

**Clinical trial results:****A Phase 2/3 , Open-label, Single Arm, Multicentre Study to Assess Safety, Tolerability, Pharmacokinetics and Efficacy of Intravenous Multiple Administrations of NI-0501, an Anti-interferon Gamma (Anti-IFN) Monoclonal Antibody, in Paediatric Patients with Primary Haemophagocytic Lymphohistiocytosis (HLH)****Summary**

EudraCT number	2012-003632-23
Trial protocol	GB IT AT CZ DE ES SE
Global end of trial date	04 January 2019

Results information

Result version number	v1 (current)
This version publication date	05 August 2020
First version publication date	05 August 2020

Trial information**Trial identification**

Sponsor protocol code	NI-0501-04
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01818492
WHO universal trial number (UTN)	-
Other trial identifiers	US IND: 111015

Notes:

Sponsors

Sponsor organisation name	NovImmune SA
Sponsor organisation address	14 Chemin des Aulx, Plan-les-Ouates, Switzerland, CH-1228
Public contact	Carl Johan Treutiger, Sobi AG, carljohan.treutiger@sobi.com
Scientific contact	Carl Johan Treutiger, Sobi AG, carljohan.treutiger@sobi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002031-PIP01-16
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	31 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 July 2017
Global end of trial reached?	Yes
Global end of trial date	04 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To determine the safety and tolerability profile of multiple intravenous (IV) administrations of NI-0501.
- To determine the efficacy and benefit/risk profile of NI-0501 in HLH patients.
- To describe the PK profile of NI-0501 in HLH patients.
- To determine the PD effects (levels of circulating Total IFN γ and biomarkers of its neutralization, namely CXCL9 and CXCL10)
- To define an appropriate NI-0501 therapeutic dose regimen for HLH.
- To determine other biomarkers, e.g. sCD25, IL-10
- To assess the immunogenicity of NI-0501.

Protection of trial subjects:

Before screening, parents of each prospective patient were given a full explanation of the study. Once the Investigator was assured that the implications of participating in the study were understood, the parent(s) were asked to give consent for their child to participate in the study by signing the informed consent form.

Background therapy:

In treatment-naïve patients, emapalumab was administered on a background of 10 mg/m² of dexamethasone. In patients who received emapalumab as second line HLH treatment, dexamethasone was administered at a dose of at least 5 mg/m², or at the dose administered prior to screening if higher. Lower dexamethasone doses were considered in the presence of signs and symptoms of glucocorticoid toxicity.

Dexamethasone could be tapered during treatment with emapalumab, depending on the patient's condition and according to the judgment of the Investigator.

Evidence for comparator:

N/A

Actual start date of recruitment	28 July 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	United Kingdom: 2

Worldwide total number of subjects	45
EEA total number of subjects	22

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)	32
Children (2-11 years)	12
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 15 investigational sites in 5 countries (ie. UK, Germany, Italy, Spain and US) treated at least 1 patient in Study NI-0501-04.

Pre-assignment

Screening details:

Patients were screened within 1 week prior to the first administration of emapalumab (NI-0501). 66 patients were screened, and 45 were enrolled and treated.

Period 1

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

Arms

Arm title	NI-0501
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Arm description:

All patients received emapalumab at a starting dose of 1 mg/kg every 3 days with possible escalation up to 10 mg/kg, for a minimum of 4 weeks.

Arm type	Experimental
Investigational medicinal product name	emapalumab
Investigational medicinal product code	NI-0501
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

The starting dose was 1 mg/kg every 3 days. Due to the expected target-mediated drug disposition (TMDD) effect and to the high interindividual variability of IFN γ concentrations in HLH patients, doses subsequent to the initial dose could be increased to 3 mg/kg and to 6 mg/kg, based on pre-specified clinical and laboratory criteria.

Dose could be further increased up to 10 mg/kg, if required, upon approval by the DMC.

If clinical and laboratory response criteria were no longer applicable, the dose of emapalumab could be decreased.

Number of subjects in period 1	NI-0501
Started	45
Completed	35
Not completed	10
Consent withdrawn by subject	1
Withdrawal criterion met in protocol	4
Adverse event, non-fatal	2
Death	3

Baseline characteristics

Reporting groups

Reporting group title	NI-0501
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Reporting group description:

All patients received emapalumab at a starting dose of 1 mg/kg every 3 days with possible escalation up to 10 mg/kg, for a minimum of 4 weeks.

Reporting group values	NI-0501	Total	
Number of subjects	45	45	
Age categorical			
In the All Treated population, the median age at entry into the study was 1.0 year, with a range of 0.1 (1 month) to 13.0 years.			
Units: Subjects			
Infants and toddlers (28 days-23 months)	32	32	
Children (2-11 years)	12	12	
Adolescents (12-17 years)	1	1	
Gender categorical			
The study population comprised patients of both genders			
Units: Subjects			
Female	23	23	
Male	22	22	
Race			
Units: Subjects			
White	30	30	
Asian	7	7	
African Descent	3	3	
Mixed/multi-racial	0	0	
Other	5	5	
Country of Origin			
Units: Subjects			
US	11	11	
Italy	6	6	
Others	19	19	
Missing	9	9	

Subject analysis sets

Subject analysis set title	Primary analysis set: All Treated
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Subject analysis set type	Full analysis
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Subject analysis set description:

Primary analysis set: All Treated (all patients who received any part of an emapalumab infusion, data collected by cut-off: 20 July 2017)

Subject analysis set title	Primary analysis set: Second Line
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Primary analysis set: Second Line (27 patients who had previously received conventional HLH therapy before enrollment, data collected by cut-off: 20 July 2017)

Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Baseline for comparison of primary endpoint	
Subject analysis set title	Follow-on analysis set: Second Line
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Follow-on analysis set: Second Line (34 patients who had previously received conventional HLH therapy before enrollment, totality of the data collected in the NI-0501-04 study)	
Subject analysis set title	Follow-on analysis set: All Treated
Subject analysis set type	Full analysis
Subject analysis set description:	
Follow-on analysis set: All Treated (45 patients who received any part of an emapalumab infusion, totality of the data collected in the NI-0501-04)	

Reporting group values	Primary analysis set: All Treated	Primary analysis set: Second Line	Baseline
Number of subjects	34	27	45
Age categorical			
In the All Treated population, the median age at entry into the study was 1.0 year, with a range of 0.1 (1 month) to 13.0 years.			
Units: Subjects			
Infants and toddlers (28 days-23 months)	21	15	32
Children (2-11 years)	12	11	12
Adolescents (12-17 years)	1	1	1
Gender categorical			
The study population comprised patients of both genders			
Units: Subjects			
Female	18	16	23
Male	16	11	22
Race			
Units: Subjects			
White	22	17	30
Asian	5	3	7
African Descent	3	3	3
Mixed/multi-racial	0	0	0
Other	4	4	5
Country of Origin			
Units: Subjects			
US	8	7	11
Italy	4	3	6
Others	16	12	19
Missing	6	5	9

Reporting group values	Follow-on analysis set: Second Line	Follow-on analysis set: All Treated	
Number of subjects	34	45	
Age categorical			
In the All Treated population, the median age at entry into the study was 1.0 year, with a range of 0.1 (1 month) to 13.0 years.			
Units: Subjects			

Infants and toddlers (28 days-23 months)	21	32	
Children (2-11 years)	12	12	
Adolescents (12-17 years)	1	1	
Gender categorical			
The study population comprised patients of both genders			
Units: Subjects			
Female	19	23	
Male	15	22	
Race			
Units: Subjects			
White	23	30	
Asian	3	7	
African Descent	3	3	
Mixed/multi-racial	0	0	
Other	5	5	
Country of Origin			
Units: Subjects			
US	8	11	
Italy	4	6	
Others	14	19	
Missing	8	9	

End points

End points reporting groups

Reporting group title	NI-0501
Reporting group description: All patients received emapalumab at a starting dose of 1 mg/kg every 3 days with possible escalation up to 10 mg/kg, for a minimum of 4 weeks.	
Subject analysis set title	Primary analysis set: All Treated
Subject analysis set type	Full analysis
Subject analysis set description: Primary analysis set: All Treated (all patients who received any part of an emapalumab infusion, data collected by cut-off: 20 July 2017)	
Subject analysis set title	Primary analysis set: Second Line
Subject analysis set type	Sub-group analysis
Subject analysis set description: Primary analysis set: Second Line (27 patients who had previously received conventional HLH therapy before enrollment, data collected by cut-off: 20 July 2017)	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description: Baseline for comparison of primary endpoint	
Subject analysis set title	Follow-on analysis set: Second Line
Subject analysis set type	Sub-group analysis
Subject analysis set description: Follow-on analysis set: Second Line (34 patients who had previously received conventional HLH therapy before enrollment, totality of the data collected in the NI-0501-04 study)	
Subject analysis set title	Follow-on analysis set: All Treated
Subject analysis set type	Full analysis
Subject analysis set description: Follow-on analysis set: All Treated (45 patients who received any part of an emapalumab infusion, totality of the data collected in the NI-0501-04)	

Primary: Overall Response

End point title	Overall Response
End point description: Achievement of either Complete (CR) or Partial Response (PR), or HLH Improvement (HI) at End of Treatment of Study NI 0501-04 (EOT 04), based on pre-specified algorithm. CR: no fever, normal spleen size, no cytopenia (ANC $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$), no hyperferritinemia (serum ferritin $< 2000 \mu g$), no coagulopathy (normal D-dimer and/or fibrinogen $> 150 \text{ mg/dL}$), no neurological and CSF abnormalities attributed to HLH, no sustained worsening of sCD25. PR: at least 3 HLH clinical and laboratory criteria (including CNS abnormalities) met the CR criteria, no progression of other aspects of HLH disease pathology. HI: improvement ($> 50\%$ change from baseline) of at least 3 HLH clinical and laboratory criteria (including CNS involvement).	
End point type	Primary
End point timeframe: End of Treatment (3 days after the last infusion of emapalumab in study NI-0501-04, occurring between 4 and 8 weeks)	

End point values	Primary analysis set: All Treated	Primary analysis set: Second Line	Baseline	Follow-on analysis set: Second Line
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	27	45	34
Units: Overall Response Rate				
number (confidence interval 95%)	0.65 (0.47 to 0.80)	0.63 (0.42 to 0.81)	0 (0 to 0)	0.59 (0.41 to 0.75)

End point values	Follow-on analysis set: All Treated			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: Overall Response Rate				
number (confidence interval 95%)	0.60 (0.44 to 0.74)			

Statistical analyses

Statistical analysis title	Exact binomial test
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Statistical analysis description:

The primary efficacy endpoint was analyzed with an exact binomial test to evaluate the null hypothesis that the Overall Response Rate was at most 40%. This test was performed at the one sided 0.025 significance level.

Due to the inability of presenting the statistical analysis for single arm studies correctly, it is described here as a comparison to baseline.

Comparison groups	Primary analysis set: Second Line v Baseline
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0134 ^[2]
Method	Exact Binomial

Notes:

[1] - Pre-specified null hypothesis that ORR is at most 40%.

[2] - This test was undertaken at the one-sided 0.025 significance level.

Statistical analysis title	Exact binomial test
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Statistical analysis description:

Due to the inability of presenting the statistical analysis for single arm studies correctly, it is described here as a comparison to baseline.

Comparison groups	Primary analysis set: All Treated v Baseline
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.0031 ^[4]
Method	Exact binomial

Notes:

[3] - Pre-specified null hypothesis that ORR is at most 40%

[4] - This test was undertaken at the one-sided 0.025 significance level.

Statistical analysis title	Exact binomial test
Statistical analysis description: Due to the inability of presenting the statistical analysis for single arm studies correctly, it is described here as a comparison to baseline.	
Comparison groups	Follow-on analysis set: Second Line v Baseline
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.0205 ^[6]
Method	Exact binomial

Notes:

[5] - Pre-specified null hypothesis that ORR is at most 40%

[6] - This test was undertaken at the one-sided 0.025 significance level.

Statistical analysis title	Exact binomial test
Statistical analysis description: Due to the inability of presenting the statistical analysis for single arm studies correctly, it is described here as a comparison to baseline.	
Comparison groups	Follow-on analysis set: All Treated v Baseline
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.0053 ^[8]
Method	Exact binomial

Notes:

[7] - Pre-specified null hypothesis that ORR is at most 40%.

[8] - This test was undertaken at the one-sided 0.025 significance level.

Secondary: Time to Overall Response

End point title	Time to Overall Response
End point description: Time from the date of the first dose of emapalumab to first achievement of response (at least HLH improvement)	
End point type	Secondary
End point timeframe: Any time during the study	

End point values	Follow-on analysis set: All Treated			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: Days				
median (confidence interval 95%)	7.0 (6.0 to 9.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Durability of First Response

End point title	Durability of First Response
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End point description:

Maintenance of response achieved any time during the study

End point type	Secondary
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End point timeframe:

Any time during the study

End point values	Follow-on analysis set: All Treated			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: At least 1 response (number)	39			

Statistical analyses

No statistical analyses for this end point

Secondary: Glucocortoid Tapering

End point title	Glucocortoid Tapering
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End point description:

Number of patients able to reduce glucocorticoids by 50% or more of baseline dose at EOT 04

End point type	Secondary
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End point timeframe:

Any time during the study up to EOT 04

End point values	Follow-on analysis set: All Treated			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: Percentage of patients				
number (not applicable)				

Reduction $\geq 50\%$	46.7			
Reduction $\geq 30\%$ - $<50\%$	11.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Survival Pre-HSCT

End point title	Survival Pre-HSCT
End point description:	
Time from the date of first dose to the date of death, expressed in Kaplan-Meier survival probability estimates. Patients who receive HSCT will be censored at that date; patients who did not receive HSCT will be censored at last date of contact.	
Where applicable, data were collected in both NI-0501-04 and long-term follow-up study NI-0501-05.	
End point type	Secondary
End point timeframe:	
End of the study and beyond	

End point values	Follow-on analysis set: All Treated			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Kaplan-Meier survival probability				
number (confidence interval 95%)				
Month 3	0.83 (0.669 to 0.915)			
Month 6	0.73 (0.524 to 0.859)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
Time from the date of first dose to the date of death, expressed in Kaplan-Meier survival probability estimates. Patients without an event will be censored at last assessment date in either the NI-0501-04 or NI-0501-05 study.	
End point type	Secondary
End point timeframe:	
End of the study and beyond	

End point values	Follow-on analysis set: All Treated			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: Kaplan-Meier survival probability number (confidence interval 95%)				
Month 6	0.68 (0.523 to 0.798)			
Month 12	0.66 (0.493 to 0.776)			

Statistical analyses

No statistical analyses for this end point

Secondary: Survival Post-HSCT

End point title	Survival Post-HSCT
End point description: Time from the date of first dose to the date of death, expressed in Kaplan-Meier survival probability estimates. Patients without an event will be censored at last assessment date in either the NI-0501-04 or NI-0501-05 study. Patients who do not proceed to HSCT will be excluded from this analysis.	
End point type	Secondary
End point timeframe: End of the study and beyond	

End point values	Follow-on analysis set: All Treated			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Kaplan-Meier survival probability number (confidence interval 95%)				
Month 6	0.82 (0.621 to 0.921)			
Month 12	0.82 (0.621 to 0.921)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Duration of Response

End point title	Cumulative Duration of Response
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End point description:

Percent of treatment time in response from the first achievement of an Overall Response until HSCT conditioning, or End of Treatment 04/05 (if the patient did not have HSCT performed) Where applicable, data were collected in both NI-0501-04 and long-term follow-up study NI-0501-05.

End point type	Secondary
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End point timeframe:

Up to start of HSCT conditioning, whenever HSCT conditioning is scheduled (at least 4 weeks after treatment start), or End of Treatment 04/05 (if the patient did not have HSCT performed)

End point values	Follow-on analysis set: All Treated			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: Percentage of treatment time				
number (confidence interval 95%)	78.6 (33.0 to 91.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event occurring after study start (i.e. signing of the informed consent) until the end of emapalumab treatment

Adverse event reporting additional description:

All patients who have received any part of an infusion of the study drug

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Pre-conditioning
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Reporting group description:

All patients before start of conditioning

Reporting group title	Post-conditioning
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Reporting group description:

All patients after start of conditioning

Serious adverse events	Pre-conditioning	Post-conditioning	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 45 (62.22%)	20 / 30 (66.67%)	
number of deaths (all causes)	9	5	
number of deaths resulting from adverse events	9	5	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	7 / 45 (15.56%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	4 / 45 (8.89%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	

Pyrexia			
subjects affected / exposed	1 / 45 (2.22%)	3 / 30 (10.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease in intestine			
subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Engraftment syndrome			
subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 45 (4.44%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			

subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine increased			
subjects affected / exposed	2 / 45 (4.44%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Blood stem cell transplant failure subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Engraft failure subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders Cardiopulmonary failure subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders Cerebral disorder subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Seizure			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural hygroma			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphocytosis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	1 / 45 (2.22%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye movement disorder			
subjects affected / exposed	1 / 45 (2.22%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 45 (8.89%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 45 (4.44%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Appendicitis perforated			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	2 / 45 (4.44%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histoplasmosis disseminated			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 45 (4.44%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	3 / 45 (6.67%)	3 / 30 (10.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sinusitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 45 (4.44%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gianotti-Crosti syndrome			

subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 45 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pre-conditioning	Post-conditioning	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 45 (95.56%)	30 / 30 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiocentric lymphoma			
subjects affected / exposed	1 / 45 (2.22%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 45 (42.22%)	11 / 30 (36.67%)	
occurrences (all)	22	12	
Hypotension			
subjects affected / exposed	5 / 45 (11.11%)	3 / 30 (10.00%)	
occurrences (all)	6	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 45 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Condition aggravated			
subjects affected / exposed	23 / 45 (51.11%)	3 / 30 (10.00%)	
occurrences (all)	29	3	
Mucosal inflammation			
subjects affected / exposed	1 / 45 (2.22%)	8 / 30 (26.67%)	
occurrences (all)	1	8	
Oedema			
subjects affected / exposed	3 / 45 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	3	
Oedema peripheral			
subjects affected / exposed	3 / 45 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	5	0	
Pain			
subjects affected / exposed	6 / 45 (13.33%)	3 / 30 (10.00%)	
occurrences (all)	6	4	
Pyrexia			
subjects affected / exposed	15 / 45 (33.33%)	15 / 30 (50.00%)	
occurrences (all)	25	25	

Immune system disorders			
Graft versus host disease			
subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Graft versus host disease in liver			
subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Graft versus host disease in skin			
subjects affected / exposed	0 / 45 (0.00%)	5 / 30 (16.67%)	
occurrences (all)	0	5	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	2 / 45 (4.44%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Cough			
subjects affected / exposed	4 / 45 (8.89%)	2 / 30 (6.67%)	
occurrences (all)	4	2	
Dyspnoea			
subjects affected / exposed	4 / 45 (8.89%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Epistaxis			
subjects affected / exposed	3 / 45 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	4	1	
Hypoxia			
subjects affected / exposed	4 / 45 (8.89%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Respiratory failure			
subjects affected / exposed	5 / 45 (11.11%)	1 / 30 (3.33%)	
occurrences (all)	5	1	
Tachypnoea			

subjects affected / exposed occurrences (all)	7 / 45 (15.56%) 11	3 / 30 (10.00%) 3	
Psychiatric disorders			
Agitation			
subjects affected / exposed	2 / 45 (4.44%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Irritability			
subjects affected / exposed	5 / 45 (11.11%)	3 / 30 (10.00%)	
occurrences (all)	7	3	
Investigations			
Blood immunoglobulin G decreased			
subjects affected / exposed	1 / 45 (2.22%)	2 / 30 (6.67%)	
occurrences (all)	1	6	
Human rhinovirus test positive			
subjects affected / exposed	0 / 45 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Polyomavirus test positive			
subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	4	
Adenovirus test positive			
subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	3	
Hypomagnesaemia			
subjects affected / exposed	3 / 45 (6.67%)	4 / 30 (13.33%)	
occurrences (all)	3	5	
Transaminases increased			
subjects affected / exposed	1 / 45 (2.22%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 45 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Skin abrasion			
subjects affected / exposed	3 / 45 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Cardiac disorders			

Bradycardia subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4	0 / 30 (0.00%) 0	
Pericardial effusion subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	2 / 30 (6.67%) 2	
Tachycardia subjects affected / exposed occurrences (all)	8 / 45 (17.78%) 11	3 / 30 (10.00%) 3	
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	0 / 30 (0.00%) 0	
Lymphocytosis subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 5	0 / 30 (0.00%) 0	
Thrombotic microangiopathy subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	5 / 30 (16.67%) 5	
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4	1 / 30 (3.33%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 7	5 / 30 (16.67%) 5	
Constipation subjects affected / exposed occurrences (all)	6 / 45 (13.33%) 7	0 / 30 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	8 / 45 (17.78%) 11	6 / 30 (20.00%) 11	
Nausea subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	3 / 30 (10.00%) 4	
Stomatitis			

subjects affected / exposed	1 / 45 (2.22%)	6 / 30 (20.00%)	
occurrences (all)	1	6	
Vomiting			
subjects affected / exposed	5 / 45 (11.11%)	7 / 30 (23.33%)	
occurrences (all)	12	9	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	4 / 45 (8.89%)	0 / 30 (0.00%)	
occurrences (all)	5	0	
Erythema			
subjects affected / exposed	4 / 45 (8.89%)	4 / 30 (13.33%)	
occurrences (all)	5	6	
Hyperhidrosis			
subjects affected / exposed	4 / 45 (8.89%)	1 / 30 (3.33%)	
occurrences (all)	6	1	
Pruritus			
subjects affected / exposed	1 / 45 (2.22%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	7 / 45 (15.56%)	6 / 30 (20.00%)	
occurrences (all)	14	9	
Rash erythematous			
subjects affected / exposed	2 / 45 (4.44%)	3 / 30 (10.00%)	
occurrences (all)	2	3	
Rash maculo-papular			
subjects affected / exposed	2 / 45 (4.44%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Skin disorder			
subjects affected / exposed	1 / 45 (2.22%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Rash macular			
subjects affected / exposed	3 / 45 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Renal and urinary disorders			
Renal failure			

subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	3 / 30 (10.00%) 3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 45 (4.44%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Back pain			
subjects affected / exposed	1 / 45 (2.22%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Infections and infestations			
BK virus infection			
subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Clostridium difficile infection			
subjects affected / exposed	3 / 45 (6.67%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Cytomegalovirus infection			
subjects affected / exposed	4 / 45 (8.89%)	5 / 30 (16.67%)	
occurrences (all)	5	7	
Otitis externa			
subjects affected / exposed	1 / 45 (2.22%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Rhinitis			
subjects affected / exposed	1 / 45 (2.22%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Staphylococcal bacteraemia			
subjects affected / exposed	3 / 45 (6.67%)	3 / 30 (10.00%)	
occurrences (all)	4	4	
Upper respiratory tract infection			
subjects affected / exposed	3 / 45 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	2 / 45 (4.44%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			

Fluid overload			
subjects affected / exposed	2 / 45 (4.44%)	4 / 30 (13.33%)	
occurrences (all)	2	5	
Hypoalbuminaemia			
subjects affected / exposed	2 / 45 (4.44%)	3 / 30 (10.00%)	
occurrences (all)	2	3	
Hypocalcaemia			
subjects affected / exposed	1 / 45 (2.22%)	3 / 30 (10.00%)	
occurrences (all)	2	4	
Hypokalaemia			
subjects affected / exposed	7 / 45 (15.56%)	4 / 30 (13.33%)	
occurrences (all)	10	7	
Hyponatraemia			
subjects affected / exposed	2 / 45 (4.44%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Hypophosphataemia			
subjects affected / exposed	3 / 45 (6.67%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Dehydration			
subjects affected / exposed	0 / 45 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2013	Protocol NI-0501-04 EU version 2.1 <ul style="list-style-type: none">- Addition of advice on contraception, and exclusion of pregnancy and lactation- Clarification on the dose escalation process- Revision of the IMP preparation form- Clarification of the 4-week follow-up period after treatment discontinuation
13 December 2013	EU version 3.0 <ul style="list-style-type: none">- Amendment of the protocol number to reflect the introduction of the US twin protocol- Implementation of a combined analysis of the data generated by the EU and US protocol- Clarifications of a few protocol sections (eg, Inclusion/Exclusion Criteria, study design, study outline and stopping rules) and introducing few additional clinical assessments (non-invasive), as well as PK and laboratory measurements, aimed at facilitating the analysis of the data
07 May 2014	US version 3.0 16 April 2014 EU version 4.0 07 May 2014 <ul style="list-style-type: none">- Broadening of the patient population eligible to receive NI-0501 in the study: In addition to primary HLH patients reactivating after having achieved Partial Response following conventional therapy, the protocol allowed the inclusion of primary HLH patients who received conventional therapy and:<ol style="list-style-type: none">1. Worsened or showed no further improvement for at least 4 weeks from initiation of treatment after achieving at least Partial or Incomplete Response2. Showed no response after at least 2 weeks from initiation of conventional therapy or worsening of the disease3. Showed intolerance to conventional treatment of HLH
15 December 2014	US version 4.0 17 November 2014 EU version 5.0 15 December 2014 <ul style="list-style-type: none">- Broadening of the target patient population to include patients naïve to HLH treatment- Revision of the title of the study to reflect the changes made to the Study Population and the Inclusion Criteria- Revision of the dose regimen, the dose determination criteria, and the background therapy requirements

26 February 2016	<p>EU version 6.0 26 February 2016 US Version 5.1 24 March 2016</p> <ul style="list-style-type: none"> - Prolongation of the study to continue as Phase 2/3, with determination of sample size for the pivotal cohort (defined as patients who receive NI-0501 in second line) - Definition of primary and secondary efficacy endpoints, consistently with the amended phase of the study consistently with the amended phase of the study - Revision of the dosing regimen and implementation of a standardized approach to dose increase. Clinical criteria were indicated to guide the dose increase by the Investigator. Dose increase was allowed at any time during the course of the study - Possibility to add other HLH treatments, primarily etoposide, if pre-defined criteria were met - Update to the stopping rules to reflect the experience gathered with the drug and the amended phase of the study
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported