



Clinical trial results:

COMBI-Aplus: Open-label, phase IIIb study of dabrafenib in COMBination with trametinib in the Adjuvant treatment of stage III BRAF V600 mutation-positive melanoma after complete resection to evaluate the impact on pyrexia related outcomes of an adapted pyrexia AE-management algorithm

Summary

| | |
|--------------------------|--|
| EudraCT number | 2018-000168-27 |
| Trial protocol | NO FI GB LT GR SI SK BE LV HU PT PL IT |
| Global end of trial date | 16 September 2021 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 04 October 2022 |
| First version publication date | 04 October 2022 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CDRB436F2410 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03551626 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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 September 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 September 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate the impact on pyrexia-related outcomes of an adapted pyrexia adverse event (AE)-management algorithm

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 29 August 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 7 |
| Country: Number of subjects enrolled | Australia: 11 |
| Country: Number of subjects enrolled | Brazil: 10 |
| Country: Number of subjects enrolled | Canada: 32 |
| Country: Number of subjects enrolled | Czechia: 32 |
| Country: Number of subjects enrolled | Finland: 16 |
| Country: Number of subjects enrolled | France: 176 |
| Country: Number of subjects enrolled | Greece: 23 |
| Country: Number of subjects enrolled | Hungary: 13 |
| Country: Number of subjects enrolled | Israel: 6 |
| Country: Number of subjects enrolled | Italy: 112 |
| Country: Number of subjects enrolled | Japan: 3 |
| Country: Number of subjects enrolled | Latvia: 3 |
| Country: Number of subjects enrolled | Lithuania: 4 |
| Country: Number of subjects enrolled | Norway: 11 |
| Country: Number of subjects enrolled | Poland: 10 |
| Country: Number of subjects enrolled | Portugal: 5 |
| Country: Number of subjects enrolled | Russian Federation: 18 |
| Country: Number of subjects enrolled | Slovakia: 9 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Slovenia: 5 |
| Country: Number of subjects enrolled | Sweden: 9 |
| Country: Number of subjects enrolled | Turkey: 2 |
| Country: Number of subjects enrolled | United Kingdom: 35 |
| Worldwide total number of subjects | 552 |
| EEA total number of subjects | 428 |

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) | 430 |
| From 65 to 84 years | 122 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients in this study were enrolled at 103 centers across 23 countries

Pre-assignment

Screening details:

A total of 748 patients were screened. Of the screened patients, 552 patients were treated.

Period 1

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

Arms

| | |
|------------------|-----------------------|
| Arm title | Dabrafenib+trametinib |
|------------------|-----------------------|

Arm description:

Subjects received dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for up to 12 months.

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

Dosage and administration details:

Trametinib 2mg once daily provided as 0.5mg and 2.0mg tablets for oral administration

| | |
|--|------------|
| Investigational medicinal product name | Dabrafenib |
| Investigational medicinal product code | DRB436 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Dabrafenib 150mg twice daily provided as 50 mg and 75 mg capsules for oral administration

| Number of subjects in period 1 | Dabrafenib+trametinib |
|--------------------------------|-----------------------|
| Started | 552 |
| Completed | 425 |
| Not completed | 127 |
| Patient decision | 5 |
| Physician decision | 4 |
| Adverse event, non-fatal | 88 |
| Technical problems | 1 |
| Protocol deviation | 1 |

| | |
|--------------------------------|----|
| Disease relapse | 18 |
| Pregnancy | 1 |
| Withdrawal of informed consent | 6 |
| Lost to follow-up | 3 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Dabrafenib+trametinib |
|-----------------------|-----------------------|

Reporting group description:

Subjects received dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for up to 12 months.

| Reporting group values | Dabrafenib+trametinib | Total | |
|--|-----------------------|-------|--|
| Number of subjects | 552 | 552 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 430 | 430 | |
| From 65-84 years | 122 | 122 | |
| 85 years and over | 0 | 0 | |
| Age Continuous Units: Years | | | |
| arithmetic mean | 53.4 | | |
| standard deviation | ± 13.09 | - | |
| Sex: Female, Male Units: Participants | | | |
| Female | 255 | 255 | |
| Male | 297 | 297 | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 377 | 377 | |
| Asian | 3 | 3 | |
| Missing | 172 | 172 | |

End points

End points reporting groups

| | |
|--|-----------------------|
| Reporting group title | Dabrafenib+trametinib |
| Reporting group description: | |
| Subjects received dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for up to 12 months. | |

Primary: Composite rate of pyrexia related events

| | |
|---|---|
| End point title | Composite rate of pyrexia related events ^[1] |
| End point description: | |
| The composite rate of pyrexia related events was calculated as the total number of participants experiencing at least one of the three components of the composite endpoint (i.e., grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia), divided by the total number of participants treated in the study and multiplied by 100. Pyrexia is defined as fever $\geq 38^{\circ}\text{C}$. Pyrexia events were graded by the investigator using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (Life-threatening) and Grade 5 (Death) | |
| End point type | Primary |
| End point timeframe: | |
| Baseline up to 12 months | |
| 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: No statistical analyses were planned for this endpoint | |

| | | | | |
|-----------------------------------|-----------------------|--|--|--|
| End point values | Dabrafenib+trametinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 552 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 7.6 (5.5 to 10.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse free survival (RFS) rate

| | |
|--|----------------------------------|
| End point title | Relapse free survival (RFS) rate |
| End point description: | |
| RFS is defined as the time from the date of first dose of the study treatment to the date of the first documented disease recurrence or death due to any cause whichever comes first. Treatment emergent malignancies other than second melanomas were not considered as events. RFS rate is the estimated percent probability that a patient will remain event-free up to the specified time point. RFS rate was obtained from the Kaplan-Meier survival estimates. RFS was censored if no RFS event was observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-cancer therapy is started. The censoring date was the date of the last adequate tumor assessment prior to data cut-off date/start of new anti-cancer therapy date. | |
| End point type | Secondary |

End point timeframe:

At 12 and 24 months

| End point values | Dabrafenib+trametinib | | | |
|----------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 552 | | | |
| Units: Percent probability | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 91.7 (89.0 to 93.8) | | | |
| 24 months | 57.5 (48.9 to 65.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) rate

| | |
|-----------------|----------------------------|
| End point title | Overall Survival (OS) rate |
|-----------------|----------------------------|

End point description:

OS is defined as the time from date of the first dose of study medication to date of death due to any cause, whichever comes first. If a patient was not known to have died, then OS rate is the estimated probability that a patient will remain event-free up to the specified time point. OS rate was obtained from the Kaplan-Meier survival estimates. OS was censored at the last contact date when the patient was known to be alive (on or before the cut-off date).

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

End point timeframe:

At 12 and 24 months

| End point values | Dabrafenib+trametinib | | | |
|----------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 552 | | | |
| Units: Percent probability | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 99.1 (97.8 to 99.6) | | | |
| 24 months | 92.6 (90.0 to 94.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who required management of pyrexia

| | |
|-----------------|---|
| End point title | Percentage of participants who required management of pyrexia |
|-----------------|---|

End point description:

Percentage of patients who experienced pyrexia and required intervention including hospitalizations, concomitant medications, and study treatment modifications (dose reductions, permanent discontinuations and/or interruptions) due to pyrexia. Pyrexia is defined as fever $\geq 38^{\circ}\text{C}$

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

End point timeframe:

Baseline up to 12 months

| End point values | Dabrafenib+trametinib | | | |
|--|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 552 | | | |
| Units: Participants | | | | |
| Hospitalizations | 24 | | | |
| Concomitant medications | 210 | | | |
| Permanent discontinuation of study treatment | 13 | | | |
| Reduction of study treatment | 29 | | | |
| Interruption of study treatment | 339 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who permanently discontinued treatment due to any adverse event (AE)

| | |
|-----------------|---|
| End point title | Percentage of participants who permanently discontinued treatment due to any adverse event (AE) |
|-----------------|---|

End point description:

Percentage of participants who permanently discontinued treatment due to any AE during treatment. An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign, symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study.

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

End point timeframe:

Baseline up to 12 months

| | | | | |
|-----------------------------|-----------------------|--|--|--|
| End point values | Dabrafenib+trametinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 552 | | | |
| Units: Participants | 87 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject-reported Quality of Life (QoL) Assessed by Functional Assessment Cancer Therapy - Melanoma subscale Score (FACT-M MS)

| | |
|-----------------|---|
| End point title | Change From Baseline in Subject-reported Quality of Life (QoL) Assessed by Functional Assessment Cancer Therapy - Melanoma subscale Score (FACT-M MS) |
|-----------------|---|

End point description:

The FACT-M is a questionnaire that assesses participant health-related quality of life. It includes a melanoma specific (FACT-M MS) subscale that consists in 16 items related to signs, symptoms, physical/social activities most relevant to participants with advanced-stage melanoma. Each item ranges from 0 (not at all) to 4 (very much). FACT-M MS score ranges from 0 to 64, with higher score indicating better quality of life. If a patient discontinued the study treatment at Month 1 or Month 2, then the follow-up assessments started at Month 3 follow-up and continued until Month 24 follow-up or at withdrawal, lost to follow-up, death, or end of study. If a patient discontinued the study treatment from Month 3 through Month 5, the follow-up assessments started at Month 6 follow-up. If a patient discontinued from Month 6 through Month 11, the follow-up assessments started from Month 12 follow-up.

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

End point timeframe:

Baseline up to 24 months

| | | | | |
|--------------------------------------|-----------------------|--|--|--|
| End point values | Dabrafenib+trametinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 552 | | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 1 | -2.46 (± 5.488) | | | |
| Month 2 | -2.42 (± 4.892) | | | |
| Month 3 | -2.26 (± 4.789) | | | |
| Month 4 | -2.34 (± 5.297) | | | |
| Month 5 | -2.03 (± 5.278) | | | |
| Month 6 | -2.19 (± 5.494) | | | |
| Month 7 | -2.39 (± 5.873) | | | |
| Month 8 | -2.32 (± 5.609) | | | |

| | | | | |
|--------------------|-----------------|--|--|--|
| Month 9 | -2.06 (± 5.534) | | | |
| Month 10 | -2.15 (± 5.743) | | | |
| Month 11 | -2.05 (± 5.578) | | | |
| Month 12 | -1.96 (± 5.757) | | | |
| End of treatment | -3.36 (± 5.944) | | | |
| Follow-up Month 3 | 2.43 (± 4.685) | | | |
| Follow-up Month 6 | -0.33 (± 4.915) | | | |
| Follow-up Month 12 | -1.71 (± 5.671) | | | |
| Follow-up Month 15 | -0.60 (± 6.018) | | | |
| Follow-up Month 18 | -0.09 (± 4.948) | | | |
| Follow-up Month 24 | -0.75 (± 5.406) | | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

| | |
|-----------------|----------------------|
| End point title | All collected deaths |
|-----------------|----------------------|

End point description:

On treatment deaths were collected from date of first administration of study treatment to 30 days after date of last administration of any study treatment (dabrafenib or trametinib).

Deaths post-treatment follow-up were collected after the on-treatment period.

All deaths refer to the sum of on-treatment and post-treatment deaths

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

On-treatment: from first study treatment to 30 days after last dose of study treatment, up to 13 months. Post-treatment: From day 31 after last study treatment up to approximately 39 months

| End point values | Dabrafenib+trametinib | | | |
|-----------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 552 | | | |
| Units: Participants | | | | |
| On-treatment deaths | 1 | | | |
| Post-treatment deaths | 47 | | | |
| All deaths | 48 | | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first administration of study treatment to 30 days after date of last actual administration of any study treatment: dabrafenib or trametinib (including start and stop date), up to approximately 13 months.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | All subjects |
|-----------------------|--------------|

Reporting group description:

All subjects

| Serious adverse events | All subjects | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 121 / 552 (21.92%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 4 / 552 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 28 / 552 (5.07%) | | |
| occurrences causally related to treatment / all | 29 / 31 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chills | | | |
| subjects affected / exposed | 2 / 552 (0.36%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 3 / 552 (0.54%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Fatigue | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperthermia | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Granuloma | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 552 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Major depression | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 19 / 552 (3.44%) | | |
| occurrences causally related to treatment / all | 23 / 23 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphocyte morphology abnormal | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutrophil count decreased | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Seroma | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 552 (0.54%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 2 / 552 (0.36%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Focal dyscognitive seizures | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Headache | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple sclerosis | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radicular pain | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Retinal vein occlusion | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Detachment of retinal pigment epithelium | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Scleritis | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uveitis | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertransaminaemia | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|--|--|
| Erythema nodosum | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash | | | |
| subjects affected / exposed | 2 / 552 (0.36%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Panniculitis | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin mass | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vasculitic rash | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|--|--|
| Nephrolithiasis | | | |
| subjects affected / exposed | 2 / 552 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 5 / 552 (0.91%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erysipelas | | | |
| subjects affected / exposed | 3 / 552 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Bacterial infection | | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Appendicitis | | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia legionella | | | | |
| subjects affected / exposed | 2 / 552 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Complicated appendicitis | | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Groin infection | | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection | | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonitis | | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate infection | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Systemic candida | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 552 (0.36%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 552 (0.18%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | All subjects | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 526 / 552 (95.29%) | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 75 / 552 (13.59%) | | |
| occurrences (all) | 97 | | |
| Amylase increased | | | |
| subjects affected / exposed | 35 / 552 (6.34%) | | |
| occurrences (all) | 40 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 74 / 552 (13.41%) | | |
| occurrences (all) | 91 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 37 / 552 (6.70%) | | |
| occurrences (all) | 46 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 168 / 552 (30.43%) | | |
| occurrences (all) | 231 | | |
| Lipase increased | | | |
| subjects affected / exposed | 72 / 552 (13.04%) | | |
| occurrences (all) | 96 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 41 / 552 (7.43%) | | |
| occurrences (all) | 51 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 31 / 552 (5.62%) | | |
| occurrences (all) | 35 | | |
| Headache | | | |
| subjects affected / exposed | 174 / 552 (31.52%) | | |
| occurrences (all) | 436 | | |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|----------------------------|--|--|
| Neutropenia subjects affected / exposed occurrences (all) | 44 / 552 (7.97%) 69 | | |
| General disorders and administration site conditions | | | |
| Chills subjects affected / exposed occurrences (all) | 146 / 552 (26.45%) 356 | | |
| Fatigue subjects affected / exposed occurrences (all) | 142 / 552 (25.72%) 264 | | |
| Pain subjects affected / exposed occurrences (all) | 28 / 552 (5.07%) 45 | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 66 / 552 (11.96%) 80 | | |
| Influenza like illness subjects affected / exposed occurrences (all) | 65 / 552 (11.78%) 149 | | |
| Asthenia subjects affected / exposed occurrences (all) | 131 / 552 (23.73%) 203 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 374 / 552 (67.75%) 1911 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 44 / 552 (7.97%) 60 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 30 / 552 (5.43%) 39 | | |
| Constipation subjects affected / exposed occurrences (all) | 46 / 552 (8.33%) 51 | | |
| Diarrhoea | | | |

| | | | |
|---|--------------------|--|--|
| subjects affected / exposed | 149 / 552 (26.99%) | | |
| occurrences (all) | 281 | | |
| Nausea | | | |
| subjects affected / exposed | 128 / 552 (23.19%) | | |
| occurrences (all) | 276 | | |
| Vomiting | | | |
| subjects affected / exposed | 84 / 552 (15.22%) | | |
| occurrences (all) | 139 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 29 / 552 (5.25%) | | |
| occurrences (all) | 32 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 36 / 552 (6.52%) | | |
| occurrences (all) | 45 | | |
| Cough | | | |
| subjects affected / exposed | 79 / 552 (14.31%) | | |
| occurrences (all) | 99 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 33 / 552 (5.98%) | | |
| occurrences (all) | 40 | | |
| Rash | | | |
| subjects affected / exposed | 116 / 552 (21.01%) | | |
| occurrences (all) | 209 | | |
| Erythema | | | |
| subjects affected / exposed | 38 / 552 (6.88%) | | |
| occurrences (all) | 42 | | |
| Pruritus | | | |
| subjects affected / exposed | 29 / 552 (5.25%) | | |
| occurrences (all) | 33 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 116 / 552 (21.01%) | | |
| occurrences (all) | 207 | | |
| Back pain | | | |

| | | | |
|------------------------------------|-------------------|--|--|
| subjects affected / exposed | 39 / 552 (7.07%) | | |
| occurrences (all) | 60 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 42 / 552 (7.61%) | | |
| occurrences (all) | 68 | | |
| Myalgia | | | |
| subjects affected / exposed | 85 / 552 (15.40%) | | |
| occurrences (all) | 148 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 48 / 552 (8.70%) | | |
| occurrences (all) | 72 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 38 / 552 (6.88%) | | |
| occurrences (all) | 39 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 31 / 552 (5.62%) | | |
| occurrences (all) | 37 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 38 / 552 (6.88%) | | |
| occurrences (all) | 48 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 03 December 2018 | The primary purpose of this protocol amendment is to implement clinically relevant feedback received from the Health Authorities and participating center's Ethics Committees upon review of the protocol. In addition, clarifications and corrections are made throughout the protocol as well as editorial change to improve flow and consistency. |
| 12 March 2019 | The primary purpose of this protocol amendment is to implement clinically relevant feedback received from the Health Authorities and participating center's Ethics Committees upon review of the protocol. In addition, study population inclusion criteria was expanded, clarifications and corrections are made throughout the protocol, as well as editorial change to improve flow and consistency. |

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.

Most patients remained relapse-free at the end of the study. Due to the design of the study, RFS and OS data consisted of a majority of censored data, the 24-months RFS rate and OS rate could not be estimated meaningfully.

Notes: