deviations of area under the curve (AUC) are reported in hours*nanograms/milliliter (hr*ng/mL) for all subjects in each dosing regimen with evaluable PK samples. Primary parameters were fit to the data using a 1 compartment model. Secondary parameters were estimated from the primary parameters.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

5 weeks

| End point values | Cohort 2 - Dose Twice Weekly | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | |
|--------------------------------------|------------------------------------|-----------------------------------|------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 1 | 3 | 1 | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 6811 (± 99999) | 74675 (± 30692) | 26373 (± 99999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean apparent distribution rate constant half life of NDT-05-0038

| | |
|-----------------|---|
| End point title | Mean apparent distribution rate constant half life of NDT-05-0038 |
|-----------------|---|

End point description:

Blood samples were drawn at weeks 1, 3 and 5 to analyze the pharmacokinetics of siRNA ingredient NDT-05-0038. Arithmetic means and standard deviations of apparent distribution rate constant half life ($t_{1/2\alpha}$) are reported in hours (hr) for all subjects in each dosing regimen with evaluable PK samples. Primary parameters were fit to the data using a 2 compartment model. Secondary parameters were estimated from the primary parameters.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 5 weeks | |

| End point values | Cohort 1 - Dose Once Weekly | Cohort 1 - Dose Twice Weekly | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly |
|--------------------------------------|-----------------------------------|------------------------------------|-----------------------------------|------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 4 | 4 | 3 |
| Units: hr | | | | |
| arithmetic mean (standard deviation) | 0.298 (± 0.116) | 1.66 (± 3.15) | 0.120 (± 0.072) | 0.078 (± 0.007) |

| End point values | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | | |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2 | 3 | | |
| Units: hr | | | | |
| arithmetic mean (standard deviation) | 0.254 (± | 3.64 (± 5.94) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean apparent elimination rate constant half life of NDT-05-0038

| | |
|-----------------|--|
| End point title | Mean apparent elimination rate constant half life of NDT-05-0038 |
|-----------------|--|

End point description:

Blood samples were drawn at weeks 1, 3 and 5 to analyze the pharmacokinetics of siRNA ingredient NDT-05-0038. Arithmetic means and standard deviations of apparent elimination rate constant half life ($t_{1/2b}$) are reported in hours (hr) for all subjects in each dosing regimen with evaluable PK samples. Primary parameters were fit to the data using a 2 compartment model. Secondary parameters were estimated from the primary parameters.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

5 weeks

| End point values | Cohort 1 - Dose Once Weekly | Cohort 1 - Dose Twice Weekly | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly |
|--------------------------------------|-----------------------------------|------------------------------------|-----------------------------------|------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 4 | 4 | 3 |
| Units: hr | | | | |
| arithmetic mean (standard deviation) | 38.3 (\pm 21.0) | 22.9 (\pm 16.8) | 34.6 (\pm 16.4) | 24.3 (\pm 15.0) |

| End point values | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | | |
|--------------------------------------|-----------------------------------|------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2 | 3 | | |
| Units: hr | | | | |
| arithmetic mean (standard deviation) | 34.3 (\pm 9.43) | 47.1 (\pm 44.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean elimination half life of NDT-05-0038 (1 compartment model)

| | |
|-----------------|---|
| End point title | Mean elimination half life of NDT-05-0038 (1 compartment model) |
|-----------------|---|

End point description:

Blood samples were drawn at weeks 1, 3 and 5 to analyze the pharmacokinetics of siRNA ingredient NDT-05-0038. Arithmetic means and standard deviations of elimination half life ($t_{1/2}$) are reported in hours (hr) for all subjects in each dosing regimen with evaluable PK samples. Primary parameters were fit to the data using a 1 compartment model. Secondary parameters were estimated from the primary parameters.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

5 weeks

| End point values | Cohort 2 - Dose Twice Weekly | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | |
|--------------------------------------|------------------------------------|-----------------------------------|------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 1 | 3 | 1 | |
| Units: hr | | | | |
| arithmetic mean (standard deviation) | 23.5 (\pm 99999) | 54.4 (\pm 20.5) | 35.3 (\pm 99999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean elimination half life of DiVA (1 compartment model)

| | |
|-----------------|--|
| End point title | Mean elimination half life of DiVA (1 compartment model) |
|-----------------|--|

End point description:

Blood samples were drawn at weeks 1, 3 and 5 to analyze the pharmacokinetics of DiVA. Arithmetic means and standard deviations of elimination half life ($t_{1/2}$) are reported in hours (hr) for all subjects in each dosing regimen with evaluable PK samples. Primary parameters were fit to the data using a 1 compartment model. Secondary parameters were estimated from the primary parameters.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

5 weeks

| End point values | Cohort 1 - Dose Once Weekly | Cohort 1 - Dose Twice Weekly | Cohort 2 - Dose Once Weekly | Cohort 2 - Dose Twice Weekly |
|--------------------------------------|-----------------------------------|------------------------------------|-----------------------------------|------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 4 | 4 | 4 |
| Units: hr | | | | |
| arithmetic mean (standard deviation) | 56.6 (\pm 11.2) | 43.2 (\pm 06.2) | 54.1 (\pm 06.1) | 62.3 (\pm 19.5) |

| End point values | Cohort 3 - Dose Once Weekly | Cohort 3 - Dose Twice Weekly | | |
|------------------|-----------------------------------|------------------------------------|--|--|
|------------------|-----------------------------------|------------------------------------|--|--|

| | | | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 5 | 4 | | |
| Units: hr | | | | |
| arithmetic mean (standard deviation) | 65.7 (\pm 11.88) | 51.9 (\pm 04.7) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After treatment for 5 consecutive weeks and follow-up through week 24

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Cohort 1 (0.2 mg/kg/wk) |
|-----------------------|-------------------------|

Reporting group description:

ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks

| | |
|-----------------------|-------------------------|
| Reporting group title | Cohort 3 (0.6 mg/kg/wk) |
|-----------------------|-------------------------|

Reporting group description:

ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks

| | |
|-----------------------|-------------------------|
| Reporting group title | Cohort 2 (0.4 mg/kg/wk) |
|-----------------------|-------------------------|

Reporting group description:

ND-L02-s0201 administered by IV infusion either once per week (once weekly) or administered in 2 divided doses per week (twice weekly) for 5 weeks

| Serious adverse events | Cohort 1 (0.2 mg/kg/wk) | Cohort 3 (0.6 mg/kg/wk) | Cohort 2 (0.4 mg/kg/wk) |
|---|-------------------------|-------------------------|-------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | 2 / 8 (25.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Squamous cell carcinoma of the cervix | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic gastric cancer | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | 0 / 8 (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 |
| Gastrointestinal disorders | | | |
| Ascites | | | |

| | | | |
|---|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 | Cohort 1 (0.2 mg/kg/wk) | Cohort 3 (0.6 mg/kg/wk) | Cohort 2 (0.4 mg/kg/wk) |
|---|-------------------------|-------------------------|-------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 8 (62.50%) | 3 / 9 (33.33%) | 6 / 8 (75.00%) |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 9 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Dizziness | | | |

| | | | |
|--|--|---|---|
| subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Epigastric discomfort subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 1 / 9 (11.11%) 1 | 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 | 1 / 9 (11.11%) 1 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 2 / 8 (25.00%) 5 |
| Infections and infestations | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 2 | 1 / 9 (11.11%) 1 | 0 / 8 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 02 October 2014 | <p>The timing of the final liver biopsy and corresponding serum HSP47 analysis was changed from Week 5 to Week 6. Screening evaluations were updated to include antibodies for hepatitis C virus (HCV) and human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and to remove testing for hepatitis B virus (HBV) and HCV viral load. A urine drug screen was added to screening. The permitted concomitant treatments were updated to remove permission for stable, suppressive therapies for HBV and to include permission for a list of commonly administered medications. The prohibited concomitant treatments were updated to prohibit ongoing therapies for HBV and HCV, as well as treatment with interferon for any indication. The timing of weekly visits for subjects receiving infusions once per week or twice per week were made more stringent during Weeks 1 to 5 to ensure that treatments and assessments were made at appropriate intervals. The timing of weekly visits was relaxed for Week 7 to 24 to ± 2 days. The weight to be used for dose determination for all doses was corrected from weight taken at screening to weight taken at baseline. A statement indicating that instructions for treating immediate or delayed infusion-related reactions would be provided to the site was removed to allow the Investigator to treat such reactions as medically appropriate at their discretion. procedures/assessments to be completed in the event of early termination from the study were added. The number of subjects screened for the study and protocol deviations was to be included in the data that is reviewed by the Data Safety Monitoring Board (DSMB) before opening the next cohort. An inclusion criterion was added to allow enrollment of active substance abusers at the discretion of the Investigator. The exclusion criterion which excludes subjects with a history of malignancy within the last 5 years was modified to include an exception for basal cell carcinoma.</p> |
| 18 November 2014 | <p>Provided windows around the timing of blood draws for PK assessments. Provided windows for blood draws for complement determination during and after study drug infusion. Clarified the difference between prior and concomitant medications. Added definition of the METAVIR score system for severity of fibrosis. Included language that the METAVIR activity grading would be collected. Specified treatment days for the twice-weekly treatment regimen and provided treatment windows for treatment days; specified minimum time between infusions during study treatment weeks. Specified a visit window for the Week 6 evaluation and clarified that the window does not apply to the liver biopsy. Changed the requirement for the Week 6 visit to occur on Monday for those dosed twice weekly to occur 1 week after the last infusion. Changed the requirement for blood pressure to be taken from the same extremity each measurement to be taken from the opposite arm from the infusion arm. Allow screening labs to serve also as baseline labs if the screening visit was within 7 days of the baseline visit. Removed collection of samples for serum heat shock protein 47 (HSP47) assessment. Changed the section on pregnancy from gaining informed consent to gaining permission to follow a pregnancy through to outcome. Clarified that temperature is to be taken orally. Removed the exclusion criterion for subjects with carcinoembryonic antigen (CEA) levels above upper limit of normal.</p> |
| 05 March 2015 | <p>Visit schedule clarified for subjects who receive treatment once weekly. Text made consistent with Section 10.1 Dosing Schedule (ie, subjects randomly assigned to receive treatment once per week should be dosed the same day of the week throughout the treatment period). A breathalyzer was added as an option for ethanol screening at European sites in the event that urine ethanol testing is unavailable. The liver fibrosis scoring system was changed. METAVIR scoring was used to evaluate liver fibrosis. Knodell scoring and Ishak scoring were removed from the protocol. Weight and height discussion moved from physical examination section to vital signs/weight/height section. The requirement to conduct a baseline physical exam and a baseline electrocardiogram (ECG) was removed if these procedures were conducted at screening within 7 days before the baseline visit.</p> |

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| 26 August 2015 | <p>Study days were corrected for Weeks 12, 16, 20, and 24: Week 12 (Day 78 ± 2 days) Week 16 (Day 106 ± 2 days) Week 20 (Day 134 ± 2 days) Week 24 (Day 162 ± 2 days) Additional timepoint was added at Week 12 (Visit 11, ± 2 days). Additional blood samples were added for liver fibrosis marker, Mac-2 binding protein glycosylation isomer (M2BPGi) before the first treatment (Week 1), after the end of infusion (EOI) of the last treatment (Week 5), and during follow-up at the Week 12 and at Week 24 visits (or at early termination). Results were added for long-term pharmacology and toxicology studies conducted with ND-L02-s0201. Modified the language to allow flexibility for the total number of enrolled subjects, to accommodate the potential of replacement subjects, and clarified that subjects who withdraw from the study during the dosing phase may have been replaced and described the procedures for their replacement. Wording revised to indicate that any potential disturbance in bone density was monitored in human subjects by dual-energy X-ray absorptiometry (DEXA) scans. Description of results from the Phase 1a Study ND-L02-s0201-001 was expanded to indicate there was no evidence of drug-related effects on biomarkers of bone turnover. Justification was expanded to include nonclinical study results. Introduced a window of ± 15 minutes to the 2 hours before the start of study drug infusion at which the premedication oral dose of levocetirizine dihydrochloride could be administered. The liver fibrosis scoring system was changed. Ishak and Knodell scoring were used in addition to METAVIR scoring to evaluate liver fibrosis. An evaluation of the analysis of the biopsy samples using quantitative reverse transcription polymerase chain reaction (qRT-PCR) and histology staining was done throughout the study. Slides for all subjects in all cohorts were stained for Sirius Red staining throughout the study not just those in Cohort 3.</p> |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported