



Clinical trial results:

A Phase 1/2 multicenter, open-label study to determine the recommended dose and regimen of Durvalumab (MEDI4736) in combination with Lenalidomide (LEN) with and without Dexamethasone (DEX) in subjects with newly diagnosed multiple myeloma (NDMM)

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2015-004831-11 |
| Trial protocol | DE ES DK FI NL |
| Global end of trial date | 06 September 2022 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v2 (current) |
| This version publication date | 14 October 2023 |
| First version publication date | 17 September 2023 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | MEDI4736-MM-002 |
|-----------------------|-----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 March 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 September 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Determine the recommended dose and regimen of durvalumab in combination with LEN with and without DEX in subjects with newly diagnosed multiple myeloma (NDMM).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 25 April 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Canada: 13 |
| Country: Number of subjects enrolled | Denmark: 7 |
| Country: Number of subjects enrolled | Finland: 5 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | Spain: 15 |
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | United States: 4 |
| Worldwide total number of subjects | 56 |
| EEA total number of subjects | 39 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---------------------------|----|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 17 |
| From 65 to 84 years | 39 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

56 subjects treated

Period 1

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--------------------------|
| Arm title | Cohort A: High risk, TNE |
|------------------|--------------------------|

Arm description:

High risk, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | LEN |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg/day on days 1 to 21 of each 28-day treatment cycle

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

Dosage and administration details:

40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle.

| | |
|--|-----------------------|
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | MEDI4736 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1500 mg on day 1 of each 28-day cycle

| | |
|------------------|------------------------------------|
| Arm title | Cohort B: \geq 65 years old, TNE |
|------------------|------------------------------------|

Arm description:

\geq 65 years old, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were not high risk were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle, up to 12 cycles.

| | |
|---|--------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | MEDI4736 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 1500 mg on day 1 of each 28-day cycle | |
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | DEX |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle. | |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | LEN |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 25 mg/day on days 1 to 21 of each 28-day treatment cycle | |
| Arm title | Cohort C: High risk, Post-transplant |
| Arm description: | |
| High risk, post-transplant NDMM participants were administered the following as maintenance therapy: • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 10 mg/day on Days 1 to 21 of each 28-day treatment cycle. | |
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | LEN |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 10 mg/day on days 1 to 21 of each 28-day treatment cycle | |
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | MEDI4736 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 1500 mg on day 1 of each 28-day cycle | |

| Number of subjects in period 1 | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant |
|---------------------------------------|-----------------------------|---------------------------------------|---|
| Started | 25 | 10 | 21 |
| Completed | 0 | 0 | 0 |
| Not completed | 25 | 10 | 21 |
| Consent withdrawn by subject | 2 | - | - |
| Adverse event, non-fatal | 2 | - | 1 |
| Progressive Disease | 2 | 1 | - |
| Full Clinical Hold by FDA | 19 | 9 | 20 |

Baseline characteristics

Reporting groups

| | |
|---|--------------------------------------|
| Reporting group title | Cohort A: High risk, TNE |
| Reporting group description: | |
| High risk, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle. | |
| Reporting group title | Cohort B: \geq 65 years old, TNE |
| Reporting group description: | |
| \geq 65 years old, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were not high risk were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle, up to 12 cycles. | |
| Reporting group title | Cohort C: High risk, Post-transplant |
| Reporting group description: | |
| High risk, post-transplant NDMM participants were administered the following as maintenance therapy: • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 10 mg/day on Days 1 to 21 of each 28-day treatment cycle. | |

| Reporting group values | Cohort A: High risk, TNE | Cohort B: \geq 65 years old, TNE | Cohort C: High risk, Post-transplant |
|---|--------------------------|------------------------------------|--------------------------------------|
| Number of subjects | 25 | 10 | 21 |
| Age Categorical Units: participants | | | |
| \leq 75 years | 12 | 7 | 20 |
| $>$ 75 years | 13 | 3 | 1 |
| Age Continuous Units: years | | | |
| arithmetic mean | 75.4 | 72.5 | 59.6 |
| standard deviation | \pm 4.17 | \pm 5.25 | \pm 7.52 |
| Sex: Female, Male Units: participants | | | |
| Female | 15 | 0 | 4 |
| Male | 10 | 10 | 17 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 1 | 1 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 1 | 0 | 0 |
| White | 21 | 9 | 17 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 2 | 0 | 4 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 56 | | |

| | | | |
|---|----|--|--|
| Age Categorical | | | |
| Units: participants | | | |
| <=75 years | 39 | | |
| >75 years | 17 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 19 | | |
| Male | 37 | | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 2 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 1 | | |
| White | 47 | | |
| More than one race | 0 | | |
| Unknown or Not Reported | 6 | | |

End points

End points reporting groups

| | |
|---|--------------------------------------|
| Reporting group title | Cohort A: High risk, TNE |
| Reporting group description: High risk, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle. | |
| Reporting group title | Cohort B: \geq 65 years old, TNE |
| Reporting group description: \geq 65 years old, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were not high risk were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle, up to 12 cycles. | |
| Reporting group title | Cohort C: High risk, Post-transplant |
| Reporting group description: High risk, post-transplant NDMM participants were administered the following as maintenance therapy: • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 10 mg/day on Days 1 to 21 of each 28-day treatment cycle. | |

Primary: Participants with Dose-Limiting Toxicities (DLTs) During the Dose-Determining Timeframe (Day 1 – Day 28)

| | |
|---|---|
| End point title | Participants with Dose-Limiting Toxicities (DLTs) During the Dose-Determining Timeframe (Day 1 – Day 28) ^[1] |
| End point description: A Dose Review Team (DRT) evaluated DLTs to determine the recommended dose (RD) of Durvalumab to use in the Expansion Period. A DLT was defined as: a. Grade 4 neutropenia for \geq 5 days. b. Grade 3 neutropenia associated with fever (\geq 38.5°C / 101.3°F) of any duration. c. Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or platelets transfusion. d. Grade 4 hematologic toxicity that does not resolve to baseline level \leq 72 hours. e. Grade 4 anemia, unexplained by underlying disease. f. Any nonhematologic toxicity Grade \geq 3 except for alopecia and nausea. g. Treatment interruption \geq 2 weeks due to AE. If \leq 1 of the 6 initial participants in each cohort experience a DLT during cycle 1, the RD was Durvalumab 1500 mg; If \geq 2 of the 6 initial participants in any cohort experience a DLT during cycle 1, the maximum tolerated dose (MTD) was exceeded and the dose level of Durvalumab was de-escalated to 750 mg | |
| End point type | Primary |
| End point timeframe: First treatment cycle: Day 1 to Day 28 | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only summary analysis planned for this endpoint. | |

| End point values | Cohort A: High risk, TNE | Cohort B: \geq 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|------------------------------|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 6 | 7 | 6 | |
| Units: Count of participants | 1 | 1 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Treatment Emergent Adverse Events (TEAE)

| | |
|-----------------|--|
| End point title | Participants with Treatment Emergent Adverse Events (TEAE) |
|-----------------|--|

End point description:

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen during the course of a study. A TEAE includes AEs between the first dose date of either study drug and 90 days after the last dose of study drug. A serious AE is any AE occurring at any dose that: • Results in death; • Is life-threatening; • Requires or prolongs existing inpatient hospitalization; • Results in persistent or significant disability/incapacity; • Is a congenital anomaly/birth defect; • Constitutes an important medical event. The Investigator assessed the relationship of each AE to study drug and graded the severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03): - Grade 1 = Mild - Grade 2 = Moderate (some limitation in activity; no/minimal medical intervention required) - Grade 3 = Severe (limitation in activity; medical intervention required) - Grade 4 = Life-threatening - Grade 5 = Death 99999=NA

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

End point timeframe:

Day 1 up to Week 84 (the longer of 90 days after discontinuing treatment with DURVA, or 28 days after the last dose of LEN or dex)

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|--|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 10 | 21 | |
| Units: Count of participants | | | | |
| ≥ 1 TEAE | 24 | 9 | 18 | |
| ≥ 1 treatment-related TEAE | 22 | 8 | 17 | |
| ≥ 1 related to DURVA | 16 | 4 | 15 | |
| ≥ 1 related to LEN | 22 | 8 | 15 | |
| ≥ 1 related to dex | 16 | 6 | 99999 | |
| ≥ 1 TEAE of severity grade 3 or 4 | 19 | 8 | 7 | |
| ≥ 1 severity 3/4, related to study drug | 13 | 8 | 6 | |
| ≥ 1 severity 3/4, related to DURVA | 7 | 4 | 4 | |
| ≥ 1 severity 3/4, related to LEN | 11 | 8 | 4 | |
| ≥ 1 severity 3/4, related to dex | 5 | 2 | 99999 | |
| ≥ 1 Grade 5 TEAE (Death) | 1 | 0 | 1 | |
| ≥ 1 Grade 5 TEAE related to study drug | 0 | 0 | 1 | |
| ≥ 1 Grade 5 TEAE related to DURVA | 0 | 0 | 1 | |
| ≥ 1 Grade 5 TEAE related to LEN | 0 | 0 | 0 | |
| ≥ 1 Grade 5 TEAE related to dex | 0 | 0 | 99999 | |
| ≥ 1 Serious TEAE | 12 | 6 | 4 | |
| ≥ 1 Serious TEAE related to study drug | 8 | 4 | 4 | |
| ≥ 1 Serious TEAE related to DURVA | 5 | 1 | 4 | |

| | | | | |
|---|----|---|-------|--|
| >=1 Serious TEAE related to LEN | 6 | 3 | 2 | |
| >=1 Serious TEAE related to dex | 5 | 1 | 99999 | |
| >=1 TEAE leading to discontinuation of study drug | 3 | 0 | 1 | |
| >= TEAE leading to discontinuation of DURVA | 2 | 0 | 1 | |
| >= TEAE leading to discontinuation of LEN | 3 | 0 | 0 | |
| >= TEAE leading to discontinuation of dex | 2 | 0 | 99999 | |
| >=1 leading to delay/reduction/interruption drug | 14 | 7 | 6 | |
| >=1 leading to dose delay of DURVA | 10 | 3 | 4 | |
| >=1 leading to infusion interruption of DURVA | 0 | 0 | 1 | |
| >=1 leading to dose reduction of LEN | 2 | 2 | 3 | |
| >=1 leading to interruption of LEN | 13 | 5 | 5 | |
| >=1 leading to dose reduction of dex | 1 | 3 | 99999 | |
| >=1 leading to interruption of dex | 9 | 3 | 99999 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) for Cohorts A and B: Percentage of Participants Who Achieved a Partial Response or Better According to the International Myeloma Working Group (IMWG) Uniform Response Criteria

| | |
|-----------------|---|
| End point title | Overall Response Rate (ORR) for Cohorts A and B: Percentage of Participants Who Achieved a Partial Response or Better According to the International Myeloma Working Group (IMWG) Uniform Response Criteria |
|-----------------|---|

End point description:

Tumor response, including progressive disease, was assessed by the investigators and captured the best assessment of response during the treatment period. ORR was defined as partial response (PR) or better which includes PR, very good partial response (VGPR), complete response (CR), or stringent complete response (sCR). A PR required $\geq 50\%$ reduction of serum M-Protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to < 200 mg per 24 hours. If present at baseline, a $\geq 50\%$ reduction in the size of soft tissue plasmacytomas was also required. sCR required - a negative immunofixation of serum and urine and - disappearance of any soft tissue plasmacytomas and - $\leq 5\%$ plasma cells in bone marrow and normal free light-chain (FLC) ratio and - absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry.

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

End point timeframe:

Day 1 of each cycle starting with Cycle 2 up to Cycle 17 plus one week for the end of treatment visit (Day 29 up to Week 73)

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|-----------------------------------|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 10 | 0 ^[2] | |
| Units: percentage of participants | | | | |
| number (confidence interval 80%) | 66.7 (51.6 to 79.5) | 50.0 (26.7 to 73.3) | (to) | |

Notes:

[2] - 0 subjects analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Response Improvement Rate (RIR) for Cohort C: Percentage of Participants Achieving a Response Improved from Cycle 1 Day 1 as Assessed by the Investigators Using the International Myeloma Working Group (IMWG) Uniform Response Criteria

| | |
|-----------------|---|
| End point title | Response Improvement Rate (RIR) for Cohort C: Percentage of Participants Achieving a Response Improved from Cycle 1 Day 1 as Assessed by the Investigators Using the International Myeloma Working Group (IMWG) Uniform Response Criteria |
|-----------------|---|

End point description:

Response Improvement Rate is defined as the percentage of participants who achieved a response from treatment as compared to the pre-autologous stem cell transplantation [ASCT] diseases measurement used as baseline for response assessment. IMWG response categories could be stable disease (SD), partial response (PR), very good partial response (VGPR), complete response (CR), or stringent complete response (sCR), as long as it represented an improvement compared to prior to transplant. 99999=NA

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

End point timeframe:

Baseline (Cycle 1 Day 1); Treatment: Day 1 of each cycle starting with Cycle 2 up to Cycle 15 plus one week for the end of treatment visit (Day 29 up to Week 61)

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|-----------------------------------|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[3] | 0 ^[4] | 21 | |
| Units: percentage of participants | | | | |
| number (confidence interval 80%) | (to) | (to) | 0 (-99999 to 99999) | |

Notes:

[3] - 0 subjects analyzed

[4] - 0 subjects analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (for Cohorts A and B)

| | |
|-----------------|--|
| End point title | Time to Response (for Cohorts A and B) |
|-----------------|--|

End point description:

Time to response (for responders only, per IMWG Uniform Response Criteria) is calculated as the time from the first date of dosing of study medication to the first date of documented response (PR or better).

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

End point timeframe:

Day 1 of each cycle starting with Cycle 2 up to Cycle 17 plus one week for the end of treatment visit (Day 29 up to Week 73)

| End point values | Cohort A: High risk, TNE | Cohort B: >=65 years old, TNE | Cohort C: High risk, Post-transplant | |
|-------------------------------|--------------------------|-------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 16 | 5 | 0 ^[5] | |
| Units: weeks | | | | |
| median (full range (min-max)) | 4.20 (3.9 to 23.1) | 4.10 (4.0 to 13.0) | (to) | |

Notes:

[5] - 0 subjects analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates for Duration of Response (for Cohort A and B)

| | |
|-----------------|--|
| End point title | Kaplan-Meier Estimates for Duration of Response (for Cohort A and B) |
|-----------------|--|

End point description:

Duration of response (for responders only) was defined as the time from earliest date of documented response (PR or better) to the earliest date of disease progression (DP) as determined by the investigator per IMWG Uniform Response criteria or death during study treatment, whichever occurred first. 99999=NA

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

End point timeframe:

Day 1 of each cycle starting with Cycle 2 up to Cycle 17 plus one week for the end of treatment visit (Day 29 up to Week 73)

| End point values | Cohort A: High risk, TNE | Cohort B: >=65 years old, TNE | Cohort C: High risk, Post-transplant | |
|----------------------------------|--------------------------|-------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 16 | 5 | 0 ^[6] | |
| Units: months | | | | |
| median (confidence interval 80%) | 10.3 (7.2 to 99999) | 99999 (99999 to 99999) | (to) | |

Notes:

[6] - 0 subjects analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Maximum Observed Concentration (Cmax)

| | |
|-----------------|--|
| End point title | Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Maximum Observed Concentration (Cmax) |
|-----------------|--|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \times \sqrt{\exp(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|---------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 23 | 10 | 20 | |
| Units: $\mu\text{g/L}$ | | | | |
| geometric mean (geometric coefficient of variation) | 449280.231 (± 36.7) | 452827.419 (± 25.5) | 482602.748 (± 39.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Area Under the Concentration-time Curve from Time Zero to Infinity (AUC0-inf)

| | |
|-----------------|--|
| End point title | Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Area Under the Concentration-time Curve from Time Zero to Infinity (AUC0-inf) |
|-----------------|--|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \times \sqrt{\exp(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|----------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 23 | 9 | 19 | |
| Units: day* $\mu\text{g/L}$ | | | | |
| geometric mean (geometric coefficient of variation) | 4944601.671 (± 60.9) | 5532568.144 (± 62.5) | 6531541.670 (± 36.4) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum Pharmacokinetic (PK) Parameters in Cycle 1: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last)

| | |
|-----------------|---|
| End point title | Durvalumab (DURVA) Serum Pharmacokinetic (PK) Parameters in Cycle 1: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last) |
|-----------------|---|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $\text{CV\%} = 100 \times \text{SQRT}(\text{EXP}(\sigma^2) - 1)$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|----------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 23 | 10 | 20 | |
| Units: day* $\mu\text{g/L}$ | | | | |
| geometric mean (geometric coefficient of variation) | 3535033.014 (± 39.8) | 3582905.960 (± 21.0) | 4026520.655 (± 39.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Time to Maximum Observed Concentration (Tmax)

| | |
|-----------------|--|
| End point title | Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Time to Maximum Observed Concentration (Tmax) |
|-----------------|--|

End point description:

Time to maximum observed concentration of Durvalumab (DURVA) after multiple doses on day 1 obtained from the observed concentration versus time data

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1 | |

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|-------------------------------|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 23 | 10 | 20 | |
| Units: day | | | | |
| median (full range (min-max)) | 0.051 (0.04 to 0.22) | 0.106 (0.04 to 0.22) | 0.180 (0.04 to 0.22) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Terminal Elimination Half-life (t_{1/2})

| | |
|-----------------|---|
| End point title | Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Terminal Elimination Half-life (t _{1/2}) |
|-----------------|---|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \times \sqrt{EXP(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 23 | 9 | 19 | |
| Units: day | | | | |
| geometric mean (geometric coefficient of variation) | 10.984 (\pm 52.1) | 13.376 (\pm 90.9) | 15.844 (\pm 29.8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Clearance (CL)

| | |
|-----------------|---|
| End point title | Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Clearance (CL) |
|-----------------|---|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \times \sqrt{\exp(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 23 | 9 | 19 | |
| Units: L/day | | | | |
| geometric mean (geometric coefficient of variation) | 0.303 (\pm 60.9) | 0.271 (\pm 62.5) | 0.230 (\pm 36.4) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Volume of Distribution (Vz)

| | |
|-----------------|--|
| End point title | Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Volume of Distribution (Vz) |
|-----------------|--|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \times \sqrt{\exp(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 23 | 9 | 19 | |
| Units: liters | | | | |
| geometric mean (geometric coefficient of variation) | 4.244 (\pm 33.5) | 4.582 (\pm 33.3) | 4.563 (\pm 42.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Maximum Observed Concentration (C_{max})

| | |
|-----------------|--|
| End point title | Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Maximum Observed Concentration (C _{max}) |
|-----------------|--|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \times \sqrt{\exp(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 10 | 21 | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 395.774 (\pm 56.2) | 354.018 (\pm 34.7) | 161.372 (\pm 33.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Area Under the Concentration-time Curve from Time Zero to Infinity (AUC_{0-inf})

| | |
|-----------------|--|
| End point title | Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Area Under the Concentration-time Curve from Time Zero to Infinity (AUC _{0-inf}) |
|-----------------|--|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \times \sqrt{\exp(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 13 | 3 | 12 | |
| Units: hour*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 2534.684 (\pm 48.6) | 2011.889 (\pm 26.8) | 768.104 (\pm 33.5) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last)

| | |
|-----------------|--|
| End point title | Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last) |
|-----------------|--|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \cdot \sqrt{\exp(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 10 | 21 | |
| Units: hour*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 1468.102 (\pm 78.6) | 1442.549 (\pm 29.9) | 591.085 (\pm 22.3) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Time to Maximum Observed Concentration (Tmax)

| | |
|-----------------|---|
| End point title | Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters |
|-----------------|---|

End point description:

Time to maximum observed concentration of Lenalidomide (LEN) after multiple doses on day 1 obtained from the observed concentration versus time data

End point type Secondary

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|-------------------------------|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 10 | 21 | |
| Units: hour | | | | |
| median (full range (min-max)) | 1.050 (0.42 to 4.08) | 1.925 (0.50 to 4.00) | 1.150 (0.43 to 4.17) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Terminal Elimination Half-life ($t_{1/2}$)

End point title Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Terminal Elimination Half-life ($t_{1/2}$)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \times \sqrt{\exp(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

End point type Secondary

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 13 | 3 | 12 | |
| Units: hour | | | | |
| geometric mean (geometric coefficient of variation) | 3.477 (± 61.3) | 3.051 (± 16.8) | 2.883 (± 29.2) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Apparent Clearance (CL/F)

| | |
|-----------------|---|
| End point title | Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Apparent Clearance (CL/F) |
|-----------------|---|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \cdot \sqrt{\exp(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 13 | 3 | 12 | |
| Units: L/hour | | | | |
| geometric mean (geometric coefficient of variation) | 8.838 (\pm 52.7) | 12.426 (\pm 26.8) | 13.019 (\pm 33.5) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Apparent Volume of Distribution (Vz/F)

| | |
|-----------------|--|
| End point title | Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Apparent Volume of Distribution (Vz/F) |
|-----------------|--|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \cdot \sqrt{\exp(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 13 | 3 | 12 | |
| Units: liters | | | | |
| geometric mean (geometric coefficient of variation) | 44.329 (± 25.4) | 54.689 (± 29.7) | 54.157 (± 22.3) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma PK parameters in Cycle 1 Day 15: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last)

| | |
|-----------------|---|
| End point title | Lenalidomide (LEN) Plasma PK parameters in Cycle 1 Day 15: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last) |
|-----------------|---|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 \times \sqrt{\exp(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

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

End point timeframe:

Cycle 1 Day 15: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 9 | 16 | |
| Units: hour*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 1911.739 (± 65.5) | 1754.349 (± 34.3) | 629.151 (± 16.8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 15: Time to Maximum Observed Concentration (Tmax)

| | |
|-----------------|--|
| End point title | Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 15: Time to Maximum Observed Concentration (Tmax) |
|-----------------|--|

End point description:

Time to maximum observed concentration of Lenalidomide (LEN) after multiple doses on day 15 obtained from the observed concentration versus time data

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Cycle 1 Day 15: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose | |

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|-------------------------------|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 9 | 16 | |
| Units: hour | | | | |
| median (full range (min-max)) | 2.000 (1.00 to 8.00) | 1.000 (0.55 to 2.00) | 1.042 (0.47 to 4.00) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 15: Maximum Observed Concentration (Cmax)

| | |
|-----------------|--|
| End point title | Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 15: Maximum Observed Concentration (Cmax) |
|-----------------|--|

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: $CV\% = 100 * \sqrt{EXP(\sigma^2) - 1}$, where σ^2 denotes the variance of the log-transformed values.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Cycle 1 Day 15: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose | |

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|---|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 9 | 16 | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 409.764 (± 66.0) | 452.850 (± 31.7) | 171.235 (± 33.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Who Had Either Disease Progression or Death

| | |
|--|--|
| End point title | Participants Who Had Either Disease Progression or Death |
| End point description: | |
| This outcome was originally defined as a Kaplan-Meier estimate of progression-free survival (PFS) which estimated the time between first date of dosing of study medication and disease progression, as determined by the investigator using the IMWG Uniform Response Criteria, or death during study treatment, whichever occurred earlier. However due to the early study termination and limited follow-up time, the majority of participants were censored for PFS analysis. Data reported instead represent the number of participants who died during study treatment or had disease progression within 90 days of the last dose of durvalumab. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 up to Week 84 | |

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|------------------------------|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 10 | 21 | |
| Units: Count of participants | 4 | 1 | 3 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Who Developed Anti-drug Antibody Against Durvalumab

| | |
|---|--|
| End point title | Participants Who Developed Anti-drug Antibody Against Durvalumab |
| End point description: | |
| The number of participants who develop antidrug antibody against durvalumab at any of the sampling timepoints during the study. | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-dose samples on Day 1 of cycles 1, 2, 4, 6, 10, and 14 (study days 1, 29, 85, 141, 253, 393) | |

| End point values | Cohort A: High risk, TNE | Cohort B: ≥ 65 years old, TNE | Cohort C: High risk, Post-transplant | |
|------------------------------|--------------------------|------------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 10 | 21 | |
| Units: Count of participants | 0 | 1 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Who Died Up To Data Cut-off Date (15 December 2017)

| | |
|-----------------|--|
| End point title | Participants Who Died Up To Data Cut-off Date (15 December 2017) |
|-----------------|--|

End point description:

This outcome was originally defined as a Kaplan-Meier estimate of overall survival (OS) and was defined as the time between first date of dosing of study medication and death due to any cause. However due to the early study termination and limited follow-up time, the majority of participants were censored for OS analysis. Data reported instead represent the number of participants who died due to any cause from Day 1 up to data cut-off.

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

End point timeframe:

Day 1 up to Week 87

| End point values | Cohort A: High risk, TNE | Cohort B: >=65 years old, TNE | Cohort C: High risk, Post-transplant | |
|------------------------------|--------------------------|-------------------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 10 | 21 | |
| Units: Count of participants | 2 | 0 | 1 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs assessed from first dose up to week 84 (the longer of 90 days after d/c treatment with DURVA, or 28 days after the last dose of LEN or DEX). Deaths (all-causes) assessed from first dose to study completion (Up to approximately 88 months)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Cohort A: High Risk, TNE |
|-----------------------|--------------------------|

Reporting group description:

High risk, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Cohort B: \geq 65 Years Old, TNE |
|-----------------------|------------------------------------|

Reporting group description:

\geq 65 years old, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were not high risk were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle, up to 12 cycles.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Cohort C: High Risk, Post-transplant |
|-----------------------|--------------------------------------|

Reporting group description:

High risk, post-transplant NDMM participants were administered the following as maintenance therapy: • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 10 mg/day on Days 1 to 21 of each 28-day treatment cycle.

| Serious adverse events | Cohort A: High Risk, TNE | Cohort B: \geq 65 Years Old, TNE | Cohort C: High Risk, Post-transplant |
|---|--------------------------|------------------------------------|--------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 25 (48.00%) | 6 / 10 (60.00%) | 4 / 21 (19.05%) |
| number of deaths (all causes) | 9 | 3 | 5 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastases to lung | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to liver | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 10 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 10 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Pubis fracture | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 2 / 21 (9.52%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Cystitis klebsiella | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 10 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parainfluenzae virus infection | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 10 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 10 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 10 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Cohort A: High Risk, TNE | Cohort B: >=65 Years Old, TNE | Cohort C: High Risk, Post-transplant |
|---|-------------------------------------|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 24 / 25 (96.00%) | 9 / 10 (90.00%) | 18 / 21 (85.71%) |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | 3 / 10 (30.00%) | 7 / 21 (33.33%) |
| occurrences (all) | 4 | 3 | 8 |
| Chills | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 1 | 0 | 2 |
| Asthenia | | | |
| subjects affected / exposed | 7 / 25 (28.00%) | 2 / 10 (20.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 7 | 2 | 1 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | 4 / 10 (40.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 4 | 5 | 3 |
| Peripheral swelling | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 25 (32.00%) | 2 / 10 (20.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 8 | 2 | 0 |
| Non-cardiac chest pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 1 | 0 | 3 |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | 2 / 10 (20.00%) | 5 / 21 (23.81%) |
| occurrences (all) | 3 | 2 | 5 |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 2 / 10 (20.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 3 / 10 (30.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 1 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 0 | 1 | 3 |
| Productive cough | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 10 (10.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 2 | 2 | 1 |
| Respiratory tract congestion | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rhinorrhoea | | | |

| | | | |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 10 (10.00%) 1 | 1 / 21 (4.76%) 1 |
| Upper-airway cough syndrome subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed occurrences (all) | 4 / 25 (16.00%) 4 | 0 / 10 (0.00%) 0 | 2 / 21 (9.52%) 2 |
| Insomnia | | | |
| subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 4 / 10 (40.00%) 4 | 3 / 21 (14.29%) 3 |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 3 | 0 / 10 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 10 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Amylase increased | | | |
| subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 10 (10.00%) 2 | 0 / 21 (0.00%) 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 10 (0.00%) 0 | 1 / 21 (4.76%) 2 |
| Blood creatinine increased | | | |
| subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 10 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Lipase increased | | | |
| subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 5 | 0 / 10 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Prostatic specific antigen increased | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 5 / 25 (20.00%) 5 | 1 / 10 (10.00%) 1 | 3 / 21 (14.29%) 3 |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 10 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Fall subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 3 | 0 / 10 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Tooth fracture subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 10 (0.00%) 0 | 3 / 21 (14.29%) 3 |
| Infusion related reaction subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 10 (0.00%) 0 | 2 / 21 (9.52%) 2 |
| Cardiac disorders | | | |
| Cardiac failure congestive subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 10 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Atrial flutter subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Nervous system disorders | | | |
| Disturbance in attention subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 25 (16.00%) 4 | 1 / 10 (10.00%) 1 | 3 / 21 (14.29%) 4 |
| Dysgeusia | | | |

| | | | |
|---|------------------------|-----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 3 | 1 / 10 (10.00%) 1 | 2 / 21 (9.52%) 2 |
| Headache subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 2 / 10 (20.00%) 2 | 1 / 21 (4.76%) 1 |
| Paraesthesia subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 10 (0.00%) 0 | 2 / 21 (9.52%) 3 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 10 (10.00%) 1 | 2 / 21 (9.52%) 2 |
| Tremor subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 3 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 13 / 25 (52.00%) 20 | 2 / 10 (20.00%) 2 | 3 / 21 (14.29%) 3 |
| Leukopenia subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 7 | 1 / 10 (10.00%) 1 | 1 / 21 (4.76%) 1 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 8 / 25 (32.00%) 16 | 2 / 10 (20.00%) 3 | 4 / 21 (19.05%) 6 |
| Neutropenia subjects affected / exposed occurrences (all) | 11 / 25 (44.00%) 21 | 5 / 10 (50.00%) 11 | 3 / 21 (14.29%) 6 |
| Ear and labyrinth disorders | | | |
| Ear pruritus subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 10 (10.00%) 1 | 1 / 21 (4.76%) 1 |
| Vomiting | | | |

| | | | |
|--|------------------|-----------------|-----------------|
| subjects affected / exposed | 5 / 25 (20.00%) | 2 / 10 (20.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 6 | 2 | 2 |
| Nausea | | | |
| subjects affected / exposed | 7 / 25 (28.00%) | 0 / 10 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 11 | 0 | 3 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Frequent bowel movements | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 1 | 0 | 2 |
| Diarrhoea | | | |
| subjects affected / exposed | 13 / 25 (52.00%) | 2 / 10 (20.00%) | 5 / 21 (23.81%) |
| occurrences (all) | 19 | 3 | 5 |
| Constipation | | | |
| subjects affected / exposed | 9 / 25 (36.00%) | 4 / 10 (40.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 12 | 5 | 4 |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Hepatobiliary disorders | | | |
| Hepatobiliary disease | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 10 (0.00%) 0 | 5 / 21 (23.81%) 7 |
| Erythema subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 2 | 1 / 10 (10.00%) 3 | 0 / 21 (0.00%) 0 |
| Night sweats subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 3 | 0 / 10 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 4 / 25 (16.00%) 4 | 1 / 10 (10.00%) 1 | 2 / 21 (9.52%) 3 |
| Rash subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 1 / 10 (10.00%) 1 | 2 / 21 (9.52%) 2 |
| Rash erythematous subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Rash generalised subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 10 (0.00%) 0 | 2 / 21 (9.52%) 2 |
| Solar dermatitis subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |
| Haematuria subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 10 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Nocturia subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 10 (10.00%) 1 | 0 / 21 (0.00%) 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Polyuria | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urethral stenosis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urine odour abnormal | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 10 (0.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 2 | 0 | 4 |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 6 / 21 (28.57%) |
| occurrences (all) | 2 | 0 | 6 |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | 0 / 10 (0.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 3 | 0 | 4 |
| Back pain | | | |
| subjects affected / exposed | 6 / 25 (24.00%) | 2 / 10 (20.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 6 | 2 | 2 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 10 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Flank pain | | | |

| | | | |
|----------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle contracture | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 10 (10.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 1 | 1 | 2 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | 1 / 10 (10.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 4 | 1 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 10 (10.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 1 | 1 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 10 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | 1 / 10 (10.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 4 | 1 | 1 |
| Pathological fracture | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 10 (10.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 2 | 1 | 1 |
| Infections and infestations | | | |
| Candida infection | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| | | | |
|------------------------------------|-----------------|-----------------|-----------------|
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 10 (10.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 1 | 1 | 2 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 10 (0.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 0 | 0 | 7 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 1 | 2 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 10 (10.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 1 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 10 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 2 | 0 | 4 |
| Urinary tract infection | | | |
| subjects affected / exposed | 5 / 25 (20.00%) | 0 / 10 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | 3 / 10 (30.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 4 | 3 | 2 |
| Dehydration | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 10 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 4 | 0 | 1 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 4 / 25 (16.00%) | 1 / 10 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 7 | 1 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|-----------------------------------|
| 27 June 2016 | Table of Events Update |
| 06 April 2017 | Inclusion Criteria Update |
| 05 December 2019 | Clinical Hold on the Study Update |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Study was placed on full clinical hold by the US FDA on 05 Sep 2017. Study was closed for further enrollment and subjects were discontinued from all treatments. Subjects were followed for SPMs for 5 years after last subject was enrolled per protocol.

Notes: