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

Subject analysis set description:
Cohort 3 subjects receiving 0.3 mg/kg twice weekly

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 (Cmax) of NDT-05-0038

End point title	Mean maximum plasma concentration (Cmax) 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 (Cmax) 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 (Cmax) of DiVA (1 compartment model)

End point title	Mean maximum plasma concentration (Cmax) 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 (Cmax) 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 (Cmax) of NDT-05-0038 (1 compartment model)

End point title	Mean maximum plasma concentration (Cmax) 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 (Cmax) 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 (t1/2a) 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)		

0.063)

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 (t1/2b) 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 (± 21.0)	22.9 (± 16.8)	34.6 (± 16.4)	24.3 (± 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 (± 9.43)	47.1 (± 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 (t1/2) 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 (± 99999)	54.4 (± 20.5)	35.3 (± 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 (t1/2) 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 (± 11.2)	43.2 (± 06.2)	54.1 (± 06.1)	62.3 (± 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 (± 11.88)	51.9 (± 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	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Epigastric discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthtralgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Muscle spasms			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	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	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.
18 November 2014	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.
05 March 2015	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.

26 August 2015	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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported