



## Clinical trial results:

### A PHASE 3, MULTICENTRE, RANDOMIZED, CONTROLLED STUDY TO DETERMINE THE EFFICACY AND SAFETY OF LENALIDOMIDE, MELPHALAN AND PREDNISONE (MPR) versus MELPHALAN (200 mg/m<sup>2</sup>) FOLLOWED BY STEM CELL TRANSPLANT IN NEWLY DIAGNOSED MULTIPLE MYELOMA SUBJECTS

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2007-001610-16 |
| Trial protocol           | IT             |
| Global end of trial date | 30 June 2024   |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 16 January 2025 |
| First version publication date | 16 January 2025 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | RV-MM-PI-209 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00551928 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Fondazione EMN Italy Onlus   |
| Sponsor organisation address | Via Saluzzo 1/A, Torino, Italy, 10126  |
| Public contact               | Clinical Trial Office, Fondazione EMN Italy Onlus, 0039 0110243236, clinicaltrialoffice@emnitaly.org |
| Scientific contact           | Clinical Trial Office, Fondazione EMN Italy Onlus, 0039 0110243236, clinicaltrialoffice@emnitaly.org |

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                       | 04 December 2024 |
| Is this the analysis of the primary completion data? | No               |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 30 June 2024 |
| Was the trial ended prematurely? | No           |

Notes:

## General information about the trial

Main objective of the trial:

To compare the efficacy of the combination of lenalidomide with low-dose melphalan versus high-dose melphalan in newly diagnosed, symptomatic MM patients.

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                          | 20 November 2007 |
| 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: 355 |
| Country: Number of subjects enrolled | Israel: 44 |
| Worldwide total number of subjects   | 399        |
| EEA total number of subjects         | 355        |

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) | 386 |
| From 65 to 84 years  | 13  |
| 85 years and over    | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This is a multicenter, randomized, open label, 2x2 factorial design, study aimed at comparing the efficacy and safety of lenalidomide in combination with low-dose melphalan versus high-dose melphalan followed by stem cell support in newly diagnosed symptomatic MM patients who are 65 years of age or younger.

### Pre-assignment

Screening details:

Screening visits, performed at study entry. After providing written informed consent to participate in the study, patients will be evaluated for study eligibility. The screening period includes the evaluation of inclusion criteria. Subjects who meet all the inclusion criteria will be enrolled.

### Period 1

|                              |                |
|------------------------------|----------------|
| Period 1 title               | Induction      |
| Is this the baseline period? | Yes            |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | No           |
| <b>Arm title</b>             | Rd Induction |

Arm description:

Patients will start induction treatment with lenalidomide and dexamethasone (RD) for 4 cycles every 28 days:

- Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28),
- Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15 and 22 every 28 days.

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

Dosage and administration details:

Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28) for 4 cycles every 28 days

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

Dosage and administration details:

Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15 and 22 every 28 days, for 4 cycles every 28 days

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | CY infusion |
|------------------|-------------|

Arm description:

After 1-2 months from the completion of the last RD cycle, i.v. cyclophosphamide (CY) will be given at the dose of 4 g/m<sup>2</sup> followed by G-CSF (10 ug/kg/day starting at day 5 until completion of PBSC collection) to collect an adequate number of PBSC (4 to 10 x 10<sup>6</sup>/kg CD 34+ cells). Patients who fail to collect the minimum of 4 x 10<sup>6</sup>/kg CD 34+ cells will receive a second course of CY for a second mobilization attempt. Patients who fails to collect a minimum of 4 x 10<sup>6</sup>/kg CD 34+ will be withdrawn from the study.

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

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | Cyclophosphamide                  |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

Dosage and administration details:

4 g/m2

| Number of subjects in period 1 | Rd Induction | CY infusion |
|--------------------------------|--------------|-------------|
| Started                        | 399          | 332         |
| Completed                      | 332          | 274         |
| Not completed                  | 67           | 58          |
| Adverse event, serious fatal   | 6            | -           |
| Consent withdrawn by subject   | 4            | 7           |
| Physician decision             | 8            | 16          |
| Adverse event, non-fatal       | 16           | 2           |
| Lost to follow-up              | 2            | -           |
| Lack of efficacy               | 30           | 16          |
| Protocol deviation             | 1            | 17          |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Consolidation           |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

## Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| Arm title                    | ARM A (MPR) |

Arm description:

Patients will start consolidation treatment with the association of lenalidomide, melphalan and prednisone (MPR) for 6 cycles every 28 days:

- Lenalidomide will be given orally at the dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28),
- Melphalan will be given orally at the dose of 0.18 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28)
- Prednisone will be given orally at the dose of 2 mg/Kg for 4 days followed by a 24 day rest period (days 5 to 28),

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

|  |               |
|--|---------------|
| Investigational medicinal product name | Lenalidomide  |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Lenalidomide will be given orally at the dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28), for 6 cycles every 28 days

|  |               |
|--|---------------|
| Investigational medicinal product name | Melphalan     |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Coated tablet |
| Routes of administration               | Oral use      |

Dosage and administration details:

Melphalan will be given orally at the dose of 0.18 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28), for 6 cycles every 28 days

|  |            |
|--|------------|
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

Dosage and administration details:

Prednisone will be given orally at the dose of 2 mg/Kg for 4 days followed by a 24 day rest period (days 5 to 28), for 6 cycles every 28 days

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | ARM B (MEL200) |
|------------------|----------------|

Arm description:

Patients will start consolidation treatment with melphalan 200 mg/m<sup>2</sup> followed by stem cell support (MEL200) for 2 cycles every 4 months (only 1 cycle if the patient reached almost a VGPR after the 1st MEL200):

- Melphalan will be given iv at the dose of 200 mg/m<sup>2</sup> for 1 day followed by stem cell support and 120 days rest period.

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

Dosage and administration details:

Melphalan will be given iv at the dose of 200 mg/m<sup>2</sup> for 1 day followed by stem cell support and 120 days rest period.

| <b>Number of subjects in period 2</b> | <b>ARM A (MPR)</b> | <b>ARM B (MEL200)</b> |
|---------------------------------------|--------------------|-----------------------|
| Started                               | 133                | 141                   |
| Completed                             | 115                | 134                   |
| Not completed                         | 18                 | 7                     |
| Consent withdrawn by subject          | 1                  | -                     |
| Physician decision                    | 1                  | -                     |
| Adverse event, non-fatal              | 5                  | -                     |
| Lost to follow-up                     | -                  | 1                     |

|                    |    |   |
|--------------------|----|---|
| Lack of efficacy   | 10 | 6 |
| Protocol deviation | 1  | - |

### Period 3

|                              |                         |
|------------------------------|-------------------------|
| Period 3 title               | Maintenance             |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| <b>Arm title</b>             | ARM A1 and B1 (no Maint) |

Arm description:

No therapy

|   |                   |
|---|-------------------|
| Arm type  | No intervention   |
| No investigational medicinal product assigned in this arm |                   |
| <b>Arm title</b>  | ARM A2 and B2 (R) |

Arm description:

Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period. Each cycle will be repeated every 28 days, until any sign of disease progression (PD).

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

Dosage and administration details:

Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period. Each cycle will be repeated every 28 days, until any sign of disease progression (PD).

| <b>Number of subjects in period 3</b> | ARM A1 and B1 (no Maint) | ARM A2 and B2 (R) |
|---------------------------------------|--------------------------|-------------------|
| Started                               | 124                      | 125               |
| Completed                             | 3                        | 4                 |
| Not completed                         | 121                      | 121               |
| Adverse event, serious fatal          | 1                        | 1                 |
| Physician decision                    | 19                       | 18                |
| Consent withdrawn by subject          | 8                        | 15                |
| Adverse event, non-fatal              | 1                        | 13                |
| Lost to follow-up                     | 2                        | 2                 |

|                    |    |    |
|--------------------|----|----|
| Lack of efficacy   | 89 | 68 |
| Protocol deviation | 1  | 4  |



## Baseline characteristics

### Reporting groups

|                                |           |
|--------------------------------|-----------|
| Reporting group title          | Induction |
| Reporting group description: - |           |

| Reporting group values       | Induction | Total |  |
|------------------------------|-----------|-------|--|
| Number of subjects           | 399       | 399   |  |
| Age categorical              |           |       |  |
| Units: Subjects              |           |       |  |
| <=60                         | 194       | 194   |  |
| >60                          | 205       | 205   |  |
| Age continuous               |           |       |  |
| Units: years                 |           |       |  |
| median                       | 57        |       |  |
| inter-quartile range (Q1-Q3) | 51 to 61  | -     |  |
| Gender categorical           |           |       |  |
| Units: Subjects              |           |       |  |
| Female                       | 194       | 194   |  |
| Male                         | 205       | 205   |  |
| ISS Stage                    |           |       |  |
| Units: Subjects              |           |       |  |
| ISS Stage I                  | 204       | 204   |  |
| ISS Stage II                 | 119       | 119   |  |
| ISS Stage III                | 76        | 76    |  |

### Subject analysis sets

|   |                    |
|---|--------------------|
| Subject analysis set title                  | ITT R1             |
| Subject analysis set type                   | Intention-to-treat |
| Subject analysis set description:           |                    |
| Intention to treat population from Random 1 |                    |
| Subject analysis set title                  | ITT R2             |
| Subject analysis set type                   | Intention-to-treat |
| Subject analysis set description:           |                    |
| Intention to Treat from R2                  |                    |

| Reporting group values       | ITT R1   | ITT R2   |  |
|------------------------------|----------|----------|--|
| Number of subjects           | 274      | 249      |  |
| Age categorical              |          |          |  |
| Units: Subjects              |          |          |  |
| <=60                         | 205      | 187      |  |
| >60                          | 69       | 62       |  |
| Age continuous               |          |          |  |
| Units: years                 |          |          |  |
| median                       | 56       | 56       |  |
| inter-quartile range (Q1-Q3) | 50 to 61 | 49 to 60 |  |

|                    |     |     |  |
|--------------------|-----|-----|--|
| Gender categorical |     |     |  |
| Units: Subjects    |     |     |  |
| Female             | 131 | 119 |  |
| Male               | 143 | 130 |  |
| ISS Stage          |     |     |  |
| Units: Subjects    |     |     |  |
| ISS Stage I        | 150 | 141 |  |
| ISS Stage II       | 83  | 75  |  |
| ISS Stage III      | 41  | 33  |  |

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## End points

### End points reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Rd Induction |
|-----------------------|--------------|

Reporting group description:

Patients will start induction treatment with lenalidomide and dexamethasone (RD) for 4 cycles every 28 days:

- Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28),
- Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15 and 22 every 28 days.

|                       |             |
|-----------------------|-------------|
| Reporting group title | CY infusion |
|-----------------------|-------------|

Reporting group description:

After 1-2 months from the completion of the last RD cycle, i.v. cyclophosphamide (CY) will be given at the dose of 4 g/m<sup>2</sup> followed by G-CSF (10 ug/kg/day starting at day 5 until completion of PBSC collection) to collect an adequate number of PBSC (4 to 10 x 10<sup>6</sup>/kg CD 34+ cells). Patients who fail to collect the minimum of 4 x 10<sup>6</sup>/kg CD 34+ cells will receive a second course of CY for a second mobilization attempt. Patients who fails to collect a minimum of 4 x 10<sup>6</sup>/kg CD 34+ will be withdrawn from the study.

|                       |             |
|-----------------------|-------------|
| Reporting group title | ARM A (MPR) |
|-----------------------|-------------|

Reporting group description:

Patients will start consolidation treatment with the association of lenalidomide, melphalan and prednisone (MPR) for 6 cycles every 28 days:

- Lenalidomide will be given orally at the dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28),
- Melphalan will be given orally at the dose of 0.18 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28)
- Prednisone will be given orally at the dose of 2 mg/Kg for 4 days followed by a 24 day rest period (days 5 to 28),

|                       |                |
|-----------------------|----------------|
| Reporting group title | ARM B (MEL200) |
|-----------------------|----------------|

Reporting group description:

Patients will start consolidation treatment with melphalan 200 mg/m<sup>2</sup> followed by stem cell support (MEL200) for 2 cycles every 4 months (only 1 cycle if the patient reached almost a VGPR after the 1st MEL200):

- Melphalan will be given iv at the dose of 200 mg/m<sup>2</sup> for 1 day followed by stem cell support and 120 days rest period.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | ARM A1 and B1 (no Maint) |
|-----------------------|--------------------------|

Reporting group description:

No therapy

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | ARM A2 and B2 (R) |
|-----------------------|-------------------|

Reporting group description:

Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period. Each cycle will be repeated every 28 days, until any sign of disease progression (PD).

|                            |        |
|----------------------------|--------|
| Subject analysis set title | ITT R1 |
|----------------------------|--------|

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

Subject analysis set description:

Intention to treat population from Random 1

|                            |        |
|----------------------------|--------|
| Subject analysis set title | ITT R2 |
|----------------------------|--------|

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

Subject analysis set description:

Intention to Treat from R2

### Primary: Progression Free Survival

|                 |                           |
|-----------------|---------------------------|
| End point title | Progression Free Survival |
|-----------------|---------------------------|

End point description:

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

End point timeframe:

End of trial

| End point values                      | ARM A (MPR)     | ARM B (MEL200)  | ARM A1 and B1 (no Maint) | ARM A2 and B2 (R) |
|---------------------------------------|-----------------|-----------------|--------------------------|-------------------|
| Subject group type                    | Reporting group | Reporting group | Reporting group          | Reporting group   |
| Number of subjects analysed           | 133             | 141             | 124                      | 125               |
| Units: month                          |                 |                 |                          |                   |
| median (inter-quartile range (Q1-Q3)) | 17 (15 to 21)   | 33 (29 to 42)   | 15 (12 to 20)            | 25 (20 to 42)     |

## Statistical analyses

|   |                              |
|---|------------------------------|
| Statistical analysis title              | Log rank test                |
| Comparison groups                       | ARM B (MEL200) v ARM A (MPR) |
| Number of subjects included in analysis | 274                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | < 0.001                      |
| Method                                  | Logrank                      |
| Parameter estimate                      | Hazard ratio (HR)            |
| Point estimate                          | 0.56                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.44                         |
| upper limit                             | 0.74                         |
| Variability estimate                    | Standard deviation           |
| Dispersion value                        | 0.13                         |

|   |  |
|---|--|
| Statistical analysis title              | Log rank test                                |
| Comparison groups                       | ARM A1 and B1 (no Maint) v ARM A2 and B2 (R) |
| Number of subjects included in analysis | 249  |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.002                                      |
| Method                                  | Logrank                                      |
| Parameter estimate                      | Hazard ratio (HR)                            |
| Point estimate                          | 0.66   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | 0.5  |
| upper limit                             | 0.86   |

|                      |                    |
|----------------------|--------------------|
| Variability estimate | Standard deviation |
| Dispersion value     | 0.14               |

## Secondary: time to progression (TTP)

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

| End point values                 | ARM A (MPR)     | ARM B (MEL200)  | ARM A1 and B1 (no Maint) | ARM A2 and B2 (R) |
|----------------------------------|-----------------|-----------------|--------------------------|-------------------|
| Subject group type               | Reporting group | Reporting group | Reporting group          | Reporting group   |
| Number of subjects analysed      | 133             | 141             | 124                      | 125               |
| Units: month                     |                 |                 |                          |                   |
| median (confidence interval 95%) | 17 (16 to 21)   | 36 (30 to 47)   | 15 (12 to 21)            | 26 (21 to 43)     |

## Statistical analyses

|   |                              |
|---|------------------------------|
| Statistical analysis title              | Log rank test                |
| Comparison groups                       | ARM A (MPR) v ARM B (MEL200) |
| Number of subjects included in analysis | 274                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | < 0.001                      |
| Method                                  | Logrank                      |
| Parameter estimate                      | Hazard ratio (HR)            |
| Point estimate                          | 0.55                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.42                         |
| upper limit                             | 0.71                         |
| Variability estimate                    | Standard deviation           |
| Dispersion value                        | 0.13                         |

|                            |  |
|----------------------------|--|
| Statistical analysis title | Log rank test                                |
| Comparison groups          | ARM A1 and B1 (no Maint) v ARM A2 and B2 (R) |

|   |                    |
|---|--------------------|
| Number of subjects included in analysis | 249                |
| Analysis specification                  | Pre-specified      |
| Analysis type                           | superiority        |
| P-value                                 | = 0.001            |
| Method                                  | Logrank            |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.64               |
| Confidence interval                     |                    |
| level                                   | 95 %               |
| sides                                   | 2-sided            |
| lower limit                             | 0.49               |
| upper limit                             | 0.84               |
| Variability estimate                    | Standard deviation |
| Dispersion value                        | 0.14               |

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

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

| End point values                 | ARM A (MPR)     | ARM B (MEL200)  | ARM A1 and B1 (no Maint) | ARM A2 and B2 (R) |
|----------------------------------|-----------------|-----------------|--------------------------|-------------------|
| Subject group type               | Reporting group | Reporting group | Reporting group          | Reporting group   |
| Number of subjects analysed      | 133             | 141             | 124                      | 125               |
| Units: month                     |                 |                 |                          |                   |
| median (confidence interval 95%) | 23 (21 to 29)   | 42 (36 to 56)   | 22 (17 to 28)            | 37 (26 to 54)     |

### Statistical analyses

|   |                              |
|---|------------------------------|
| Statistical analysis title              | Log rank test                |
| Comparison groups                       | ARM A (MPR) v ARM B (MEL200) |
| Number of subjects included in analysis | 274                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | < 0.001                      |
| Method                                  | Logrank                      |
| Parameter estimate                      | Hazard ratio (HR)            |
| Point estimate                          | 0.56                         |

|                      |                    |
|----------------------|--------------------|
| Confidence interval  |                    |
| level                | 95 %               |
| sides                | 2-sided            |
| lower limit          | 0.43               |
| upper limit          | 0.74               |
| Variability estimate | Standard deviation |
| Dispersion value     | 0.14               |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Log rank test                                |
| Comparison groups                       | ARM A1 and B1 (no Maint) v ARM A2 and B2 (R) |
| Number of subjects included in analysis | 249  |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | < 0.001                                      |
| Method                                  | Logrank                                      |
| Parameter estimate                      | Hazard ratio (HR)                            |
| Point estimate                          | 0.59   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | 0.45   |
| upper limit                             | 0.79   |
| Variability estimate                    | Standard deviation                           |
| Dispersion value                        | 0.15   |

### Secondary: overall survival (OS)

|   |                       |
|---|-----------------------|
| End point title                         | overall survival (OS) |
| End point description:                  |                       |
| End point type                          | Secondary             |
| End point timeframe:                    |                       |
| End of trial - Probability at 96 months |                       |

| End point values                 | ARM A (MPR)         | ARM B (MEL200)      | ARM A1 and B1 (no Maint) | ARM A2 and B2 (R)   |
|----------------------------------|---------------------|---------------------|--------------------------|---------------------|
| Subject group type               | Reporting group     | Reporting group     | Reporting group          | Reporting group     |
| Number of subjects analysed      | 133                 | 141                 | 124                      | 125                 |
| Units: month                     |                     |                     |                          |                     |
| number (confidence interval 95%) | 0.47 (0.37 to 0.59) | 0.58 (0.49 to 0.68) | 0.56 (0.47 to 0.68)      | 0.53 (0.44 to 0.65) |

## Statistical analyses

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Log rank test                |
| Comparison groups                       | ARM A (MPR) v ARM B (MEL200) |
| Number of subjects included in analysis | 274                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.054                      |
| Method                                  | Logrank                      |
| Parameter estimate                      | Hazard ratio (HR)            |
| Point estimate                          | 0.69                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.47                         |
| upper limit                             | 1.01                         |
| Variability estimate                    | Standard deviation           |
| Dispersion value                        | 0.19                         |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Log rank test                                |
| Comparison groups                       | ARM A2 and B2 (R) v ARM A1 and B1 (no Maint) |
| Number of subjects included in analysis | 249  |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.73                                       |
| Method                                  | Logrank                                      |
| Parameter estimate                      | Hazard ratio (HR)                            |
| Point estimate                          | 0.93   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | 0.62   |
| upper limit                             | 1.4  |
| Variability estimate                    | Standard deviation                           |
| Dispersion value                        | 0.21   |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Per protocol

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 27 |
|--------------------|----|

### Reporting groups

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

Reporting group description:

Per protocol

| Serious adverse events  | Per protocol     |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed   | 38 / 399 (9.52%) |  |  |
| number of deaths (all causes)                                       | 176              |  |  |
| number of deaths resulting from adverse events                      | 19               |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Adenocarcinoma  |                  |  |  |
| subjects affected / exposed   | 1 / 399 (0.25%)  |  |  |
| occurrences causally related to treatment / all                     | 1 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Adenocarcinoma gastric  |                  |  |  |
| subjects affected / exposed   | 1 / 399 (0.25%)  |  |  |
| occurrences causally related to treatment / all                     | 1 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Adenocarcinoma of colon   |                  |  |  |
| subjects affected / exposed   | 2 / 399 (0.50%)  |  |  |
| occurrences causally related to treatment / all                     | 2 / 2            |  |  |
| deaths causally related to treatment / all                          | 1 / 1            |  |  |
| Basal cell carcinoma  |                  |  |  |
| subjects affected / exposed   | 3 / 399 (0.75%)  |  |  |
| occurrences causally related to treatment / all                     | 2 / 3            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |

|  |                 |  |  |  |
|--|-----------------|--|--|--|
| Bladder transitional cell carcinoma<br>subjects affected / exposed | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to<br>treatment / all                 | 0 / 1           |  |  |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           |  |  |  |
| Breast cancer<br>subjects affected / exposed                       | 4 / 399 (1.00%) |  |  |  |
| occurrences causally related to<br>treatment / all                 | 3 / 4           |  |  |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           |  |  |  |
| Cholangiocarcinoma<br>subjects affected / exposed                  | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to<br>treatment / all                 | 0 / 1           |  |  |  |
| deaths causally related to<br>treatment / all                      | 0 / 1           |  |  |  |
| Colon cancer<br>subjects affected / exposed                        | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to<br>treatment / all                 | 1 / 1           |  |  |  |
| deaths causally related to<br>treatment / all                      | 1 / 1           |  |  |  |
| Colorectal adenocarcinoma<br>subjects affected / exposed           | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to<br>treatment / all                 | 0 / 1           |  |  |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           |  |  |  |
| Endometrial cancer<br>subjects affected / exposed                  | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to<br>treatment / all                 | 1 / 1           |  |  |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           |  |  |  |
| Gastrointestinal carcinoma<br>subjects affected / exposed          | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to<br>treatment / all                 | 0 / 1           |  |  |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           |  |  |  |
| Lung neoplasm malignant<br>subjects affected / exposed             | 2 / 399 (0.50%) |  |  |  |
| occurrences causally related to<br>treatment / all                 | 1 / 2           |  |  |  |
| deaths causally related to<br>treatment / all                      | 1 / 1           |  |  |  |
| Metastases to liver  |                 |  |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Myelodysplastic syndrome                        |                 |  |  |  |
| subjects affected / exposed                     | 3 / 399 (0.75%) |  |  |  |
| occurrences causally related to treatment / all | 3 / 3           |  |  |  |
| deaths causally related to treatment / all      | 2 / 2           |  |  |  |
| Ovarian adenoma                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Parathyroid tumour benign                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Prostate cancer                                 |                 |  |  |  |
| subjects affected / exposed                     | 2 / 399 (0.50%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Skin cancer                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Squamous cell carcinoma of skin                 |                 |  |  |  |
| subjects affected / exposed                     | 2 / 399 (0.50%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Transitional cell carcinoma                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Tumour flare                                    |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Uterine cancer                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Aortic stenosis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Deep vein thrombosis                            |                 |  |  |
| subjects affected / exposed                     | 5 / 399 (1.25%) |  |  |
| occurrences causally related to treatment / all | 4 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Superficial vein thrombosis                     |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thrombosis                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Venous thrombosis limb                          |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Surgical and medical procedures                 |                 |  |  |
| Coronary artery bypass                          |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hip arthroplasty                                |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Ileostomy                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Incisional hernia repair                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Jaw operation                                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Knee arthroplasty                               |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Meniscus removal                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Spinal stabilisation                            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Thyroidectomy                                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Umbilical hernia repair                         |                 |  |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Vertebroplasty                                       |                 |  |  |
| subjects affected / exposed                          | 3 / 399 (0.75%) |  |  |
| occurrences causally related to treatment / all      | 0 / 4           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Fatigue  |                 |  |  |
| subjects affected / exposed                          | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Multiple organ dysfunction syndrome                  |                 |  |  |
| subjects affected / exposed                          | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |
| Pyrexia  |                 |  |  |
| subjects affected / exposed                          | 5 / 399 (1.25%) |  |  |
| occurrences causally related to treatment / all      | 4 / 5           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders      |                 |  |  |
| Cough  |                 |  |  |
| subjects affected / exposed                          | 2 / 399 (0.50%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Dyspnoea   |                 |  |  |
| subjects affected / exposed                          | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Lung infiltration                                    |                 |  |  |
| subjects affected / exposed                          | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Obstructive sleep apnoea syndrome               |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pleural effusion                                |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary artery thrombosis                     |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 3 / 399 (0.75%) |  |  |
| occurrences causally related to treatment / all | 3 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary oedema                                |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory distress                            |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 2 / 399 (0.50%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Investigations                                  |                 |  |  |
| Aspartate aminotransferase increased            |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Blood pressure diastolic increased<br>subjects affected / exposed | 1 / 399 (0.25%) |  |  |
| occurrences causally related to<br>treatment / all                | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           |  |  |
| Hepatic enzyme increased<br>subjects affected / exposed           | 2 / 399 (0.50%) |  |  |
| occurrences causally related to<br>treatment / all                | 1 / 2           |  |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           |  |  |
| Transaminases increased<br>subjects affected / exposed            | 2 / 399 (0.50%) |  |  |
| occurrences causally related to<br>treatment / all                | 1 / 2           |  |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           |  |  |
| Injury, poisoning and procedural<br>complications                 |                 |  |  |
| Humerus fracture<br>subjects affected / exposed                   | 1 / 399 (0.25%) |  |  |
| occurrences causally related to<br>treatment / all                | 0 / 2           |  |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           |  |  |
| Meniscus injury<br>subjects affected / exposed                    | 1 / 399 (0.25%) |  |  |
| occurrences causally related to<br>treatment / all                | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           |  |  |
| Spinal compression fracture<br>subjects affected / exposed        | 2 / 399 (0.50%) |  |  |
| occurrences causally related to<br>treatment / all                | 0 / 2           |  |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           |  |  |
| Spinal fracture<br>subjects affected / exposed                    | 1 / 399 (0.25%) |  |  |
| occurrences causally related to<br>treatment / all                | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           |  |  |
| Thoracic vertebral fracture<br>subjects affected / exposed        | 1 / 399 (0.25%) |  |  |
| occurrences causally related to<br>treatment / all                | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           |  |  |



|  |                                   |  |  |
|--|-----------------------------------|--|--|
| Traumatic fracture<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all           | 2 / 399 (0.50%)<br>0 / 2<br>0 / 0 |  |  |
| Cardiac disorders  |                                   |  |  |
| Acute coronary syndrome<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all      | 1 / 399 (0.25%)<br>1 / 1<br>1 / 1 |  |  |
| Acute myocardial infarction<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | 2 / 399 (0.50%)<br>1 / 3<br>0 / 0 |  |  |
| Atrioventricular block<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all       | 1 / 399 (0.25%)<br>1 / 1<br>1 / 1 |  |  |
| Cardiac arrest<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all               | 1 / 399 (0.25%)<br>1 / 1<br>0 / 0 |  |  |
| Cardiac failure congestive<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 399 (0.25%)<br>2 / 2<br>0 / 0 |  |  |
| Myocardial ischaemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all         | 1 / 399 (0.25%)<br>1 / 1<br>0 / 0 |  |  |
| Supraventricular tachycardia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 1 / 399 (0.25%)<br>0 / 1<br>0 / 0 |  |  |
| Blood and lymphatic system disorders   |                                   |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Anaemia   |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Febrile neutropenia                             |                 |  |  |
| subjects affected / exposed                     | 5 / 399 (1.25%) |  |  |
| occurrences causally related to treatment / all | 4 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancytopenia                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 399 (0.50%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Colitis   |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diarrhoea                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diverticular perforation                        |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal obstruction                          |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nausea  |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Small intestinal obstruction                    |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Acute hepatic failure                           |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Cholecystitis                                   |                 |  |  |
| subjects affected / exposed                     | 2 / 399 (0.50%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Jaundice  |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Dermatitis allergic                             |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dermatitis exfoliative generalised              |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Erythema  |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rash  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 3 / 399 (0.75%) |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Acute kidney injury                             |                 |  |  |
| subjects affected / exposed                     | 2 / 399 (0.50%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 3 / 399 (0.75%) |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endocrine disorders                             |                 |  |  |
| Goitre  |                 |  |  |
| subjects affected / exposed                     | 2 / 399 (0.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypothyroidism                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bone pain                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Osteonecrosis of jaw                            |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Osteoporotic fracture                           |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rhabdomyolysis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal pain                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Bacterial infection                             |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bacterial sepsis                                |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bronchitis                                      |                 |  |  |
| subjects affected / exposed                     | 2 / 399 (0.50%) |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholangitis infective                           |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cytomegalovirus colitis                         |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cytomegalovirus infection                       |                 |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| reactivation                                    |                  |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |  |
| Enterobacter pneumonia                          |                  |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Escherichia sepsis                              |                  |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Herpes zoster                                   |                  |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Herpes zoster cutaneous disseminated            |                  |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Klebsiella sepsis                               |                  |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |  |
| Pneumocystis jirovecii pneumonia                |                  |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Pneumonia                                       |                  |  |  |  |
| subjects affected / exposed                     | 17 / 399 (4.26%) |  |  |  |
| occurrences causally related to treatment / all | 10 / 18          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Pneumonia bacterial                             |                  |  |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia cytomegaloviral                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia pseudomonal                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Sepsis  |                 |  |  |  |
| subjects affected / exposed                     | 2 / 399 (0.50%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Septic shock                                    |                 |  |  |  |
| subjects affected / exposed                     | 3 / 399 (0.75%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 2           |  |  |  |
| Staphylococcal infection                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Tooth abscess                                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Tuberculosis                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Urinary tract infection                         |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Cachexia  |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypokalaemia                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 399 (0.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 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                           | 379 / 399 (94.99%) |  |  |
| Investigations  |                    |  |  |
| Alanine aminotransferase increased                    |                    |  |  |
| subjects affected / exposed                           | 21 / 399 (5.26%)   |  |  |
| occurrences (all)                                     | 21                 |  |  |
| Blood creatinine increased                            |                    |  |  |
| subjects affected / exposed                           | 21 / 399 (5.26%)   |  |  |
| occurrences (all)                                     | 21                 |  |  |
| Nervous system disorders                              |                    |  |  |
| Paraesthesia  |                    |  |  |
| subjects affected / exposed                           | 29 / 399 (7.27%)   |  |  |
| occurrences (all)                                     | 29                 |  |  |
| Neuropathy peripheral                                 |                    |  |  |



|   |                        |  |  |
|---|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)        | 22 / 399 (5.51%)<br>22 |  |  |
| Blood and lymphatic system disorders                    |                        |  |  |
| Neutropenia   |                        |  |  |
| subjects affected / exposed                             | 331 / 399 (82.96%)     |  |  |
| occurrences (all)                                       | 331                    |  |  |
| Anaemia   |                        |  |  |
| subjects affected / exposed                             | 309 / 399 (77.44%)     |  |  |
| occurrences (all)                                       | 309                    |  |  |
| Thrombocytopenia  |                        |  |  |
| subjects affected / exposed                             | 290 / 399 (72.68%)     |  |  |
| occurrences (all)                                       | 290                    |  |  |
| Febrile neutropenia                                     |                        |  |  |
| subjects affected / exposed                             | 28 / 399 (7.02%)       |  |  |
| occurrences (all)                                       | 28                     |  |  |
| General disorders and administration<br>site conditions |                        |  |  |
| Pyrexia   |                        |  |  |
| subjects affected / exposed                             | 149 / 399 (37.34%)     |  |  |
| occurrences (all)                                       | 149                    |  |  |
| Fatigue   |                        |  |  |
| subjects affected / exposed                             | 94 / 399 (23.56%)      |  |  |
| occurrences (all)                                       | 94                     |  |  |
| Asthenia  |                        |  |  |
| subjects affected / exposed                             | 69 / 399 (17.29%)      |  |  |
| occurrences (all)                                       | 69                     |  |  |
| Mucosal inflammation                                    |                        |  |  |
| subjects affected / exposed                             | 57 / 399 (14.29%)      |  |  |
| occurrences (all)                                       | 57                     |  |  |
| Pain  |                        |  |  |
| subjects affected / exposed                             | 37 / 399 (9.27%)       |  |  |
| occurrences (all)                                       | 37                     |  |  |
| Gastrointestinal disorders                              |                        |  |  |
| Diarrhoea   |                        |  |  |
| subjects affected / exposed                             | 87 / 399 (21.80%)      |  |  |
| occurrences (all)                                       | 87                     |  |  |
| Nausea  |                        |  |  |

|   |   |  |  |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leukopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>81 / 399 (20.30%)</p> <p>81</p> <p>60 / 399 (15.04%)</p> <p>60</p> <p>60 / 399 (15.04%)</p> <p>60</p> <p>43 / 399 (10.78%)</p> <p>43</p> |  |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>32 / 399 (8.02%)</p> <p>32</p>   |  |  |
| <p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Erythema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                         | <p>62 / 399 (15.54%)</p> <p>62</p> <p>42 / 399 (10.53%)</p> <p>42</p> <p>25 / 399 (6.27%)</p> <p>25</p>                                     |  |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bone pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>27 / 399 (6.77%)</p> <p>27</p> <p>27 / 399 (6.77%)</p> <p>27</p>   |  |  |
| <p>Infections and infestations</p> <p>Bronchitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>23 / 399 (5.76%)</p> <p>23</p>   |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 03 June 2008     | Amendment 1: Update to examinations, risks and benefits, and informed consent.        |
| 30 November 2009 | Amendment 2: Update on protocol procedures and drug risks.                            |
| 27 July 2010     | Amendment Sponsor: Change of sponsor's legal representative.                          |
| 27 April 2011    | Amendment ICF v.4: Urgent drug side effects update.                                   |
| 30 April 2013    | Amendment 3: Statistical updates.   |
| 16 May 2017      | Amendment 4: Updates: Sponsor contacts, disease assessment, and drug side effects.    |
| 05 February 2019 | Amendment 5: Adding new drug depot and implementing pregnancy prevention program.     |
| 18 June 2019     | Amendment 6: Side effects update.   |
| 20 March 2020    | Urgent Amendment 1: COVID updates.  |
| 03 August 2020   | Amendment 7: Side effects update and Sponsor name.                                    |
| 30 October 2023  | Amendment CEC-CET: Change from CEC to CET.  |
| 05 February 2024 | Amendment 8: Central laboratory change, study duration updates, and drug information. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/17785703>

<http://www.ncbi.nlm.nih.gov/pubmed/21637283>