



Clinical trial results:

Phase I/II study on safety and efficacy of NMS-01940153E in adult patients with unresectable hepatocellular carcinoma (HCC) previously treated with systemic therapy.

Summary

EudraCT number	2020-001002-26
Trial protocol	IT
Global end of trial date	06 August 2024

Results information

Result version number	v1 (current)
This version publication date	23 May 2025
First version publication date	23 May 2025

Trial information

Trial identification

Sponsor protocol code	MPSA-153-001
-----------------------	--------------

Additional study identifiers

ISRCTN number	ISRCTN000000000
ClinicalTrials.gov id (NCT number)	NCT000000000
WHO universal trial number (UTN)	U0000-0000-0000
Other trial identifiers	NA: NA

Notes:

Sponsors

Sponsor organisation name	Nerviano Medical Sciences S.r.l.
Sponsor organisation address	Viale Pasteur, 10 - Nerviano, Milan, Italy,
Public contact	Anders Elm Pedersen, Global Clinical Development, Nerviano Medical Sciences S.r.l., 39 0331 58 1111, DL-Clinicaltrials@nervianoms.com
Scientific contact	Anders Elm Pedersen, Global Clinical Development, Nerviano Medical Sciences S.r.l., 39 0331 58 1111, DL-Clinicaltrials@nervianoms.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 August 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 August 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To determine the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of NMS-01940153E administered as single agent to adult patients with unresectable hepatocellular carcinoma (HCC) previously treated with systemic therapy (Phase I).
- To assess the anti-tumor efficacy of NMS-01940153E administered as single agent to adult patients with unresectable hepatocellular carcinoma previously treated with systemic therapy (Phase II).

Protection of trial subjects:

Patients might have continued with therapy unless the occurrence of any of the following:

- Disease progression by RECIST 1.1 at any time, unless there is reasonable evidence of clinical benefit to justify continuation on treatment, to be discussed with the Sponsor;
- Unacceptable drug-related toxicities incompatible with continuation of treatment with NMS-01940153E according to the judgment of the Investigator, even at a reduced dose;
- Any medical event requiring administration of an unauthorised concomitant treatment if it interferes with the study evaluations and/or if it jeopardises patient's safety (see Section 9.2.7 of the study protocol);
- Change in the patient's medical status (including pregnancy) such that the Investigator believes that patient safety may be compromised or that it would be in the best patient's interest to stop treatment;
- Occurrence of permanent or significant incapacity or disability;
- Treatment delay for >1 week from day 28 of any cycle due to treatment related toxicity, unless the investigator believes treatment continuation is in the best patient's interest. In this case a maximum delay of 2 weeks is allowed;
- More than two dose de-escalations required;
- Substantial deviation from specified inclusion or exclusion criteria or non-compliance by the patient with protocol requirements;
- Patient's refusal to continue study treatment;
- Withdrawal of consent;
- Patient lost to follow up;
- Death;
- Study terminated by the Sponsor.

Patients were withdrawn from the study in case of:

- Withdrawal of consent;
- Patient lost to follow up;
- Death;
- Study terminated by the Sponsor.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2020
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	Spain: 9
Country: Number of subjects enrolled	Italy: 22
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	17
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects with histological, cytological or radiological diagnosis of HCC, according to the American Association for the Study of Liver Diseases/European Association for the Study of the Liver criteria, in subjects that were refractory or not able to tolerate the standard therapy, or for whom the standard therapy is not considered appropriate.

Pre-assignment period milestones

Number of subjects started	31
Number of subjects completed	30

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Enrolled but not treated: 1
----------------------------	-----------------------------

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I Participants: 100 mg/m2/week

Arm description:

All participants in Phase I who received 100 mg/m2/week intravenous NMS-01940153E. All participants who completed the study were followed up until death.

Arm type	Experimental
Investigational medicinal product name	NMS-01940153E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

NMS-01940153E was administered IV for 3 consecutive weeks on days 1, 8, 15 followed by 1 week of rest, in a 28-day cycle. The total dose to be administered was calculated based on patient's body surface area. The duration of infusion was dependent on the total dose to be administered:

- 1 hour infusion if ≤ 255 mg are administered
- 1 hour 30 minutes infusion if > 255 mg but < 375 mg are administered

The starting dose for the Phase I portion of the study was 100 mg/m2/week, then according to the observed safety profile, dose increments of 25-35% were to be applied until the maximum tolerated dose was reached. In presence of unacceptable toxicity observed at 100 mg/m2/week, a lower dose level by 25-35% could be tested.

Arm title	Phase II Participants: 100 mg/m2/week
------------------	---------------------------------------

Arm description:

All participants in Phase II who received 100 mg/m2/week intravenous NMS-01940153E. All participants who completed the study were followed up until death.

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

Investigational medicinal product name	NMS-01940153E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the Phase II portion of the study, NMS-01940153E was administered at the recommended Phase 2 dose of 100 mg/m²/week defined in the Phase I as starting dose.

Arm title	Phase I Participants: 135 mg/m ² /week
------------------	---

Arm description:

All participants in Phase I who received 135 mg/m²/week intravenous NMS-01940153E. All participants who completed the study were followed up until death.

Arm type	Experimental
Investigational medicinal product name	NMS-01940153E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

NMS-01940153E was administered IV for 3 consecutive weeks on days 1, 8, 15 followed by 1 week of rest, in a 28-day cycle. The total dose to be administered was calculated based on patient's body surface area. The duration of infusion was dependent on the total dose to be administered:

- 1 hour infusion if ≤255 mg are administered
- 1 hour 30 minutes infusion if >255 mg but <375 mg are administered

The starting dose for the Phase I portion of the study was 100 mg/m²/week, then according to the observed safety profile, dose increments of 25-35% were to be applied until the maximum tolerated dose was reached. In presence of unacceptable toxicity observed at 100 mg/m²/week, a lower dose level by 25-35% could be tested.

Number of subjects in period 1^[1]	Phase I Participants: 100 mg/m ² /week	Phase II Participants: 100 mg/m ² /week	Phase I Participants: 135 mg/m ² /week
Started	6	18	6
Completed	5	9	5
Not completed	1	9	1
Study terminated by sponsor	1	8	1
Lost to follow-up	-	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1 participant was enrolled but did not receive treatment.

Baseline characteristics

Reporting groups

Reporting group title	Phase I Participants: 100 mg/m2/week
Reporting group description: All participants in Phase I who received 100 mg/m2/week intravenous NMS-01940153E. All participants who completed the study were followed up until death.	
Reporting group title	Phase II Participants: 100 mg/m2/week
Reporting group description: All participants in Phase II who received 100 mg/m2/week intravenous NMS-01940153E. All participants who completed the study were followed up until death.	
Reporting group title	Phase I Participants: 135 mg/m2/week
Reporting group description: All participants in Phase I who received 135 mg/m2/week intravenous NMS-01940153E. All participants who completed the study were followed up until death.	

Reporting group values	Phase I Participants: 100 mg/m2/week	Phase II Participants: 100 mg/m2/week	Phase I Participants: 135 mg/m2/week
Number of subjects	6	18	6
Age categorical Units: Subjects			
Adults (18-64 years)	3	10	3
From 65-84 years	3	8	3
Gender categorical Units: Subjects			
Female	1	1	0
Male	5	17	6
Race Units: Subjects			
White	5	18	6
Black or African American	1	0	0
Eastern cooperative oncology group performance status			
When multiple Eastern cooperative oncology group performance status (ECOG PS) determinations were available, the most recent not missing baseline assessment was considered.			
Units: Subjects			
ECOG PS 0	3	10	3
ECOG PS 1	3	8	3

Reporting group values	Total		
Number of subjects	30		
Age categorical Units: Subjects			
Adults (18-64 years)	16		
From 65-84 years	14		
Gender categorical Units: Subjects			
Female	2		
Male	28		

Race			
Units: Subjects			
White	29		
Black or African American	1		
Eastern cooperative oncology group performance status			
When multiple Eastern cooperative oncology group performance status (ECOG PS) determinations were available, the most recent not missing baseline assessment was considered.			
Units: Subjects			
ECOG PS 0	16		
ECOG PS 1	14		

End points

End points reporting groups

Reporting group title	Phase I Participants: 100 mg/m2/week
Reporting group description: All participants in Phase I who received 100 mg/m2/week intravenous NMS-01940153E. All participants who completed the study were followed up until death.	
Reporting group title	Phase II Participants: 100 mg/m2/week
Reporting group description: All participants in Phase II who received 100 mg/m2/week intravenous NMS-01940153E. All participants who completed the study were followed up until death.	
Reporting group title	Phase I Participants: 135 mg/m2/week
Reporting group description: All participants in Phase I who received 135 mg/m2/week intravenous NMS-01940153E. All participants who completed the study were followed up until death.	
Subject analysis set title	All Treated Participants (Phase I and II; all dose levels)
Subject analysis set type	Full analysis
Subject analysis set description: Includes all treated participants in the Phase I and Phase II parts of this study, at all dose levels	
Subject analysis set title	100 mg/m2/weeks (Phase I and II)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Includes all participants who received 100 mg/m2/weeks in the Phase I and Phase II of this study	
Subject analysis set title	135 mg/m2/weeks (Phase I only)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Includes all participants who received 135 mg/m2/weeks in the Phase I of this study	
Subject analysis set title	100 mg/m2/weeks (Phase I only)
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants in Phase I who received 100 mg/m2/week intravenous NMS-01940153E	
Subject analysis set title	Phase II Evaluable Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants of the treated set who had measurable disease at baseline assessed according to RECIST 1.1 and at least one tumor evaluation on treatment, unless they died before the first tumor on-treatment assessment, in which case they were considered treatment failure.	

Primary: Phase I drug related dose limiting toxicities (DLTs)

End point title	Phase I drug related dose limiting toxicities (DLTs) ^[1]
End point description: All 12 Phase I treated patients were evaluable for DLT (Dose-Limiting Toxicity Evaluable Set) and included 6 patients treated at each of the two dose levels explored (i.e., 100 mg/m2/week and 135 mg/m2/week) who received at least 66% of the study drug in the first 28-day cycle of treatment and underwent a DLT assessment within the DLT window. Participants who experienced DLTs are presented.	
End point type	Primary
End point timeframe: Phase I: From screening to end of first 28-day cycle (17 months)	

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: Not applicable for this endpoint

End point values	135 mg/m2/weeks (Phase I only)	100 mg/m2/weeks (Phase I only)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: participants	2	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase II objective response rate

End point title	Phase II objective response rate ^[2]
-----------------	---

End point description:

The objective response rate (ORR) was calculated as the proportion of evaluable patients who achieved, as best overall response (BOR), confirmed complete response (CR) or partial response (PR) measured by investigator-assessed RECIST 1.1 (Phase II).

End point type	Primary
----------------	---------

End point timeframe:

Phase II: From Phase II start to Study Completion (23 months)

Notes:

[2] - 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: Not applicable for this endpoint

End point values	Phase II Evaluable Population			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: participants				
Stable Disease	3			
Progressive Disease	11			
Complete Response	0			
Partial Response	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-emergent adverse by maximum CTC grade

End point title	Treatment-emergent adverse by maximum CTC grade
-----------------	---

End point description:

The number of events are presented by maximum Common Terminology Criteria (CTC) grade (graded using National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0).

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.

Grade 4 Life-threatening consequences; urgent intervention indicated.

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

End point timeframe:

Phase I: From the Study Start Date to Phase I Completion (32 months) - Phase II: From Phase II start to Study Completion (23 months). Phase 2 started before Phase 1 completed.

End point values	Phase I Participants: 100 mg/m2/week	Phase II Participants: 100 mg/m2/week	Phase I Participants: 135 mg/m2/week	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	18	6	
Units: participants				
Grade 1	0	3	0	
Grade 2	1	8	1	
Grade 3	3	7	3	
Grade 4	1	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-emergent adverse events related to NMS-01940153E

End point title	Treatment-emergent adverse events related to NMS-01940153E
-----------------	--

End point description:

The number of treatment-emergent adverse events related to NMS-01940153E by maximum CTC grade experienced (graded using NCI CTCAE Version 5.0). Whether the the AE was related or not was assessed by the investigator. If an AE was reported for a participant more than once during treatment, the worst CTC Grade is presented.

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.

Grade 4 Life-threatening

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

End point timeframe:

Phase I: From the Study Start Date to Phase I Completion (32 months) - Phase II: From Phase II start to Study Completion (23 months). Phase 2 started before Phase 1 completed.

End point values	Phase I Participants: 100 mg/m2/week	Phase II Participants: 100 mg/m2/week	Phase I Participants: 135 mg/m2/week	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	18	6	
Units: events				
Grade 1	0	7	0	
Grade 2	1	3	1	
Grade 3	2	2	2	
Grade 4	1	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Hematology: Overall treatment-emergent abnormalities by dose level and maximum CTC grade

End point title	Hematology: Overall treatment-emergent abnormalities by dose level and maximum CTC grade
-----------------	--

End point description:

Number of treatment emergent abnormalities (at any grade) at all dose levels are presented.

CTC = Common Terminology Criteria

WBC = white blood cells

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

End point timeframe:

From screening to 28 days follow-up, an average 6 months

End point values	All Treated Participants (Phase I and II; all dose levels)	100 mg/m2/weeks (Phase I and II)	135 mg/m2/weeks (Phase I only)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	24	6	
Units: events				
Hemoglobin Decreased	18	13	5	
Neutrophil Count Decreased	10	6	4	
WBC Decreased	14	8	6	
Platelet Count Decreased	10	6	4	

Statistical analyses

Secondary: Neutrophils count decrease: Time to first occurrence of $\geq$ Grade 3 and time to recovery to Grade 1

End point title	Neutrophils count decrease: Time to first occurrence of $\geq$ Grade 3 and time to recovery to Grade 1
-----------------	--

End point description:

The mean days to first occurrence of neutrophil count decrease are presented for all dose levels.

Grade 0: $\geq 2,000/\text{mm}^3$

Grade 1: $\geq 1,500 - < 2,000/\text{mm}^3$

Grade 2: $\geq 1,000 - < 1,500/\text{mm}^3$

Grade 3: $\geq 500 - < 1,000/\text{mm}^3$

Grade 4: $< 500/\text{mm}^3$

$\geq$ G3 = Time (days) to Treatment Start to First Occurrence of Neutrophil Count Decrease $\geq$ Grade 3
 $\geq$ G3 to Recovery to G1 = Time (days) to First Occurrence of Neutrophil Count Decrease $\geq$ Grade 3 to Recovery to Grade 1

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

End point timeframe:

From screening to 28 days follow-up, an average 6 months

End point values	All Treated Participants (Phase I and II; all dose levels)	100 mg/m ² /weeks (Phase I and II)	135 mg/m ² /weeks (Phase I only)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6 ^[3]	2	4 ^[4]	
Units: days				
arithmetic mean (standard deviation)				
$\geq$ G3	39.67 ($\pm$ 23.38)	63.00 ($\pm$ 19.80)	28.00 ($\pm$ 15.36)	
$\geq$ G3 to Recovery to G1	7.20 ($\pm$ 2.59)	7.00 ($\pm$ 1.41)	7.33 ($\pm$ 3.51)	

Notes:

[3] - Only 5 participants were included in the $\geq$ G3 to Recovery to G1 assessment.

[4] - Only 3 participants were included in the $\geq$ G3 to Recovery to G1 assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Blood chemistry: Treatment-emergent abnormalities by dose level

End point title	Blood chemistry: Treatment-emergent abnormalities by dose level
-----------------	---

End point description:

Treatment-emergent abnormalities in blood chemistry at any grade are presented by dose level.

ALP = Alkaline phosphatase

ALT = Alanine aminotransferase

AST = Aspartate aminotransferase

GGT = Gamma-glutamyl transferase

LDH = Lactate dehydrogenase

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

End point timeframe:

From screening to 28 days follow-up, an average 6 months

End point values	All Treated Participants (Phase I and II; all dose levels)	100 mg/m2/weeks (Phase I and II)	135 mg/m2/weeks (Phase I only)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24	6	30	
Units: events				
Hypoalbuminemia	8	4	12	
Hypoglycemia	0	1	1	
AST Increased	12	3	15	
ALT Increased	8	2	10	
GGT Increased	9	1	10	
Creatinine Increased	6	3	9	
Blood Bilirubin Increased	7	1	8	
ALP Increased	10	1	11	
Blood LDH Increased	14	4	18	
Hypocalcemia	1	1	2	
Hypernatremia	0	1	1	
Hyperkalemia	7	0	7	
Hypomagnesemia	5	3	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Blood chemistry and coagulation: Treatment-emergent abnormalities

End point title	Blood chemistry and coagulation: Treatment-emergent abnormalities
-----------------	---

End point description:

Treatment Emergent abnormalities by dose Level are presented for blood chemistry and coagulation parameters.

INR = international normalized ratio

LNL = lower normal limit

NL = normal limit

ULN = upper limit of normal

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

End point timeframe:

From screening to 28 days follow-up, an average 6 months

End point values	All Treated Participants (Phase I and II; all dose levels)	100 mg/m2/weeks (Phase I and II)	135 mg/m2/weeks (Phase I only)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	24	6	
Units: events				
Hyponatremia: Total	6	4	2	
Hyponatremia: Below LNL	6	4	2	
Hypokalemia: Total	1	0	1	
Hypokalemia: Below LNL	1	0	1	
Phosphatemia: Total	13	11	2	
Phosphatemia: Above ULN	3	3	0	
Phosphatemia: Below LNL	9	7	2	
Phosphatemia: Above/Below NL	1	1	0	
Hyperglycemia: Total	11	9	2	
Hyperglycemia: Above ULN	10	9	1	
Hyperglycemia: Above/Below NL	1	0	1	
Blood Urea Nitrogen: Total	2	2	0	
Blood Urea Nitrogen: Above ULN	2	2	0	
Urea: Total	6	6	0	
Urea: Above ULN	5	5	0	
Urea: Below LNL	1	1	0	
Unconjugated Bilirubin: Total	3	3	0	
Unconjugated Bilirubin: Above ULN	3	3	0	
Total Protein: Total	9	7	2	
Total Protein: Above ULN	2	2	0	
Total Protein: Below LNL	6	4	2	
Total Protein: Above/Below NL	1	1	0	
INR: Total	12	11	1	
INR: Above ULN	9	8	1	
INR: Below LNL	1	1	0	
INR: Above/Below NL	2	2	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Electrocardiogram abnormalities

End point title	Electrocardiogram abnormalities
-----------------	---------------------------------

End point description:

The number of participants who experienced electrocardiogram abnormalities are presented.

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

End point timeframe:

From screening to 28 days follow-up, an average 6 months

End point values	Phase I Participants: 100 mg/m2/week	Phase II Participants: 100 mg/m2/week	Phase I Participants: 135 mg/m2/week	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	18	6	
Units: participants				
ECG Abnormalities	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax and Tlast of NMS-01940153E

End point title	Tmax and Tlast of NMS-01940153E
End point description: Plasma pharmacokinetic (PK) profiles of NMS-01940153E were characterized on Day 1 and 15 of the first Cycle after infusion. Tmax = Time to maximum observed plasma concentration Tlast = Time of last detectable concentration	
End point type	Secondary
End point timeframe: Day 1 to Day 15	

End point values	135 mg/m2/weeks (Phase I only)	100 mg/m2/weeks (Phase I only)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6 ^[5]		
Units: hours				
arithmetic mean (standard deviation)				
Tmax: Day 1	1.19 (± 0.513)	0.933 (± 0.0327)		
Tmax: Day 15	1.87 (± 1.90)	1.10 (± 0.216)		
Tlast: Day 1	154 (± 39.2)	169 (± 3.01)		
Tlast: Day 15	169 (± 0.418)	144 (± 48.5)		

Notes:

[5] - Only 4 evaluable participants on Day 15

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax and Clast of NMS-01940153E

End point title	Cmax and Clast of NMS-01940153E
End point description: Plasma pharmacokinetic (PK) profiles of NMS-01940153E were characterized on Day 1 and 15 of the first Cycle after infusion.	

C_{max} = Maximum observed plasma concentration

C_{last} = Last detectable concentration

End point type	Secondary
End point timeframe:	
Day 1 to Day 15	

End point values	135 mg/m ² /weeks (Phase I only)	100 mg/m ² /weeks (Phase I only)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6 ^[6]		
Units: µM				
arithmetic mean (standard deviation)				
C _{max} : Day 1	1.91 (± 0.640)	0.754 (± 0.174)		
C _{max} : Day 15	1.59 (± 1.31)	1.35 (± 1.10)		
C _{last} : Day 1	0.0840 (± 0.0335)	0.0590 (± 0.0191)		
C _{last} : Day 15	0.133 (± 0.0779)	0.113 (± 0.0454)		

Notes:

[6] - Only 4 evaluable participants on Day 15

Statistical analyses

No statistical analyses for this end point

Secondary: AUCl_{ast}, AUC_{weekly}, and AUC_{inf} of NMS-01940153E

End point title	AUCl _{ast} , AUC _{weekly} , and AUC _{inf} of NMS-01940153E
End point description:	
Plasma pharmacokinetic (PK) profiles of NMS-01940153E were characterized on Day 1 and 15 of the first Cycle after infusion. Infusions occurred on Days 1, 8, and 15.	
AUCl _{ast} = Area under the interpolated observed plasma time-concentration curve from infusion start to the last observed plasma concentration	
AUC _{weekly} = Area under the interpolated observed plasma time-concentration curve from infusion start to 168 hours	
AUC _{inf} = Area under the interpolated observed plasma time-concentration curve from infusion start extrapolated to infinity based on the last observed plasma concentration	
End point type	Secondary
End point timeframe:	
From Day 1 to 21 (168 hours after the Day 15 infusion)	

End point values	135 mg/m2/weeks (Phase I only)	100 mg/m2/weeks (Phase I only)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6 ^[7]		
Units: h·µM				
arithmetic mean (standard deviation)				
AUClast: Day 1	24.8 (± 8.55)	20.8 (± 4.31)		
AUClast: Day 15	39.1 (± 14.9)	30.0 (± 9.16)		
AUCweekly: Day 1	25.7 (± 7.11)	20.8 (± 4.35)		
AUCweekly: Day 15	39.0 (± 14.8)	32.4 (± 6.49)		
AUCinf: Day 1	37.1 (± 14.9)	28.7 (± 6.88)		
AUCinf: Day 15	62.9 (± 34.1)	48.1 (± 19.6)		

Notes:

[7] - Only 4 evaluable participants on Day 15

Statistical analyses

No statistical analyses for this end point

Secondary: t_{1/2,z} of NMS-01940153E

End point title	t _{1/2,z} of NMS-01940153E
-----------------	-------------------------------------

End point description:

Plasma pharmacokinetic (PK) PK profiles of NMS-01940153E were characterized on Day 1 and 15 of the first Cycle after infusion.

t_{1/2,z} = Half-life of the terminal phase of observed plasma concentration

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

End point timeframe:

Day 1 to Day 15

End point values	135 mg/m2/weeks (Phase I only)	100 mg/m2/weeks (Phase I only)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6 ^[8]		
Units: days				
arithmetic mean (standard deviation)				
t _{1/2,z} Day 1	4.17 (± 1.40)	3.74 (± 0.800)		
t _{1/2,z} Day 15	4.79 (± 1.15)	4.38 (± 2.64)		

Notes:

[8] - Only 4 evaluable participants on Day 15

Statistical analyses

No statistical analyses for this end point

Secondary: CL and CLss of NMS-01940153E

End point title	CL and CLss of NMS-01940153E
-----------------	------------------------------

End point description:

Plasma pharmacokinetic (PK) PK profiles of NMS-01940153E were characterized on Day 1 and 15 of the first Cycle after infusion.

CL = Clearance based on last observed concentration and extrapolation to infinity

CL_{ss} = Clearance calculated for a dosing period of 168 h either after a single dose or in steady-state

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

End point timeframe:

Day 1 to Day 15

End point values	135 mg/m2/weeks (Phase I only)	100 mg/m2/weeks (Phase I only)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6 ^[9]		
Units: L/h				
arithmetic mean (standard deviation)				
CL: Day 1	10.2 (± 4.01)	10.1 (± 3.16)		
CL: Day 15	6.19 (± 2.08)	6.12 (± 2.24)		
CL _{ss} : Day 1	13.8 (± 3.73)	13.8 (± 4.14)		
CL _{ss} : Day 15	9.31 (± 2.52)	8.53 (± 2.50)		

Notes:

[9] - Only 4 evaluable participants on Day 15

Statistical analyses

No statistical analyses for this end point

Secondary: V_{ss} and V_{ss,SS} of NMS-01940153E

End point title	V _{ss} and V _{ss,SS} of NMS-01940153E
-----------------	---

End point description:

Plasma pharmacokinetic (PK) profiles of NMS-01940153E were characterized on Day 1 and 15 of the first Cycle after infusion.

V_{ss} = Volume of distribution at steady state based last observed concentration extrapolated to infinity and Clearance calculated for a dosing period of 168 h either after a single dose or in steady-state

V_{ss,SS} = Volume of distribution at steady state based last observed concentration extrapolated to infinity and clearance based on last observed concentration and extrapolation to infinity

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

End point timeframe:

Day 1 to Day 15

End point values	135 mg/m2/weeks (Phase I only)	100 mg/m2/weeks (Phase I only)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6 ^[10]		
Units: L				
arithmetic mean (standard deviation)				
Vss: Day 1	1210 (± 199)	1230 (± 395)		
Vss: Day 15	919 (± 245)	787 (± 304)		
Vss,SS: Day 1	1630 (± 285)	1700 (± 620)		
Vss,SS: Day 15	1380 (± 354)	1180 (± 649)		

Notes:

[10] - Only 4 evaluable participants on Day 15

Statistical analyses

No statistical analyses for this end point

Secondary: RA AUCweekly and RA Cmax of NMS-01940153E

End point title	RA AUCweekly and RA Cmax of NMS-01940153E
-----------------	---

End point description:

Plasma pharmacokinetic (PK) profiles of NMS-01940153E were characterized on Day 1 and 15 of the first Cycle after infusion. Infusions occurred on Days 1, 8, and 15.

RA AUCweekly = Accumulation ratio Day 1 to 15 calculated using area under the interpolated observed plasma time-concentration curve from infusion start to 168 hours

RA Cmax = Accumulation ratio Day 1 to 15 calculated using maximum observed plasma concentration

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

End point timeframe:

From Day 1 to 21 (168 hours after the Day 15 infusion)

End point values	135 mg/m2/weeks (Phase I only)	100 mg/m2/weeks (Phase I only)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6 ^[11]		
Units: ratio				
arithmetic mean (standard deviation)				
RA AUCweekly: Day 15	1.51 (± 0.293)	1.66 (± 0.188)		
RA Cmax: Day 15	0.858 (± 0.547)	1.78 (± 1.36)		

Notes:

[11] - Only 4 evaluable participants on Day 15

Statistical analyses

No statistical analyses for this end point

Secondary: FE of NMS-01940153E

End point title	FE of NMS-01940153E
-----------------	---------------------

End point description:

Plasma pharmacokinetic (PK) profiles of NMS-01940153E were characterized on Day 1 and 15 of the first Cycle after infusion.

FE = Molar fraction of excreted compound relative to the administered molar dose calculated using urine concentration and volume data

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

End point timeframe:

Day 1 to Day 15

End point values	135 mg/m2/weeks (Phase I only)	100 mg/m2/weeks (Phase I only)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6 ^[12]		
Units: percentage				
arithmetic mean (standard deviation)				
FE Day 1	0.357 (± 0.260)	0.458 (± 0.374)		
FE Day 15	0.826 (± 0.713)	0.563 (± 0.424)		

Notes:

[12] - Only 4 evaluable participants on Day 15

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I objective tumor response (partial and complete response)

End point title	Phase I objective tumor response (partial and complete response) ^[13]
-----------------	--

End point description:

Phase I any dose level, objective response and best overall tumor response are presented, as measured by investigator assessed RECIST 1.1 (Phase I).

The objective response rate was calculated as the proportion of evaluable patients who achieved best overall response (BOR), confirmed complete response (CR) or partial response (PR).

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

End point timeframe:

Phase I: From the Study Start Date to Phase I Completion (32 months)

Notes:

[13] - 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 applicable for this endpoint

End point values	Phase I Participants: 100 mg/m2/week	Phase I Participants: 135 mg/m2/week		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: participants				
Objective Response (Partial Response)	1	1		
Objective Response (Complete Response)	0	0		
Stable Disease	1	2		
Progressive Disease	4	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II objective response rate as measured by investigator-assessed mRECIST

End point title	Phase II objective response rate as measured by investigator-assessed mRECIST ^[14]
-----------------	---

End point description:

Objective response rate as measured by investigator-assessed mRECIST in Phase II.

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

End point timeframe:

Phase II: From Phase II start to Study Completion (23 months)

Notes:

[14] - 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 applicable for this endpoint

End point values	Phase II Participants: 100 mg/m2/week			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: participants				
Stable Disease	3			
Progressive Disease	11			
Objective Response (Partial Response)	0			
Objective Response (Complete Response)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival, as measured by investigator-assessed RECIST

1.1, in Phases I and II

End point title	Progression free survival, as measured by investigator-assessed RECIST 1.1, in Phases I and II ^[15]
-----------------	--

End point description:

Progression Free Survival as measured by investigator assessed RECIST 1.1, for all treated participants in Phase I and Phase II.

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

End point timeframe:

Phase I: From the Study Start Date to Phase I Completion (32 months) - Phase II: From Phase II start to Study Completion (23 months). Phase 2 started before Phase 1 completed.

Notes:

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

Justification: Not applicable for this endpoint

End point values	Phase I Participants: 100 mg/m2/week	Phase I Participants: 135 mg/m2/week	Phase II Evaluable Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	6	14	
Units: months				
median (confidence interval 95%)	1.9 (1.7 to 6.5)	7.8 (1.8 to 25.1)	1.9 (1.8 to 4.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival in Phases I and II

End point title	Overall survival in Phases I and II ^[16]
-----------------	---

End point description:

Overall Survival for all treated participants in Phases I and II. The estimates are based on the Kaplan-Meier (KM) method.

9999 = not applicable

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

End point timeframe:

Phase I: From the Study Start Date to Phase I Completion (32 months) - Phase II: From Phase II start to Study Completion (23 months). Phase 2 started before Phase 1 completed.

Notes:

[16] - 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 applicable for this endpoint

End point values	Phase I Participants: 100 mg/m2/week	Phase I Participants: 135 mg/m2/week	Phase II Evaluable Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	6	14	
Units: months				

median (confidence interval 95%)	9.7 (5.2 to 9999)	15.7 (4.7 to 9999)	7.3 (3.9 to 9999)	
----------------------------------	-------------------	--------------------	-------------------	--

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Duration of response (DoR) as measured by investigator-assessed RECIST 1.1

End point title	Phase I: Duration of response (DoR) as measured by investigator-assessed RECIST 1.1 ^[17]
-----------------	---

End point description:

Duration of response (DoR) as measured by investigator-assessed Response evaluation criteria in solid tumours (RECIST) 1.1.

Duration of Response (months): was time in months from response start date to either date of disease progression/death due to progression of disease. It was calculated only for participants with complete response or partial response as best overall response.

8.888 = not calculated

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

End point timeframe:

Phase I: From the Study Start Date to Phase I Completion (32 months)

Notes:

[17] - 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 applicable for this endpoint

End point values	Phase I Participants: 100 mg/m2/week	Phase I Participants: 135 mg/m2/week		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: months				
number (not applicable)	2.6	9.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Duration of response (DoR) as measured by investigator-assessed RECIST 1.1. and investigator-assessed mRECIST

End point title	Phase II: Duration of response (DoR) as measured by investigator-assessed RECIST 1.1. and investigator-assessed mRECIST ^[18]
-----------------	---

End point description:

Duration of response (DoR) as measured by investigator-assessed Response evaluation criteria in solid tumours (RECIST) 1.1. and investigator-assessed modified RECIST (mRECIST) . No participants had a RECIST or mRECIST complete or partial response observed.

Duration of Response (months): was time in months from response start date to either date of disease progression/death due to progression of disease. It was calculated only for participants with complete response or partial response as best overall response.

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

End point timeframe:

Phase II: From Phase II start to Study Completion (23 months)

Notes:

[18] - 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 applicable for this endpoint

End point values	Phase II Participants: 100 mg/m2/week			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[19]			
Units: participants				
RECIST Response Observed mRECIST Response Observed				

Notes:

[19] - Phase II participants who experienced partial response

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Phase I: From the Study Start Date to Phase I Completion (32 months) - Phase II: From Phase II start to Study Completion (23 months). Phase 2 started before Phase 1 completed.

Adverse event reporting additional description:

For non-serious AEs, the number of participants who experienced at least 1 occurrence of a treatment-emergent non-serious AEs, by MedDRA System Organ Class and Preferred Term are presented.

The one participant who was enrolled but not treated was not assessed for adverse events and therefore this cohort has not been included.

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Phase I: 100 mg/m2/weeks
-----------------------	--------------------------

Reporting group description:

Includes all participants who received 100 mg/m2/weeks in the Phase I of this study

Reporting group title	Phase I: 135 mg/m2/weeks
-----------------------	--------------------------

Reporting group description:

Includes all participants who received 135 mg/m2/weeks in the Phase I of this study

Reporting group title	Phase II: 100 mg/m2/weeks
-----------------------	---------------------------

Reporting group description:

Includes all participants who received 100 mg/m2/weeks in the Phase II of this study

Serious adverse events	Phase I: 100 mg/m2/weeks	Phase I: 135 mg/m2/weeks	Phase II: 100 mg/m2/weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	5 / 18 (27.78%)
number of deaths (all causes)	5	5	9
number of deaths resulting from adverse events	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 18 (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
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Disease progression subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Musculoskeletal and connective tissue disorders			
Pathological fracture subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related bacteraemia subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
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: 0 %

Non-serious adverse events	Phase I: 100 mg/m2/weeks	Phase I: 135 mg/m2/weeks	Phase II: 100 mg/m2/weeks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	6 / 6 (100.00%)	18 / 18 (100.00%)
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	3 / 18 (16.67%) 8
Hypotension subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	2 / 18 (11.11%) 2
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	1 / 6 (16.67%) 1	8 / 18 (44.44%) 10
Infusion site reaction subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 6 (33.33%) 2	3 / 18 (16.67%) 3
Oedema peripheral subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	1 / 6 (16.67%) 1	1 / 18 (5.56%) 1
Pyrexia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	2 / 18 (11.11%) 2
Influenza like illness subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	2 / 18 (11.11%) 2
Fatigue subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	1 / 18 (5.56%) 1
Infusion site pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	1 / 18 (5.56%) 1
Non-cardiac chest pain subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 4	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0
Infusion site extravasation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1
Infusion site pruritus			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infusion site phlebitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	15
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 18 (11.11%)
occurrences (all)	1	1	2
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	3 / 18 (16.67%)
occurrences (all)	1	0	3
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	3 / 18 (16.67%)
occurrences (all)	0	1	4
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 18 (11.11%)
occurrences (all)	0	1	3
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Blood creatinine increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 18 (5.56%)
occurrences (all)	0	1	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Coronavirus test positive			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Adverse event following immunisation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	3
Presyncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	2 / 18 (11.11%)
occurrences (all)	7	6	4
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	2 / 18 (11.11%)
occurrences (all)	0	2	2
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Thrombocytosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	4 / 18 (22.22%)
occurrences (all)	7	0	4
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	3 / 6 (50.00%)	2 / 18 (11.11%)
occurrences (all)	0	3	5
Ascites			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Nausea			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 18 (11.11%)
occurrences (all)	0	2	2
Dysphagia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Haemoperitoneum			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Melaena			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Peptic ulcer			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tooth loss			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Eczema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Actinic keratosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2

Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	2 / 18 (11.11%)
occurrences (all)	1	2	2
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	3 / 18 (16.67%)
occurrences (all)	2	2	5
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	3 / 6 (50.00%)	1 / 18 (5.56%)
occurrences (all)	1	4	2
Arthralgia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	2 / 18 (11.11%)
occurrences (all)	4	0	2
Bone pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Joint effusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Musculoskeletal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	4

Myalgia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 3	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0
Osteoarthritis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0
Infections and infestations			
COVID-19 subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	1 / 18 (5.56%) 1
Acarodermatitis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1
Burn infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0
Device related infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1
Oral fungal infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0
Metabolism and nutrition disorders			
Gout subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1
Hypophosphataemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2021	The main reason for this amendment to study protocol was to address the Spanish competent authority (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS) request to include an independent Data Safety Monitoring Board (DSMB) as a body to make recommendations on study progress and provide periodic study safety oversight. Moreover, a typo error in the inclusion criterion number 5 has been corrected (Child-Pugh score ≤ 6).
18 February 2022	The primary purpose of this update was to refine the treatment administration and dose modifications (dose increase, reduction, interruption) and define the sampling times for the population PK analysis in the Phase II portion of the study, based on data collected during the Phase I portion, and update the schedule of events. The protocol amendment also includes updates on background information, compound shelf-life and concomitant medications and minor changes on eligibility criteria. Besides, some typos and inaccuracies were corrected and to clarity and readability were enhanced.
30 June 2022	The primary purpose of this protocol amendment was to update the study endpoints for Phase II part of the study, in line with single arm studies, expectations and study design and futility analysis were aligned accordingly; to update inclusion criterion 4 to be in line with the Standard of Care proposed by both National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines; to request collection of cfDNA samples to correlate with clinical outcome; to introduce additional assessments of tumor responses with mRECIST criteria, as by European Association for the Study of the Liver (EASL), ESMO and American Association for the Study of Liver Diseases (AASLD) guidelines, with the possibility to perform a retrospective centralized analysis on tumors' assessment performed both with RECIST1.1 and mRECIST criteria. The protocol amendment also introduces and modifies exploratory analysis to match with the new assessments introduced, and requests retention of digital data of all radiological scans performed to evaluate tumoral burden. Amendment #3 clarifies possibility of enrollment for patients with controlled chronic HIV infection and modifies requirement for assessing presence of esophageal varices as by guidelines. Besides, few inconsistencies were corrected and other minor specifications and changes were added. Administrative changes were also applied.
09 January 2023	The main reason for this amendment to study protocol was to address the US competent authority (FDA) comments. Few DLT definitions were updated, the justification of the RP2D was added, intra-patient dose escalation was removed, dose modification rules were updated, stopping criteria for unacceptable toxicity were added, ECG monitoring added in cycle 1 and contraception period following the discontinuation of the study drug was extended for female patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
------	--------------	--------------

10 July 2024	In the Phase II part of the study, among the patients evaluable for efficacy, no objective response (PR or CR) was observed at the first futility analysis. Therefore, this study was terminated for clinical futility, according to the protocol rules. In the protocol it was considered that if less than one response (i.e., patients who achieved CR or PR) as best overall response, was observed among the first 10 evaluable patients, the study should be terminated. In the Phase II part of the study, three of the patients evaluable for efficacy experienced SD, with one patient experiencing SD lasting for more than six months. In addition, three patients that were excluded from the evaluable population, also experienced SD as best overall response and two of these were lasting for more than six months. Also, two patients (one evaluable and one non-evaluable for efficacy) continued treatment on nominal use, outside the study.	-
--------------	---	---

Notes:

Limitations and caveats

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

In the Phase II part of the study, among the patients evaluable for efficacy, no objective response (PR or CR) was observed at the first futility analysis. Therefore, this study was terminated for clinical futility, according to the protocol rules.

Notes: