



## 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 |
|-----------------------|------------|

##### 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 $\gamma$  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/m<sup>2</sup> of dexamethasone. In patients who received emapalumab as second line HLH treatment, dexamethasone was administered at a dose of at least 5 mg/m<sup>2</sup>, 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:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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 |
|-----------|---------|

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 $\gamma$  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 |
|-----------------------|---------|

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 |
|----------------------------|-----------------------------------|

|                           |               |
|---------------------------|---------------|
| 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)                              |                                     |

| 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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Achievement of either Complete (CR) or Partial Response (PR), or HLH Improvement (HI) at End of Treatment of Study<br>NI 0501-04 (EOT 04), based on pre-specified algorithm.<br>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.<br>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.<br>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:<br>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:<br>All Treated | Primary analysis set:<br>Second Line | Baseline             | Follow-on analysis set:<br>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:<br>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 |
|----------------------------|---------------------|
|----------------------------|---------------------|

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 <sup>[1]</sup>                   |
| P-value                                 | = 0.0134 <sup>[2]</sup>                      |
| 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 |
|----------------------------|---------------------|
|----------------------------|---------------------|

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 <sup>[3]</sup>                   |
| P-value                                 | = 0.0031 <sup>[4]</sup>                      |
| 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.

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Exact binomial test                            |
| Statistical analysis description:<br>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 <sup>[5]</sup>                     |
| P-value  | = 0.0205 <sup>[6]</sup>                        |
| 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.

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Exact binomial test                            |
| Statistical analysis description:<br>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 <sup>[7]</sup>                     |
| P-value  | = 0.0053 <sup>[8]</sup>                        |
| 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:<br>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:<br>Any time during the study  |                          |

|                                  |                                     |  |  |  |
|----------------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>          | 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 |
|-----------------|------------------------------|

End point description:

Maintenance of response achieved any time during the study

|                |           |
|----------------|-----------|
| 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: At least 1 response (number) | 39                                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Glucocortoid Tapering

|                 |                       |
|-----------------|-----------------------|
| End point title | Glucocortoid Tapering |
|-----------------|-----------------------|

End point description:

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

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

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   |                   |

|  |  |  |  |  |
|--|--|--|--|--|
| <b>End point values</b>                  | Follow-on analysis set:<br>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   |                  |

|   |  |  |  |  |
|---|--|--|--|--|
| <b>End point values</b>   | Follow-on analysis set:<br>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:<br>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:<br>End of the study and beyond  |                    |

|   |  |  |  |  |
|---|--|--|--|--|
| <b>End point values</b>   | Follow-on analysis set:<br>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

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**Secondary: Cumulative Duration of Response**

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|                 |                                 |
|-----------------|---------------------------------|
| End point title | Cumulative Duration of Response |
|-----------------|---------------------------------|

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 |
|----------------|-----------|

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)

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|                                     |                                     |  |  |  |
|-------------------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>             | 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)                 |  |  |  |

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**Statistical analyses**

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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 |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Pre-conditioning |
|-----------------------|------------------|

Reporting group description:

All patients before start of conditioning

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Post-conditioning |
|-----------------------|-------------------|

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

| <b>Non-serious adverse events</b>                                   | 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<br>occurrences (all) | 7 / 45 (15.56%)<br>11 | 3 / 30 (10.00%)<br>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          | 4 / 45 (8.89%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                    | 4               | 0               |  |
| Pericardial effusion                 |                 |                 |  |
| subjects affected / exposed          | 0 / 45 (0.00%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                    | 0               | 2               |  |
| Tachycardia                          |                 |                 |  |
| subjects affected / exposed          | 8 / 45 (17.78%) | 3 / 30 (10.00%) |  |
| occurrences (all)                    | 11              | 3               |  |
| Blood and lymphatic system disorders |                 |                 |  |
| Lymphadenopathy                      |                 |                 |  |
| subjects affected / exposed          | 3 / 45 (6.67%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                    | 3               | 0               |  |
| Lymphocytosis                        |                 |                 |  |
| subjects affected / exposed          | 4 / 45 (8.89%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                    | 5               | 0               |  |
| Thrombotic microangiopathy           |                 |                 |  |
| subjects affected / exposed          | 2 / 45 (4.44%)  | 5 / 30 (16.67%) |  |
| occurrences (all)                    | 2               | 5               |  |
| Gastrointestinal disorders           |                 |                 |  |
| Abdominal distension                 |                 |                 |  |
| subjects affected / exposed          | 3 / 45 (6.67%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                    | 4               | 1               |  |
| Abdominal pain                       |                 |                 |  |
| subjects affected / exposed          | 5 / 45 (11.11%) | 5 / 30 (16.67%) |  |
| occurrences (all)                    | 7               | 5               |  |
| Constipation                         |                 |                 |  |
| subjects affected / exposed          | 6 / 45 (13.33%) | 0 / 30 (0.00%)  |  |
| occurrences (all)                    | 7               | 0               |  |
| Diarrhoea                            |                 |                 |  |
| subjects affected / exposed          | 8 / 45 (17.78%) | 6 / 30 (20.00%) |  |
| occurrences (all)                    | 11              | 11              |  |
| Nausea                               |                 |                 |  |
| subjects affected / exposed          | 0 / 45 (0.00%)  | 3 / 30 (10.00%) |  |
| occurrences (all)                    | 0               | 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<br>occurrences (all) | 0 / 45 (0.00%)<br>0 | 3 / 30 (10.00%)<br>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<br>- Addition of advice on contraception, and exclusion of pregnancy and lactation<br>- Clarification on the dose escalation process<br>- Revision of the IMP preparation form<br>- Clarification of the 4-week follow-up period after treatment discontinuation  |
| 13 December 2013 | EU version 3.0<br>- Amendment of the protocol number to reflect the introduction of the US twin protocol<br>- Implementation of a combined analysis of the data generated by the EU and US protocol<br>- 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<br>EU version 4.0 07 May 2014<br>- 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:<br>1. Worsened or showed no further improvement for at least 4 weeks from initiation of treatment after achieving at least Partial or Incomplete Response<br>2. Showed no response after at least 2 weeks from initiation of conventional therapy or worsening of the disease<br>3. Showed intolerance to conventional treatment of HLH |
| 15 December 2014 | US version 4.0 17 November 2014<br>EU version 5.0 15 December 2014<br>- Broadening of the target patient population to include patients naïve to HLH treatment<br>- Revision of the title of the study to reflect the changes made to the Study Population and the Inclusion Criteria<br>- 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<br/>US Version 5.1 24 March 2016</p> <ul style="list-style-type: none"> <li>- 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)</li> <li>- Definition of primary and secondary efficacy endpoints, consistently with the amended phase of the study consistently with the amended phase of the study</li> <li>- 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</li> <li>- Possibility to add other HLH treatments, primarily etoposide, if pre-defined criteria were met</li> <li>- Update to the stopping rules to reflect the experience gathered with the drug and the amended phase of the study</li> </ul> |
|------------------|--|

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported