

**Clinical trial results:****A MULTIARM, OPEN LABEL, RANDOMIZED PHASE II STUDY OF MLN9708 PLUS ORAL DEXAMETHASONE or PLUS ORAL CYCLOPHOSPHAMIDE AND DEXAMETHASONE or PLUS BENDAMUSTINE AND DEXAMETHASONE or PLUS ORAL THALIDOMIDE AND DEXAMETHASONE FOLLOWED BY MAINTENANCE WITH MLN9708 IN NEWLY DIAGNOSED ELDERLY MULTIPLE MYELOMA PATIENTS.****Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-004859-31 |
| Trial protocol           | IT             |
| Global end of trial date | 14 May 2024    |

**Results information**

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 15 June 2024 |
| First version publication date | 15 June 2024 |

**Trial information****Trial identification**

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | UNITO-EMN10 |
|-----------------------|-------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02586038 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |                                                                                                                                                                   |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Dipartimento di Biotecnologie Molecolari e Scienze per la Salute - Università degli Studi di Torino                                                               |
| Sponsor organisation address | Via Nizza 52, Torino, Italy, 10126                                                                                                                                |
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| Scientific contact           | Francesco Novelli, Dipartimento di Biotecnologie Molecolari e Scienze per la Salute - Università degli Studi di Torino, 0039 0110243236, clinical.trials@unito.it |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

|                                                      |             |
|------------------------------------------------------|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 14 May 2024 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 14 May 2024 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

Primary objective:

- To select the more promising association(s) among three induction treatments, followed by maintenance with MLN9708, including:
    - MLN9708 plus dexamethasone (MLN-DEX)
    - MLN9708 plus dexamethasone and cyclophosphamide (MLN-CYCLO-DEX)
    - MLN9708 plus dexamethasone and thalidomide (MLN-THAL-DEX)
- in terms of Progression Free Survival (PFS) at 2 years from randomization.

Protection of trial subjects:

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 01 October 2015  |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 2 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Italy: 175 |
| Worldwide total number of subjects   | 175        |
| EEA total number of subjects         | 175        |

Notes:

### Subjects enrolled per age group

|          |   |
|----------|---|
| In utero | 0 |
|----------|---|

|                                           |     |
|-------------------------------------------|-----|
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 2   |
| From 65 to 84 years                       | 171 |
| 85 years and over                         | 2   |

## Subject disposition

### Recruitment

Recruitment details:

This is an open-label, multiarm, randomized Phase II trial of MLN9708 combined with different drugs (alkylating or immunomodulatory agents), and followed by MLN9708 maintenance, aiming to select the more promising regimen(s) to consider as an experimental arm in a future randomized phase III trial.

### Pre-assignment

Screening details:

After providing written informed consent to participate in the study, patients will be evaluated for study eligibility. The screening period includes the availability of inclusion criteria described below.

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Treatment period        |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | MLN-DEX |

Arm description:

MLN-DEX arm for patients already enrolled before amendment 2.0.

MLN9708: 4,0 mg orally on days 1, 8, 15

Dexamethasone: 40 mg orally on days 1, 8, 15, 22.

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Ninlaro       |
| Investigational medicinal product code | MLN9708       |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

4,0 mg orally on days 1, 8, 15

|                                        |               |
|----------------------------------------|---------------|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Oral drops    |
| Routes of administration               | Oral use      |

Dosage and administration details:

40 mg orally on days 1, 8, 15, 22

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | MLN-DEX-CYCLO |
|------------------|---------------|

Arm description:

MLN9708: 4,0 mg orally on days 1, 8, 15

Dexamethasone: 40 mg orally on days 1, 8, 15, 22.

Cyclophosphamide: 300 mg/sqm orally on days 1, 8, 15

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Ninlaro       |
| Investigational medicinal product code | MLN9708       |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

4,0 mg orally on days 1, 8, 15

|                                                                                                                                                                        |                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Investigational medicinal product name                                                                                                                                 | Dexamethasone                              |
| Investigational medicinal product code                                                                                                                                 |                                            |
| Other name                                                                                                                                                             |                                            |
| Pharmaceutical forms                                                                                                                                                   | Oral drops                                 |
| Routes of administration                                                                                                                                               | Oral use                                   |
| Dosage and administration details:<br>40 mg orally on days 1, 8, 15, 22                                                                                                |                                            |
| Investigational medicinal product name                                                                                                                                 | Cyclophosphamide                           |
| Investigational medicinal product code                                                                                                                                 |                                            |
| Other name                                                                                                                                                             |                                            |
| Pharmaceutical forms                                                                                                                                                   | Tablet                                     |
| Routes of administration                                                                                                                                               | Oral use                                   |
| Dosage and administration details:<br>300 mg/sqm orally on days 1, 8, 15                                                                                               |                                            |
| <b>Arm title</b>                                                                                                                                                       | MLN-DEX-THAL                               |
| Arm description:<br>MLN9708: 4,0 mg orally on days 1, 8, 15<br>Dexamethasone: 40 mg orally on days 1, 8, 15, 22.<br>Thalidomide: 100 mg/day orally                     |                                            |
| Arm type                                                                                                                                                               | Experimental                               |
| Investigational medicinal product name                                                                                                                                 | Ninlaro                                    |
| Investigational medicinal product code                                                                                                                                 | MLN9708                                    |
| Other name                                                                                                                                                             |                                            |
| Pharmaceutical forms                                                                                                                                                   | Capsule, hard                              |
| Routes of administration                                                                                                                                               | Oral use                                   |
| Dosage and administration details:<br>4,0 mg orally on days 1, 8, 15                                                                                                   |                                            |
| Investigational medicinal product name                                                                                                                                 | Dexamethasone                              |
| Investigational medicinal product code                                                                                                                                 |                                            |
| Other name                                                                                                                                                             |                                            |
| Pharmaceutical forms                                                                                                                                                   | Oral drops                                 |
| Routes of administration                                                                                                                                               | Oral use                                   |
| Dosage and administration details:<br>40 mg orally on days 1, 8, 15, 22                                                                                                |                                            |
| Investigational medicinal product name                                                                                                                                 | Thalidomide                                |
| Investigational medicinal product code                                                                                                                                 |                                            |
| Other name                                                                                                                                                             |                                            |
| Pharmaceutical forms                                                                                                                                                   | Coated tablet                              |
| Routes of administration                                                                                                                                               | Oral use                                   |
| Dosage and administration details:<br>100 mg/day orally                                                                                                                |                                            |
| <b>Arm title</b>                                                                                                                                                       | MLN-DEX-BENDA (First Amendment closed arm) |
| Arm description:<br>MLN9708: 4,0 mg orally on days 1, 8, 15<br>Dexamethasone: 40 mg orally on days 1, 8, 15, 22.<br>Bendamustine: 75 mg/sqm intravenously on days 1, 8 |                                            |
| Arm type                                                                                                                                                               | Experimental                               |
| Investigational medicinal product name                                                                                                                                 | Ninlaro                                    |
| Investigational medicinal product code                                                                                                                                 | MLN9708                                    |
| Other name                                                                                                                                                             |                                            |
| Pharmaceutical forms                                                                                                                                                   | Capsule, hard                              |
| Routes of administration                                                                                                                                               | Oral use                                   |

Dosage and administration details:

4,0 mg orally on days 1, 8, 15

|                                        |               |
|----------------------------------------|---------------|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Oral drops    |
| Routes of administration               | Oral use      |

Dosage and administration details:

40 mg orally on days 1, 8, 15, 22

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Investigational medicinal product name | Bedamustine                           |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

75 mg/sqm intravenously on days 1, 8

| <b>Number of subjects in period 1</b> | MLN-DEX | MLN-DEX-CYCLO | MLN-DEX-THAL |
|---------------------------------------|---------|---------------|--------------|
| Started                               | 42      | 61            | 61           |
| Completed                             | 21      | 38            | 38           |
| Not completed                         | 21      | 23            | 23           |
| Adverse event, serious fatal          | 1       | 3             | 2            |
| Consent withdrawn by subject          | 2       | 3             | -            |
| Physician decision                    | 2       | -             | -            |
| Adverse event, non-fatal              | 3       | 6             | 11           |
| Lost to follow-up                     | -       | 2             | -            |
| Lack of efficacy                      | 13      | 9             | 10           |

| <b>Number of subjects in period 1</b> | MLN-DEX-BENDA<br>(First Amendment<br>closed arm) |
|---------------------------------------|--------------------------------------------------|
| Started                               | 11                                               |
| Completed                             | 5                                                |
| Not completed                         | 6                                                |
| Adverse event, serious fatal          | -                                                |
| Consent withdrawn by subject          | 1                                                |
| Physician decision                    | -                                                |
| Adverse event, non-fatal              | 2                                                |
| Lost to follow-up                     | -                                                |
| Lack of efficacy                      | 3                                                |

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**Period 2**

|                              |                               |
|------------------------------|-------------------------------|
| Period 2 title               | Maintenance (up to two years) |
| Is this the baseline period? | No                            |
| Allocation method            | Not applicable                |
| Blinding used                | Not blinded                   |

**Arms**

|                  |         |
|------------------|---------|
| <b>Arm title</b> | MLN ARM |
|------------------|---------|

Arm description:

MLN9708: 4,0 mg orally on days 1, 8, 15

Patients will be stopped at progression disease (PD) or intolerance (maximum duration of maintenance therapy 2 years). In case of dose reduction during induction phase, patients will continue with the same dose, also during maintenance.

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Ninlaro       |
| Investigational medicinal product code | MLN9708       |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

4,0 mg orally on days 1, 8, 15

| <b>Number of subjects in period 2</b> | MLN ARM |
|---------------------------------------|---------|
| Started                               | 102     |
| Completed                             | 31      |
| Not completed                         | 71      |
| Adverse event, serious fatal          | 3       |
| Adverse event, non-fatal              | 12      |
| Lack of efficacy                      | 56      |

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Treatment period |
|-----------------------|------------------|

Reporting group description: -

| Reporting group values                | Treatment period | Total |  |
|---------------------------------------|------------------|-------|--|
| Number of subjects                    | 175              | 175   |  |
| Age categorical<br>Units: Subjects    |                  |       |  |
| < 75                                  | 98               | 98    |  |
| >= 75                                 | 77               | 77    |  |
| Age continuous<br>Units: years        |                  |       |  |
| median                                | 74               |       |  |
| full range (min-max)                  | 53 to 88         | -     |  |
| Gender categorical<br>Units: Subjects |                  |       |  |
| Female                                | 90               | 90    |  |
| Male                                  | 85               | 85    |  |
| ISS Stage<br>Units: Subjects          |                  |       |  |
| ISS I                                 | 51               | 51    |  |
| ISS II                                | 78               | 78    |  |
| ISS III                               | 46               | 46    |  |

### Subject analysis sets

|                            |     |
|----------------------------|-----|
| Subject analysis set title | ITT |
|----------------------------|-----|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

ITT

| Reporting group values                | ITT      |  |  |
|---------------------------------------|----------|--|--|
| Number of subjects                    | 175      |  |  |
| Age categorical<br>Units: Subjects    |          |  |  |
| < 75                                  | 98       |  |  |
| >= 75                                 | 77       |  |  |
| Age continuous<br>Units: years        |          |  |  |
| median                                | 74       |  |  |
| full range (min-max)                  | 53 to 88 |  |  |
| Gender categorical<br>Units: Subjects |          |  |  |
| Female                                | 90       |  |  |
| Male                                  | 85       |  |  |

| ISS Stage       |    |  |  |
|-----------------|----|--|--|
| Units: Subjects |    |  |  |
| ISS I           | 51 |  |  |
| ISS II          | 78 |  |  |
| ISS III         | 46 |  |  |

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## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                         |                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                   | MLN-DEX                                    |
| Reporting group description:<br>MLN-DEX arm for patients already enrolled before amendment 2.0.<br>MLN9708: 4,0 mg orally on days 1, 8, 15<br>Dexamethasone: 40 mg orally on days 1, 8, 15, 22.                                                                                                                         |                                            |
| Reporting group title                                                                                                                                                                                                                                                                                                   | MLN-DEX-CYCLO                              |
| Reporting group description:<br>MLN9708: 4,0 mg orally on days 1, 8, 15<br>Dexamethasone: 40 mg orally on days 1, 8, 15, 22.<br>Cyclophosphamide: 300 mg/sqm orally on days 1, 8, 15                                                                                                                                    |                                            |
| Reporting group title                                                                                                                                                                                                                                                                                                   | MLN-DEX-THAL                               |
| Reporting group description:<br>MLN9708: 4,0 mg orally on days 1, 8, 15<br>Dexamethasone: 40 mg orally on days 1, 8, 15, 22.<br>Thalidomide: 100 mg/day orally                                                                                                                                                          |                                            |
| Reporting group title                                                                                                                                                                                                                                                                                                   | MLN-DEX-BENDA (First Amendment closed arm) |
| Reporting group description:<br>MLN9708: 4,0 mg orally on days 1, 8, 15<br>Dexamethasone: 40 mg orally on days 1, 8, 15, 22.<br>Bendamustine: 75 mg/sqm intravenously on days 1, 8                                                                                                                                      |                                            |
| Reporting group title                                                                                                                                                                                                                                                                                                   | MLN ARM                                    |
| Reporting group description:<br>MLN9708: 4,0 mg orally on days 1, 8, 15<br>Patients will be stopped at progression disease (PD) or intolerance (maximum duration of maintenance therapy 2 years). In case of dose reduction during induction phase, patients will continue with the same dose, also during maintenance. |                                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                              | ITT                                        |
| Subject analysis set type                                                                                                                                                                                                                                                                                               | Intention-to-treat                         |
| Subject analysis set description:<br>ITT                                                                                                                                                                                                                                                                                |                                            |

### Primary: Progression Free Survival

|                                   |                           |
|-----------------------------------|---------------------------|
| End point title                   | Progression Free Survival |
| End point description:            |                           |
| End point type                    | Primary                   |
| End point timeframe:<br>24 months |                           |

| End point values                 | MLN-DEX          | MLN-DEX-CYCLO       | MLN-DEX-THAL       | MLN-DEX-BENDA (First Amendment closed arm) |
|----------------------------------|------------------|---------------------|--------------------|--------------------------------------------|
| Subject group type               | Reporting group  | Reporting group     | Reporting group    | Reporting group                            |
| Number of subjects analysed      | 42               | 61                  | 61                 | 11                                         |
| Units: month                     |                  |                     |                    |                                            |
| median (confidence interval 95%) | 10.3 (7 to 20.1) | 17.9 (13.3 to 27.5) | 12.3 (9.7 to 18.2) | 13.9 (3.3 to 99)                           |

## Statistical analyses

|                                         |                                                                                     |
|-----------------------------------------|-------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Log rank test                                                                       |
| Comparison groups                       | MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm) v MLN-DEX |
| Number of subjects included in analysis | 175                                                                                 |
| Analysis specification                  | Pre-specified                                                                       |
| Analysis type                           | superiority <sup>[1]</sup>                                                          |
| P-value                                 | = 0.15 <sup>[2]</sup>                                                               |
| Method                                  | Logrank                                                                             |
| Parameter estimate                      | Log rank test                                                                       |
| Point estimate                          | 0.15                                                                                |
| Confidence interval                     |                                                                                     |
| level                                   | 95 %                                                                                |
| sides                                   | 2-sided                                                                             |
| lower limit                             | 0.15                                                                                |
| upper limit                             | 0.15                                                                                |
| Variability estimate                    | Standard deviation                                                                  |
| Dispersion value                        | 0                                                                                   |

Notes:

[1] - Log rank test

[2] - Log rank test

## Secondary: VGPR Rate

|                        |           |
|------------------------|-----------|
| End point title        | VGPR Rate |
| End point description: |           |
| End point type         | Secondary |
| End point timeframe:   |           |
| Response rate (VGPR)   |           |

| <b>End point values</b>     | MLN-DEX         | MLN-DEX-CYCLO   | MLN-DEX-THAL    | MLN-DEX-BENDA (First Amendment closed arm) |
|-----------------------------|-----------------|-----------------|-----------------|--------------------------------------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group                            |
| Number of subjects analysed | 39              | 58              | 60              | 11                                         |
| Units: patients             |                 |                 |                 |                                            |
| < VGPR                      | 27              | 28              | 30              | 8                                          |
| >= VGPR                     | 12              | 30              | 30              | 3                                          |

## Statistical analyses

|                                                              |                                                                                     |
|--------------------------------------------------------------|-------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                            | no statistical analysys                                                             |
| Statistical analysis description:<br>no statistical analysys |                                                                                     |
| Comparison groups                                            | MLN-DEX v MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm) |
| Number of subjects included in analysis                      | 168                                                                                 |
| Analysis specification                                       | Pre-specified                                                                       |
| Analysis type                                                | superiority <sup>[3]</sup>                                                          |
| P-value                                                      | = 0                                                                                 |
| Method                                                       | no statistical analysys                                                             |
| Parameter estimate                                           | no statistical analysys                                                             |
| Point estimate                                               | 1                                                                                   |
| Confidence interval                                          |                                                                                     |
| level                                                        | 95 %                                                                                |
| sides                                                        | 2-sided                                                                             |
| lower limit                                                  | 0                                                                                   |
| upper limit                                                  | 2                                                                                   |
| Variability estimate                                         | Standard error of the mean                                                          |
| Dispersion value                                             | 0                                                                                   |

Notes:

[3] - no statistical analysys

## Secondary: progression-free survival-2 (PFS2)

|                                             |                                    |
|---------------------------------------------|------------------------------------|
| End point title                             | progression-free survival-2 (PFS2) |
| End point description:                      |                                    |
| End point type                              | Secondary                          |
| End point timeframe:<br>4 years probability |                                    |

| <b>End point values</b>          | MLN-DEX            | MLN-DEX-CYCLO      | MLN-DEX-THAL      | MLN-DEX-BENDA (First Amendment closed arm) |
|----------------------------------|--------------------|--------------------|-------------------|--------------------------------------------|
| Subject group type               | Reporting group    | Reporting group    | Reporting group   | Reporting group                            |
| Number of subjects analysed      | 42                 | 61                 | 61                | 11                                         |
| Units: month                     |                    |                    |                   |                                            |
| number (confidence interval 95%) | 0.3 (0.15 to 0.62) | 0.47 (0.3 to 0.72) | 0.4 (0.2 to 0.81) | 0.78 (0.55 to 1)                           |

## Statistical analyses

|                                   |                                                                                     |
|-----------------------------------|-------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b> | Log rank test                                                                       |
| Comparison groups                 | MLN-DEX v MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm) |

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 175                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | equivalence <sup>[4]</sup> |
| P-value                                 | = 0.52                     |
| Method                                  | Logrank                    |
| Parameter estimate                      | Log rank test              |
| Point estimate                          | 0.52                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.52                       |
| upper limit                             | 0.52                       |
| Variability estimate                    | Standard deviation         |
| Dispersion value                        | 0                          |

Notes:

[4] - Log rank test

### Secondary: time to next therapy (TNT)

|                            |                            |
|----------------------------|----------------------------|
| End point title            | time to next therapy (TNT) |
| End point description:     |                            |
| End point type             | Secondary                  |
| End point timeframe:       |                            |
| time to next therapy (TNT) |                            |

| End point values                 | MLN-DEX             | MLN-DEX-CYCLO       | MLN-DEX-THAL        | MLN-DEX-BENDA (First Amendment closed arm) |
|----------------------------------|---------------------|---------------------|---------------------|--------------------------------------------|
| Subject group type               | Reporting group     | Reporting group     | Reporting group     | Reporting group                            |
| Number of subjects analysed      | 42                  | 61                  | 61                  | 11                                         |
| Units: month                     |                     |                     |                     |                                            |
| median (confidence interval 95%) | 32.4 (30.9 to 38.2) | 33.1 (28.2 to 44.8) | 29.9 (28.7 to 34.4) | 48.4 (37.1 to 99)                          |

### Statistical analyses

|                                   |                                                                                     |
|-----------------------------------|-------------------------------------------------------------------------------------|
| Statistical analysis title        | Log rank test                                                                       |
| Statistical analysis description: |                                                                                     |
| Log rank test                     |                                                                                     |
| Comparison groups                 | MLN-DEX v MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm) |

|                                         |                      |
|-----------------------------------------|----------------------|
| Number of subjects included in analysis | 175                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | equivalence          |
| P-value                                 | = 0.2 <sup>[5]</sup> |
| Method                                  | Logrank              |
| Parameter estimate                      | Log rank test        |
| Point estimate                          | 0.2                  |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 0.2                  |
| upper limit                             | 0.2                  |
| Variability estimate                    | Standard deviation   |
| Dispersion value                        | 0                    |

Notes:

[5] - Log rank test

### Secondary: time to progression (TTP)

|                           |                           |
|---------------------------|---------------------------|
| End point title           | time to progression (TTP) |
| End point description:    |                           |
| End point type            | Secondary                 |
| End point timeframe:      |                           |
| time to progression (TTP) |                           |

| End point values                 | MLN-DEX          | MLN-DEX-CYCLO       | MLN-DEX-THAL     | MLN-DEX-BENDA (First Amendment closed arm) |
|----------------------------------|------------------|---------------------|------------------|--------------------------------------------|
| Subject group type               | Reporting group  | Reporting group     | Reporting group  | Reporting group                            |
| Number of subjects analysed      | 42               | 61                  | 61               | 11                                         |
| Units: month                     |                  |                     |                  |                                            |
| median (confidence interval 95%) | 10.9 (7 to 24.4) | 19.1 (14.1 to 36.3) | 13 (9.9 to 19.5) | 13.8 (3.3 to 99)                           |

### Statistical analyses

|                                   |                                                                                     |
|-----------------------------------|-------------------------------------------------------------------------------------|
| Statistical analysis title        | Log rank test                                                                       |
| Statistical analysis description: |                                                                                     |
| Log rank test                     |                                                                                     |
| Comparison groups                 | MLN-DEX v MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm) |

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 175                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | equivalence <sup>[6]</sup> |
| P-value                                 | = 0.1 <sup>[7]</sup>       |
| Method                                  | Logrank                    |
| Parameter estimate                      | Log rank test              |
| Point estimate                          | 0.1                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.1                        |
| upper limit                             | 0.1                        |
| Variability estimate                    | Standard deviation         |
| Dispersion value                        | 0                          |

Notes:

[6] - Log rank test

[7] - Log rank test

### Secondary: overall survival (OS)

|                                                                  |                       |
|------------------------------------------------------------------|-----------------------|
| End point title                                                  | overall survival (OS) |
| End point description:<br>4 years probabiliy                     |                       |
| End point type                                                   | Secondary             |
| End point timeframe:<br>overall survival (OS) 4 years probabiliy |                       |

| End point values                 | MLN-DEX             | MLN-DEX-CYCLO      | MLN-DEX-THAL        | MLN-DEX-BENDA (First Amendment closed arm) |
|----------------------------------|---------------------|--------------------|---------------------|--------------------------------------------|
| Subject group type               | Reporting group     | Reporting group    | Reporting group     | Reporting group                            |
| Number of subjects analysed      | 42                  | 61                 | 61                  | 11                                         |
| Units: month                     |                     |                    |                     |                                            |
| number (confidence interval 95%) | 0.65 (0.49 to 0.86) | 0.57 (0.4 to 0.83) | 0.59 (0.39 to 0.91) | 0.78 (0.55 to 1)                           |

### Statistical analyses

|                                                    |                                                                                     |
|----------------------------------------------------|-------------------------------------------------------------------------------------|
| Statistical analysis title                         | Log rank test                                                                       |
| Statistical analysis description:<br>Log rank test |                                                                                     |
| Comparison groups                                  | MLN-DEX v MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm) |

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 175                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | equivalence <sup>[8]</sup> |
| P-value                                 | = 0.74                     |
| Method                                  | Logrank                    |
| Parameter estimate                      | Log rank test              |
| Point estimate                          | 0.74                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.74                       |
| upper limit                             | 0.74                       |
| Variability estimate                    | Standard deviation         |
| Dispersion value                        | 0                          |

Notes:

[8] - Log rank test

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Per protocol

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 26.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Per protocol |
|-----------------------|--------------|

Reporting group description: -

| <b>Serious adverse events</b>                                       | Per protocol      |  |  |
|---------------------------------------------------------------------|-------------------|--|--|
| Total subjects affected by serious adverse events                   |                   |  |  |
| subjects affected / exposed                                         | 74 / 171 (43.27%) |  |  |
| number of deaths (all causes)                                       | 44                |  |  |
| number of deaths resulting from adverse events                      | 17                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Bladder papilloma                                                   |                   |  |  |
| subjects affected / exposed                                         | 1 / 171 (0.58%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Breast cancer                                                       |                   |  |  |
| subjects affected / exposed                                         | 1 / 171 (0.58%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Lung adenocarcinoma                                                 |                   |  |  |
| subjects affected / exposed                                         | 1 / 171 (0.58%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Malignant melanoma                                                  |                   |  |  |
| subjects affected / exposed                                         | 1 / 171 (0.58%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 1             |  |  |
| Papillary renal cell carcinoma                                      |                   |  |  |

|                                                      |                 |  |  |
|------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                          | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Plasma cell myeloma                                  |                 |  |  |
| subjects affected / exposed                          | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |
| Prostate cancer                                      |                 |  |  |
| subjects affected / exposed                          | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Vascular disorders                                   |                 |  |  |
| Deep vein thrombosis                                 |                 |  |  |
| subjects affected / exposed                          | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Chest pain                                           |                 |  |  |
| subjects affected / exposed                          | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Death                                                |                 |  |  |
| subjects affected / exposed                          | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |
| Oedema peripheral                                    |                 |  |  |
| subjects affected / exposed                          | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Pyrexia                                              |                 |  |  |
| subjects affected / exposed                          | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Acute pulmonary oedema                          |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Bronchospasm                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Chronic obstructive pulmonary disease           |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspnoea                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonitis                                     |                 |  |  |
| subjects affected / exposed                     | 2 / 171 (1.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 2 / 171 (1.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Confusional state                               |                 |  |  |

|                                                       |                 |  |  |
|-------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                           | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Injury, poisoning and procedural complications</b> |                 |  |  |
| <b>Fall</b>                                           |                 |  |  |
| subjects affected / exposed                           | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Fracture</b>                                       |                 |  |  |
| subjects affected / exposed                           | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Humerus fracture</b>                               |                 |  |  |
| subjects affected / exposed                           | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Lumbar vertebral fracture</b>                      |                 |  |  |
| subjects affected / exposed                           | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Overdose</b>                                       |                 |  |  |
| subjects affected / exposed                           | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Pelvic fracture</b>                                |                 |  |  |
| subjects affected / exposed                           | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Rib fracture</b>                                   |                 |  |  |
| subjects affected / exposed                           | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Skull fracture</b>                                 |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Subdural haematoma                              |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Acute coronary syndrome                         |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aortic valve disease                            |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 3 / 171 (1.75%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac arrest                                  |                 |  |  |
| subjects affected / exposed                     | 3 / 171 (1.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 2           |  |  |
| Cardiac failure                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Cerebral haemorrhage                            |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Cerebral ischaemia                              |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cerebrovascular accident</b>                 |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Intracranial mass</b>                        |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| <b>Paraparesis</b>                              |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Peripheral sensory neuropathy</b>            |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Polyneuropathy</b>                           |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Seizure</b>                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Syncope</b>                                  |                 |  |  |
| subjects affected / exposed                     | 7 / 171 (4.09%) |  |  |
| occurrences causally related to treatment / all | 3 / 7           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Transient ischaemic attack</b>               |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Blood and lymphatic system disorders</b>     |                 |  |  |
| <b>Anaemia</b>                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 171 (1.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cytopenia</b>                                |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Leukopenia</b>                               |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Thrombocytopenia</b>                         |                 |  |  |
| subjects affected / exposed                     | 2 / 171 (1.17%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Eye disorders</b>                            |                 |  |  |
| <b>Amaurosis fugax</b>                          |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| <b>Retinal vascular thrombosis</b>              |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Gastrointestinal disorders</b>               |                 |  |  |
| <b>Abdominal pain</b>                           |                 |  |  |
| subjects affected / exposed                     | 2 / 171 (1.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Constipation                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diarrhoea                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 171 (1.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal haemorrhage                    |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal obstruction                          |                 |  |  |
| subjects affected / exposed                     | 2 / 171 (1.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Volvulus                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting                                        |                 |  |  |
| subjects affected / exposed                     | 3 / 171 (1.75%) |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Faecaloma                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Bile duct stone                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Cholecystitis                                   |                 |  |  |

|                                                        |                 |  |  |
|--------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                            | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Skin and subcutaneous tissue disorders</b>          |                 |  |  |
| Urticaria                                              |                 |  |  |
| subjects affected / exposed                            | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Renal and urinary disorders</b>                     |                 |  |  |
| Acute kidney injury                                    |                 |  |  |
| subjects affected / exposed                            | 4 / 171 (2.34%) |  |  |
| occurrences causally related to treatment / all        | 2 / 4           |  |  |
| deaths causally related to treatment / all             | 0 / 1           |  |  |
| Renal colic                                            |                 |  |  |
| subjects affected / exposed                            | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Renal failure                                          |                 |  |  |
| subjects affected / exposed                            | 2 / 171 (1.17%) |  |  |
| occurrences causally related to treatment / all        | 0 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |  |  |
| Back pain                                              |                 |  |  |
| subjects affected / exposed                            | 2 / 171 (1.17%) |  |  |
| occurrences causally related to treatment / all        | 0 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Bone pain                                              |                 |  |  |
| subjects affected / exposed                            | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Infections and infestations</b>                     |                 |  |  |
| Bacterial infection                                    |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Bronchitis</b>                               |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Campylobacter infection</b>                  |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>COVID-19</b>                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| <b>Fungal infection</b>                         |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Herpes zoster</b>                            |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Infection</b>                                |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Meningitis listeria</b>                      |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Orchitis</b>                                 |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Peritonitis</b>                              |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Pneumonia</b>                                |                 |  |  |
| subjects affected / exposed                     | 7 / 171 (4.09%) |  |  |
| occurrences causally related to treatment / all | 5 / 7           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| <b>Sepsis</b>                                   |                 |  |  |
| subjects affected / exposed                     | 8 / 171 (4.68%) |  |  |
| occurrences causally related to treatment / all | 2 / 8           |  |  |
| deaths causally related to treatment / all      | 0 / 2           |  |  |
| <b>Superinfection bacterial</b>                 |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Upper respiratory tract infection</b>        |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Metabolism and nutrition disorders</b>       |                 |  |  |
| <b>Hyperglycaemia</b>                           |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hypoglycaemia</b>                            |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hypokalaemia</b>                             |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hyponatraemia</b>                            |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Tumour lysis syndrome</b>                    |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Dehydration</b>                              |                 |  |  |
| subjects affected / exposed                     | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                           | Per protocol       |  |  |
|-------------------------------------------------------------|--------------------|--|--|
| Total subjects affected by non-serious adverse events       |                    |  |  |
| subjects affected / exposed                                 | 157 / 171 (91.81%) |  |  |
| <b>Vascular disorders</b>                                   |                    |  |  |
| Hypertension                                                |                    |  |  |
| subjects affected / exposed                                 | 9 / 171 (5.26%)    |  |  |
| occurrences (all)                                           | 9                  |  |  |
| <b>Nervous system disorders</b>                             |                    |  |  |
| Peripheral sensory neuropath                                |                    |  |  |
| subjects affected / exposed                                 | 32 / 171 (18.71%)  |  |  |
| occurrences (all)                                           | 32                 |  |  |
| Paraesthesia                                                |                    |  |  |
| subjects affected / exposed                                 | 29 / 171 (16.96%)  |  |  |
| occurrences (all)                                           | 29                 |  |  |
| <b>General disorders and administration site conditions</b> |                    |  |  |

|                                      |                   |  |  |
|--------------------------------------|-------------------|--|--|
| Pain                                 |                   |  |  |
| subjects affected / exposed          | 52 / 171 (30.41%) |  |  |
| occurrences (all)                    | 52                |  |  |
| Fatigue                              |                   |  |  |
| subjects affected / exposed          | 35 / 171 (20.47%) |  |  |
| occurrences (all)                    | 35                |  |  |
| Pyrexia                              |                   |  |  |
| subjects affected / exposed          | 31 / 171 (18.13%) |  |  |
| occurrences (all)                    | 31                |  |  |
| Oedema peripheral                    |                   |  |  |
| subjects affected / exposed          | 30 / 171 (17.54%) |  |  |
| occurrences (all)                    | 30                |  |  |
| Vomiting                             |                   |  |  |
| subjects affected / exposed          | 23 / 171 (13.45%) |  |  |
| occurrences (all)                    | 23                |  |  |
| Influenza like illness               |                   |  |  |
| subjects affected / exposed          | 9 / 171 (5.26%)   |  |  |
| occurrences (all)                    | 9                 |  |  |
| Blood and lymphatic system disorders |                   |  |  |
| Anaemia                              |                   |  |  |
| subjects affected / exposed          | 28 / 171 (16.37%) |  |  |
| occurrences (all)                    | 28                |  |  |
| Neutropenia                          |                   |  |  |
| subjects affected / exposed          | 16 / 171 (9.36%)  |  |  |
| occurrences (all)                    | 16                |  |  |
| Thrombocytopenia                     |                   |  |  |
| subjects affected / exposed          | 10 / 171 (5.85%)  |  |  |
| occurrences (all)                    | 10                |  |  |
| Gastrointestinal disorders           |                   |  |  |
| Nausea                               |                   |  |  |
| subjects affected / exposed          | 37 / 171 (21.64%) |  |  |
| occurrences (all)                    | 37                |  |  |
| Constipation                         |                   |  |  |
| subjects affected / exposed          | 32 / 171 (18.71%) |  |  |
| occurrences (all)                    | 32                |  |  |
| Diarrhoea                            |                   |  |  |

|                                                                                                                                                                                                                                                                        |                                                                                               |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--|--|
| <p>subjects affected / exposed<br/>occurrences (all)</p> <p>Abdominal pain<br/>subjects affected / exposed<br/>occurrences (all)</p>                                                                                                                                   | <p>32 / 171 (18.71%)<br/>32</p> <p>9 / 171 (5.26%)<br/>9</p>                                  |  |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough<br/>subjects affected / exposed<br/>occurrences (all)</p>                                                                                                                                              | <p>14 / 171 (8.19%)<br/>14</p>                                                                |  |  |
| <p>Skin and subcutaneous tissue disorders</p> <p>Rash maculo-papular<br/>subjects affected / exposed<br/>occurrences (all)</p> <p>Rash<br/>subjects affected / exposed<br/>occurrences (all)</p> <p>Pruritus<br/>subjects affected / exposed<br/>occurrences (all)</p> | <p>22 / 171 (12.87%)<br/>22</p> <p>12 / 171 (7.02%)<br/>12</p> <p>10 / 171 (5.85%)<br/>10</p> |  |  |
| <p>Infections and infestations</p> <p>Upper respiratory tract infection<br/>subjects affected / exposed<br/>occurrences (all)</p> <p>Bronchitis<br/>subjects affected / exposed<br/>occurrences (all)</p>                                                              | <p>15 / 171 (8.77%)<br/>15</p> <p>13 / 171 (7.60%)<br/>13</p>                                 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                         |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| 26 January 2017   | Eliminate an experimental arm, to reduce the sample size of the study.                                                            |
| 26 March 2018     | Closure of a treatment arm due to ineffectiveness compared to the expected in the statistical design of the protocol.             |
| 20 September 2018 | Change to the total number of patients to be enrolled in the study due to the closure of an experimental arm for ineffectiveness. |
| 16 July 2020      | Updates on side effects of the experimental drug.                                                                                 |
| 23 February 2021  | CRO name change.                                                                                                                  |
| 17 June 2021      | Updates on side effects of the experimental drug.                                                                                 |
| 21 July 2022      | Clarify timelines and procedures for reporting serious adverse events and SUSARs.                                                 |
| 09 November 2023  | Change from CEC to national CET.                                                                                                  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34876566>