NOVARTIS

**Clinical Trial Results Website**

## Sponsor

Novartis

## Generic Drug Name

Dabrafenib/Tafinlar

## Trial Indication(s)

Subjects with BRAF V600 mutant melanoma that has metastasized to the brain.

## Protocol Number

117277

## Protocol Title

BRF117277: A Phase II, Open-Label, Multicentre Study of Dabrafenib plus Trametinib in Subjects with BRAF Mutation-Positive Melanoma that has Metastasized to the Brain

## Clinical Trial Phase

Phase 2

## Phase of Drug Development

II

## Study Start/End Dates

Study Start Date: February 2014 (Actual)
Primary Completion Date: May 2017 (Actual)
Study Completion Date: February 2018 (Actual)

## Reason for Termination (If applicable)

## Study Design/Methodology

This was a Phase II, open-label, multicenter, multi-cohort study with dabrafenib and trametinib combination therapy in subjects with BRAF V600 mutation-positive melanoma that has metastasized to the brain. The study evaluated the safety and efficacy of four cohorts:

- **Cohort A**: Subjects with BRAF V600E mutant melanoma with asymptomatic brain metastasis without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- **Cohort B**: Subjects with BRAF V600E mutant melanoma with asymptomatic brain metastases with prior local brain-directed therapy and ECOG performance status of 0 or 1.
- **Cohort C**: Subjects with BRAF V600D/K/R mutant melanoma with asymptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- **Cohort D**: Subjects with BRAF V600D/E/K/R melanoma with symptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0, 1 or 2.

Subjects received dabrafenib capsules 150 mg twice daily and trametinib tablets 2 mg once daily until evidence of disease progression, death, withdrawal of consent or unacceptable toxicity.
Subjects were required to meet all eligibility criteria and return to clinic on a monthly basis for clinical and laboratory assessments. Intracranial and extracranial disease were assessed at baseline, week 4, week 8, every 8 weeks until week 40 and every 12 weeks thereafter unless response confirmation is indicted. The primary endpoint of the study was intracranial response in Cohort A, defined as the percentage of patients with a confirmed intracranial response assessed by the investigator using modified RECIST version 1.1 criteria.

## Centers

53 centers in 7 countries: Spain(8), France(11), Italy(3), Australia(4), United States(15), Germany(7), Canada(5)

## Objectives:

**Primary objective**:

- To assess the intracranial response (IR) of subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, without prior local therapy and ECOG score of 0 or 1 (cohort A).

IR was defined as the proportion of subjects with a confirmed intracranial complete response (CR) or partial response (PR) by investigator assessment using modified RECIST 1.1 guidelines

**Secondary objectives:**

- To assess cohort B for IR of subjects with locally confirmed BRAF V600E cutaneous

melanoma with metastases to the brain confirmed by MRI, asymptomatic with prior local therapy for brain metastases; ECOG score of 0 or 1.
- To assess cohort C for IR of subjects with locally confirmed BRAF V600 D/K/R cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, with or without prior local therapy; ECOG score of 0 or 1.
- To assess cohort D for IR of subjects with locally confirmed BRAF V600 D/E/K/R cutaneous melanoma with metastases to the brain confirmed by MRI, symptomatic; with or without prior local therapy; ECOG score of 0 or 1 or 2.
- To assess cohorts A, B, C and D for Disease Control for intracranial, extracranial and overall response (IDC, EDC and ODC respectively).
- To assess cohorts A, B, C and D for extracranial response (ER), overall response (OR) and duration of response (DoR).
- To assess cohorts A, B, C and D for progression- free survival (PFS).
- To assess cohorts A, B, C and D for overall survival (OS) and long-term (particularly 3-year) OS.

## Test Product (s), Dose(s), and Mode(s) of Administration

Dabrafenib 50 capsules,
Dabrafenib 75 mg capsules
Trametinib 2 mg tablets
Trametinib 0.5 mg tablets

## Statistical Methods

**Analysis sets:**
- **All treated population:** All subjects who received at least one dose of study medication comprised the All Treated subjects (ATS) population. Efficacy analyses were based on the ATS population.

The V600E population comprised all BRAF V600E mutation positive subjects in the ATS population.
The V600D/K/R population comprised all BRAF V600D/K/R mutation positive subjects in the ATS population.
- **Safety population:** same as ATS population (described above); safety analyses also used this population.

**Primary efficacy analyses:** The primary efficacy variable was Intracranial response (IR) and the primary endpoint was Intracranial response rate (IRR) in Cohort A; IRR was defined as the percentage of subjects achieving a confirmed intracranial CR or PR from the start of treatment until disease

progression or the start of new anti-cancer therapy. This was based on Investigator-assessed best intracranial response. The exact 95% CI for the intracranial response rate was calculated.
**Secondary efficacy analyses:** The secondary variables were defined as IR in cohorts B, C, and D (assessed by investigator), extracranial response (ER), overall response (OR), duration of intracranial response (DIR), duration of extracranial response (DER), duration of overall response (DOR), disease control for intracranial, extracranial and overall response (IDC, EDC and ODC respectively), progression free-survival (PFS), overall survival (OS) in all cohorts.
Intracranial response rate (IRR), extracranial response rate (ERR), overall response rate (ORR), DIR, DER, DOR, IDC, EDC, ODC and PFS were also summarized based on independent reviewer assessed response.
The exact 95% CI was calculated for all the secondary efficacy endpoints: ERR, ORR, DIR, DOR, DCR IDC, EDC, and ODC (per investigator and independent reviewer).
PFS (per investigator and independent reviewer) was summarized using Kaplan-Meier estimates. Frequency of subjects with PFS events was presented and also separately by types of PFS event, i.e. progression or death.

Survival was summarized using the Kaplan-Meier estimates for each cohort

## Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- ECOG Performance Status range of 0-2
- Histologically confirmed cutaneous metastatic melanoma of V600 E, K, D or R.
- May be systemic naïve or received up to two previous systemic treatment regimens for metastatic melanoma.
- Must be able to undergo MRI and have at least one measurable intracranial lesion for which specific criteria have to be met.

Exclusion Criteria:
- Prior treatment with any BRAF inhibitor or any mitogen-activated protein/extracellular signal–regulated kinase inhibitor.
- Anti-cancer therapy or investigational anti-cancer therapy or chemotherapy without delayed toxicity within treatment specific timeframe.
- Treatment with stereotactic radiosurgery or treatment with whole-brain radiation within treatment specific timeframe.
- Any presence of leptomeningeal disease or any parenchymal brain metastasis
- History of another malignancy, some exceptions may apply.
- A history or evidence of cardiovascular risk- specific criteria have to be met
- A history or current evidence/risk of retinal vein occlusion or retinal pigment epithelial detachment - specific criteria have to be met.

# Participant Flow Table

## Overall Study

| | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| **Started** | 76 | 16 | 16 | 17 |
| **Completed** | 76 | 16 | 16 | 17 |
| **Not Completed** | 0 | 0 | 0 | 0 |

# Baseline Characteristics

| | Cohort A | Cohort B | Cohort C | Cohort D | Total |
|---|---|---|---|---|---|
| **Number of Participants [units: participants]** | 76 | 16 | 16 | 17 | 125 |
| **Age Continuous** (units: Years) Median ± Standard Deviation | | | | | |
| | 53.2±14.69 | 55.1±11.05 | 65.6±10.40 | 47.5±13.01 | 54.2±14.29 |
| **Sex: Female, Male** (units: ) Count of Participants (Not Applicable) | | | | | |
| Female | 36 | 6 | 5 | 6 | 53 |
| Male | 40 | 10 | 11 | 11 | 72 |
| **Race (NIH/OMB)** (units: ) Count of Participants (Not Applicable) | | | | | |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| Asian | 0 | 0 | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 | 0 | 0 |
| White | 76 | 16 | 16 | 17 | 125 |
| More than one race | 0 | 0 | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 | 0 | 0 |

## Summary of Efficacy

## Primary Outcome Result(s)

### Intracranial response (IR) rate in cohort A

| | Cohort A |
|---|---|
| **Number of Participants Analyzed [units: participants]** | 76 |
| **Intracranial response (IR) rate in cohort A** (units: Number of participants) | |
| | 45 |

### Statistical Analysis

| Groups | Cohort A | |
|---|---|---|
| P Value | <.0001 | |
| Method | Other percent | |
| Other Response rate | 59 | Percent |
| 95 % Confidence Interval 2-Sided | 47.3 to 70.4 | |

## Secondary Outcome Result(s)

### Intracranial response rate of cohorts B, C and D

| | Cohort B | Cohort C | Cohort D |
|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 16 | 16 | 17 |
| **Intracranial response rate of cohorts B, C and D** (units: Number of participants) | | | |
| | 9 | 7 | 10 |

### Disease Control for intracranial, extracranial and overall response for each cohort

| | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 76 | 16 | 16 | 17 |

**Disease Control for intracranial, extracranial and overall response for each cohort**
(units: Number of participants)

| | | | | |
|---|---|---|---|---|
| Intracranial | 59 | 14 | 12 | 15 |
| Extra cranial | 60 | 11 | 15 | 11 |
| Overall rate | 60 | 14 | 12 | 15 |

## Extracranial response rate (ER) for each cohort

| | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 76 | 16 | 16 | 17 |
| **Extracranial response rate (ER) for each cohort** (units: Number of participants) | | | | |
| | 42 | 7 | 12 | 7 |

## Overall response (OR) for each cohort

| | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 76 | 16 | 16 | 17 |
| **Overall response (OR) for each cohort** (units: Number of participants) | | | | |
| | 45 | 9 | 7 | 11 |

## Duration of intracranial, extracranial and overall response for each cohort

| | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 76 | 16 | 16 | 17 |
| **Duration of intracranial, extracranial and overall response for each cohort** (units: Month) Median (95% Confidence Interval) | | | | |
| Duration of intracranial | 6.5 (4.9 to 8.6) | 7.3 (3.6 to 12.6) | 8.3 (1.3 to 15.0) | 4.5 (2.8 to 5.9) |
| Duration of extracranial | 10.2 (5.8 to NA)[] | NA (NA to NA)[] | 4.9 (3.0 to 22.4) | 5.9 (1.8 to NA)[] |
| Duration of Overall Response | 6.2 (4.9 to 8.3) | 12.5 (5.3 to NA)[] | 6.6 (1.3 to 16.3) | 4.5 (2.8 to 11.2) |

## Progression-free survival (PFS) for each cohort Based on investigator assessment

| | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 76 | 16 | 16 | 17 |
| **Progression-free survival (PFS) for each cohort Based on investigator assessment** (units: Month) Median (95% Confidence Interval) | | | | |
| | 5.7 (5.3 to 7.3) | 7.2 (4.7 to 14.6) | 3.7 (1.7 to 6.5) | 5.5 (3.7 to 11.6) |

## Overall survival (OS) for each cohort

| | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 76 | 16 | 16 | 17 |
| **Overall survival (OS) for each cohort** (units: Month) Median (95% Confidence Interval) | | | | |
| | 10.8 (8.7 to 17.9) | 24.3 (7.9 to NA)[1] | 10.1 (4.6 to 17.6) | 11.5 (6.8 to 22.4) |

## Summary of Safety

## Safety Results

### All-Cause Mortality

| | Cohort A N = 76 | Cohort B N = 16 | Cohort C N = 16 | Cohort D N = 17 | Total N = 125 |
|---|---|---|---|---|---|
| **Total participants affected** | 54 (71.05%) | 10 (62.50%) | 15 (93.75%) | 13 (76.47%) | 92 (73.60%) |

### Serious Adverse Events by System Organ Class

**Time Frame** Timeframe for AE

| | |
|---|---|
| **Additional Description** | AE additional description |
| **Source Vocabulary for Table Default** | MedDRA (19.0) |
| **Assessment Type for Table Default** | Systematic Assessment |

| | Cohort A N = 76 | Cohort B N = 16 | Cohort C N = 16 | Cohort D N = 17 | Total N = 125 |
|---|---|---|---|---|---|
| **Total participants affected** | 26 (34.21%) | 5 (31.25%) | 4 (25.00%) | 9 (52.94%) | 44 (35.20%) |
| **Cardiac disorders** | | | | | |
| Atrial fibrillation | 2 (2.63%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Cardiac failure | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Cardiomyopathy | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Cardio-respiratory arrest | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Myocardial ischaemia | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Myocarditis | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Pericardial effusion | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Tachyarrhythmia | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| **Eye disorders** | | | | | |
| Detachment of retinal pigment epithelium | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Macular detachment | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Vision blurred | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| **Gastrointestinal disorders** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Abdominal pain | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Constipation | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Diarrhoea | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Gastrointestinal haemorrhage | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Intestinal perforation | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Melaena | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Nausea | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Pancreatitis | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Vomiting | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| **General disorders and administration site conditions** | | | | | |
| Chills | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 2 (1.60%) |
| Fatigue | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| General physical health deterioration | 0 (0.00%) | 1 (6.25%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Malaise | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Pyrexia | 4 (5.26%) | 1 (6.25%) | 2 (12.50%) | 2 (11.76%) | 9 (7.20%) |
| **Infections and infestations** | | | | | |
| Erysipelas | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Escherichia infection | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Lung infection | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Pneumonia | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Pneumonia pneumococcal | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Staphylococcal infection | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |

| | | | | | |
|---|---|---|---|---|---|
| **Injury, poisoning and procedural complications** | | | | | |
| Fall | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Hip fracture | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Overdose | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| **Investigations** | | | | | |
| Ejection fraction decreased | 2 (2.63%) | 0 (0.00%) | 1 (6.25%) | 2 (11.76%) | 5 (4.00%) |
| Transaminases increased | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Troponin T increased | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| **Metabolism and nutrition disorders** | | | | | |
| Dehydration | 0 (0.00%) | 1 (6.25%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| **Musculoskeletal and connective tissue disorders** | | | | | |
| Lumbar spinal stenosis | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Neck pain | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | | | | | |
| Intracranial tumour haemorrhage | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Squamous cell carcinoma | 0 (0.00%) | 1 (6.25%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| **Nervous system disorders** | | | | | |
| Aphasia | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |

| | | | | | |
|---|---|---|---|---|---|
| Cerebrovascular accident | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Epilepsy | 2 (2.63%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Headache | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Presyncope | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Seizure | 2 (2.63%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 3 (2.40%) |
| Somnolence | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Status epilepticus | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Syncope | 2 (2.63%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| **Psychiatric disorders** | | | | | |
| Confusional state | 0 (0.00%) | 1 (6.25%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| **Renal and urinary disorders** | | | | | |
| Acute kidney injury | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Renal failure | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| **Respiratory, thoracic and mediastinal disorders** | | | | | |
| Pulmonary embolism | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| **Vascular disorders** | | | | | |
| Hypotension | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Pelvic venous thrombosis | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |

## Other Adverse Events by System Organ Class

| | |
|---|---|
| **Time Frame** | Timeframe for AE |
| **Additional Description** | AE additional description |
| **Source Vocabulary for Table Default** | MedDRA (19.0) |
| **Assessment Type for Table Default** | Systematic Assessment |
| **Frequent Event Reporting Threshold** | 5% |

| | Cohort A N = 76 | Cohort B N = 16 | Cohort C N = 16 | Cohort D N = 17 | Total N = 125 |
|---|---|---|---|---|---|
| **Total participants affected** | 74 (97.37%) | 16 (100.00%) | 16 (100.00%) | 17 (100.00%) | 123 (98.40%) |
| **Blood and lymphatic system disorders** | | | | | |
| Anaemia | 4 (5.26%) | 0 (0.00%) | 0 (0.00%) | 2 (11.76%) | 6 (4.80%) |
| Lymphopenia | 4 (5.26%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 4 (3.20%) |
| Neutropenia | 11 (14.47%) | 2 (12.50%) | 1 (6.25%) | 0 (0.00%) | 14 (11.20%) |
| Thrombocytopenia | 4 (5.26%) | 0 (0.00%) | 1 (6.25%) | 2 (11.76%) | 7 (5.60%) |
| **Cardiac disorders** | | | | | |
| Cyanosis | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| **Ear and labyrinth disorders** | | | | | |
| Ear pain | 0 (0.00%) | 2 (12.50%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Hypoacusis | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Vertigo | 3 (3.95%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 4 (3.20%) |
| **Eye disorders** | | | | | |
| Asthenopia | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Cataract | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |

| | | | | | |
|---|---|---|---|---|---|
| Conjunctival irritation | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Diplopia | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 3 (2.40%) |
| Dry eye | 2 (2.63%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 3 (2.40%) |
| Eye pain | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Eye pruritus | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Eyelid oedema | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (11.76%) | 3 (2.40%) |
| Lacrimation increased | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Posterior capsule opacification | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Punctate keratitis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Retinopathy | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Vision blurred | 3 (3.95%) | 1 (6.25%) | 1 (6.25%) | 1 (5.88%) | 6 (4.80%) |
| Visual acuity reduced | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Visual impairment | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 2 (11.76%) | 3 (2.40%) |
| Vitreous detachment | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Vitreous floaters | 3 (3.95%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 4 (3.20%) |
| **Gastrointestinal disorders** | | | | | |
| Abdominal distension | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Abdominal pain | 8 (10.53%) | 1 (6.25%) | 0 (0.00%) | 5 (29.41%) | 14 (11.20%) |
| Abdominal pain lower | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Abdominal pain upper | 5 (6.58%) | 1 (6.25%) | 0 (0.00%) | 1 (5.88%) | 7 (5.60%) |
| Constipation | 8 (10.53%) | 1 (6.25%) | 4 (25.00%) | 6 (35.29%) | 19 (15.20%) |
| Diarrhoea | 24 (31.58%) | 8 (50.00%) | 3 (18.75%) | 7 (41.18%) | 42 (33.60%) |
| Dry mouth | 5 (6.58%) | 2 (12.50%) | 1 (6.25%) | 3 (17.65%) | 11 (8.80%) |
| Dyspepsia | 5 (6.58%) | 2 (12.50%) | 1 (6.25%) | 0 (0.00%) | 8 (6.40%) |
| Faecalith | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |

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| Faeces soft | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Gastrointestinal disorder | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Gastrooesophageal reflux disease | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 1 (5.88%) | 3 (2.40%) |
| Gingival bleeding | 1 (1.32%) | 1 (6.25%) | 1 (6.25%) | 0 (0.00%) | 3 (2.40%) |
| Nausea | 24 (31.58%) | 7 (43.75%) | 4 (25.00%) | 6 (35.29%) | 41 (32.80%) |
| Rectal haemorrhage | 2 (2.63%) | 2 (12.50%) | 0 (0.00%) | 0 (0.00%) | 4 (3.20%) |
| Retching | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Stomatitis | 3 (3.95%) | 1 (6.25%) | 2 (12.50%) | 0 (0.00%) | 6 (4.80%) |
| Tongue discolouration | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Vomiting | 24 (31.58%) | 2 (12.50%) | 2 (12.50%) | 6 (35.29%) | 34 (27.20%) |
| **General disorders and administration site conditions** | | | | | |
| Asthenia | 28 (36.84%) | 5 (31.25%) | 3 (18.75%) | 5 (29.41%) | 41 (32.80%) |
| Chest pain | 3 (3.95%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 4 (3.20%) |
| Chills | 18 (23.68%) | 6 (37.50%) | 7 (43.75%) | 6 (35.29%) | 37 (29.60%) |
| Face oedema | 2 (2.63%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 3 (2.40%) |
| Fatigue | 7 (9.21%) | 4 (25.00%) | 8 (50.00%) | 3 (17.65%) | 22 (17.60%) |
| Gait disturbance | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| General physical health deterioration | 2 (2.63%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 3 (2.40%) |
| Ill-defined disorder | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Influenza like illness | 5 (6.58%) | 2 (12.50%) | 1 (6.25%) | 0 (0.00%) | 8 (6.40%) |
| Mucosal inflammation | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Oedema peripheral | 11 (14.47%) | 2 (12.50%) | 2 (12.50%) | 3 (17.65%) | 18 (14.40%) |
| Pain | 2 (2.63%) | 1 (6.25%) | 0 (0.00%) | 1 (5.88%) | 4 (3.20%) |
| Pyrexia | 45 (59.21%) | 7 (43.75%) | 8 (50.00%) | 8 (47.06%) | 68 (54.40%) |

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| Temperature regulation disorder | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Thirst | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Xerosis | 3 (3.95%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 4 (3.20%) |
| **Hepatobiliary disorders** | | | | | |
| Hepatocellular injury | 2 (2.63%) | 2 (12.50%) | 0 (0.00%) | 0 (0.00%) | 4 (3.20%) |
| **Infections and infestations** | | | | | |
| Angular cheilitis | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Bronchitis | 4 (5.26%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 5 (4.00%) |
| Cellulitis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Folliculitis | 4 (5.26%) | 2 (12.50%) | 0 (0.00%) | 4 (23.53%) | 10 (8.00%) |
| Fungal skin infection | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Herpes zoster | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Influenza | 7 (9.21%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 7 (5.60%) |
| Laryngitis | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Lower respiratory tract infection | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Lung infection | 2 (2.63%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 3 (2.40%) |
| Nasopharyngitis | 7 (9.21%) | 2 (12.50%) | 2 (12.50%) | 0 (0.00%) | 11 (8.80%) |
| Onychomycosis | 2 (2.63%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 4 (3.20%) |
| Oral candidiasis | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Oral herpes | 3 (3.95%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 4 (3.20%) |
| Paronychia | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Pharyngitis streptococcal | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Pneumonia | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |

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| Postoperative wound infection | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Pulpitis dental | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Rash pustular | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Respiratory tract infection | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Rhinitis | 4 (5.26%) | 0 (0.00%) | 2 (12.50%) | 0 (0.00%) | 6 (4.80%) |
| Sialoadenitis | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Skin infection | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Tonsillitis | 2 (2.63%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 3 (2.40%) |
| Tooth infection | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Upper respiratory tract infection | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Urinary tract infection | 3 (3.95%) | 0 (0.00%) | 1 (6.25%) | 2 (11.76%) | 6 (4.80%) |
| **Injury, poisoning and procedural complications** | | | | | |
| Animal bite | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Contusion | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Fall | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Ligament sprain | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Muscle strain | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Procedural pain | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| **Investigations** | | | | | |
| Alanine aminotransferase increased | 9 (11.84%) | 2 (12.50%) | 1 (6.25%) | 3 (17.65%) | 15 (12.00%) |
| Amylase increased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |

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| Aspartate aminotransferase increased | 12 (15.79%) | 3 (18.75%) | 2 (12.50%) | 3 (17.65%) | 20 (16.00%) |
| Blood alkaline phosphatase increased | 6 (7.89%) | 1 (6.25%) | 2 (12.50%) | 3 (17.65%) | 12 (9.60%) |
| Blood cholesterol increased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Blood creatine phosphokinase increased | 7 (9.21%) | 3 (18.75%) | 0 (0.00%) | 0 (0.00%) | 10 (8.00%) |
| Blood creatinine increased | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Blood lactate dehydrogenase increased | 6 (7.89%) | 1 (6.25%) | 1 (6.25%) | 0 (0.00%) | 8 (6.40%) |
| Blood phosphorus decreased | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Blood potassium decreased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Blood pressure increased | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Blood sodium increased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| C-reactive protein increased | 4 (5.26%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 5 (4.00%) |
| Ejection fraction decreased | 4 (5.26%) | 1 (6.25%) | 1 (6.25%) | 1 (5.88%) | 7 (5.60%) |
| Electrocardiogram QT prolonged | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Gamma-glutamyltransferase increased | 7 (9.21%) | 1 (6.25%) | 1 (6.25%) | 4 (23.53%) | 13 (10.40%) |
| Lipase increased | 3 (3.95%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 4 (3.20%) |

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| Neutrophil count decreased | 4 (5.26%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 6 (4.80%) |
| Neutrophil count increased | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Platelet count decreased | 2 (2.63%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 3 (2.40%) |
| Weight decreased | 4 (5.26%) | 2 (12.50%) | 3 (18.75%) | 3 (17.65%) | 12 (9.60%) |
| Weight increased | 4 (5.26%) | 0 (0.00%) | 0 (0.00%) | 2 (11.76%) | 6 (4.80%) |
| White blood cell count decreased | 2 (2.63%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 3 (2.40%) |
| **Metabolism and nutrition disorders** | | | | | |
| Decreased appetite | 9 (11.84%) | 4 (25.00%) | 7 (43.75%) | 3 (17.65%) | 23 (18.40%) |
| Dehydration | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 2 (1.60%) |
| Diabetes mellitus | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Gout | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Hyperglycaemia | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Hypocalcaemia | 3 (3.95%) | 0 (0.00%) | 0 (0.00%) | 2 (11.76%) | 5 (4.00%) |
| Hypokalaemia | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (11.76%) | 3 (2.40%) |
| Hypomagnesaemia | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 3 (2.40%) |
| Hyponatraemia | 2 (2.63%) | 1 (6.25%) | 1 (6.25%) | 1 (5.88%) | 5 (4.00%) |
| Hypophosphataemia | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (11.76%) | 2 (1.60%) |
| **Musculoskeletal and connective tissue disorders** | | | | | |
| Arthralgia | 15 (19.74%) | 3 (18.75%) | 2 (12.50%) | 6 (35.29%) | 26 (20.80%) |
| Back pain | 11 (14.47%) | 1 (6.25%) | 3 (18.75%) | 2 (11.76%) | 17 (13.60%) |
| Bone pain | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Flank pain | 2 (2.63%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 3 (2.40%) |

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| Joint range of motion decreased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Muscle spasms | 7 (9.21%) | 0 (0.00%) | 4 (25.00%) | 1 (5.88%) | 12 (9.60%) |
| Muscular weakness | 3 (3.95%) | 1 (6.25%) | 2 (12.50%) | 3 (17.65%) | 9 (7.20%) |
| Musculoskeletal chest pain | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 1 (5.88%) | 3 (2.40%) |
| Musculoskeletal pain | 4 (5.26%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 5 (4.00%) |
| Musculoskeletal stiffness | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Myalgia | 13 (17.11%) | 5 (31.25%) | 2 (12.50%) | 6 (35.29%) | 26 (20.80%) |
| Neck pain | 3 (3.95%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 5 (4.00%) |
| Osteoarthritis | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Pain in extremity | 8 (10.53%) | 3 (18.75%) | 3 (18.75%) | 2 (11.76%) | 16 (12.80%) |
| Rhabdomyolysis | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Synovial cyst | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Tendonitis | 2 (2.63%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 3 (2.40%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | | | | | |
| Basal cell carcinoma | 0 (0.00%) | 1 (6.25%) | 2 (12.50%) | 0 (0.00%) | 3 (2.40%) |
| Lipoma | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Papilloma | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Seborrhoeic keratosis | 1 (1.32%) | 1 (6.25%) | 1 (6.25%) | 0 (0.00%) | 3 (2.40%) |
| **Nervous system disorders** | | | | | |
| Amnesia | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 2 (1.60%) |
| Aphasia | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 3 (17.65%) | 4 (3.20%) |
| Aphonia | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |

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| Cerebellar syndrome | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Dizziness | 5 (6.58%) | 5 (31.25%) | 0 (0.00%) | 3 (17.65%) | 13 (10.40%) |
| Dysarthria | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Dysgeusia | 2 (2.63%) | 1 (6.25%) | 1 (6.25%) | 0 (0.00%) | 4 (3.20%) |
| Haemorrhage intracranial | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Headache | 28 (36.84%) | 5 (31.25%) | 6 (37.50%) | 8 (47.06%) | 47 (37.60%) |
| Hemianopia | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Motor dysfunction | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Neuropathy peripheral | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Paraesthesia | 5 (6.58%) | 1 (6.25%) | 0 (0.00%) | 2 (11.76%) | 8 (6.40%) |
| Paresis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Partial seizures | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (11.76%) | 2 (1.60%) |
| Peripheral motor neuropathy | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Presyncope | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Restless legs syndrome | 0 (0.00%) | 2 (12.50%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Seizure | 2 (2.63%) | 1 (6.25%) | 3 (18.75%) | 3 (17.65%) | 9 (7.20%) |
| Syncope | 0 (0.00%) | 1 (6.25%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Temporal lobe epilepsy | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Tongue paralysis | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Tonic clonic movements | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Tremor | 3 (3.95%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 4 (3.20%) |
| Visual field defect | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| **Psychiatric disorders** | | | | | |
| Affective disorder | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |

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| Agitation | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Anxiety | 2 (2.63%) | 1 (6.25%) | 0 (0.00%) | 1 (5.88%) | 4 (3.20%) |
| Apathy | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Confusional state | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 3 (2.40%) |
| Delirium | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Depression | 2 (2.63%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 3 (2.40%) |
| Insomnia | 6 (7.89%) | 0 (0.00%) | 0 (0.00%) | 2 (11.76%) | 8 (6.40%) |
| Sleep disorder | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| **Renal and urinary disorders** | | | | | |
| Dysuria | 2 (2.63%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 3 (2.40%) |
| Nocturia | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Pollakiuria | 0 (0.00%) | 1 (6.25%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Urinary incontinence | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| **Reproductive system and breast disorders** | | | | | |
| Metrorrhagia | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Prostatomegaly | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| **Respiratory, thoracic and mediastinal disorders** | | | | | |
| Chronic obstructive pulmonary disease | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Cough | 10 (13.16%) | 2 (12.50%) | 1 (6.25%) | 3 (17.65%) | 16 (12.80%) |
| Dry throat | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Dyspnoea | 5 (6.58%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 6 (4.80%) |
| Epistaxis | 2 (2.63%) | 3 (18.75%) | 1 (6.25%) | 2 (11.76%) | 8 (6.40%) |
| Nasal congestion | 2 (2.63%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 3 (2.40%) |

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| Productive cough | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 3 (2.40%) |
| Rhinitis allergic | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Wheezing | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| **Skin and subcutaneous tissue disorders** | | | | | |
| Acne | 5 (6.58%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 6 (4.80%) |
| Actinic elastosis | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Actinic keratosis | 0 (0.00%) | 2 (12.50%) | 1 (6.25%) | 0 (0.00%) | 3 (2.40%) |
| Alopecia | 7 (9.21%) | 0 (0.00%) | 1 (6.25%) | 2 (11.76%) | 10 (8.00%) |
| Aquagenic wrinkling of palms | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Dermatitis acneiform | 3 (3.95%) | 1 (6.25%) | 3 (18.75%) | 1 (5.88%) | 8 (6.40%) |
| Dry skin | 7 (9.21%) | 2 (12.50%) | 3 (18.75%) | 3 (17.65%) | 15 (12.00%) |
| Ecchymosis | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Eczema | 2 (2.63%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 3 (2.40%) |
| Erythema | 5 (6.58%) | 0 (0.00%) | 4 (25.00%) | 1 (5.88%) | 10 (8.00%) |
| Erythema multiforme | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Generalised erythema | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 2 (1.60%) |
| Hyperhidrosis | 4 (5.26%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 6 (4.80%) |
| Hyperkeratosis | 7 (9.21%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 8 (6.40%) |
| Intertrigo | 4 (5.26%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 5 (4.00%) |
| Nail disorder | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Night sweats | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Onycholysis | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Pain of skin | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Palmar erythema | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |

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|---|---|---|---|---|---|
| Palmar-plantar erythrodysaesthesia syndrome | 1 (1.32%) | 0 (0.00%) | 3 (18.75%) | 0 (0.00%) | 4 (3.20%) |
| Palmoplantar keratoderma | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 1 (0.80%) |
| Panniculitis | 4 (5.26%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 4 (3.20%) |
| Papule | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Pruritus | 5 (6.58%) | 0 (0.00%) | 2 (12.50%) | 2 (11.76%) | 9 (7.20%) |
| Pruritus generalised | 1 (1.32%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Rash | 9 (11.84%) | 7 (43.75%) | 3 (18.75%) | 3 (17.65%) | 22 (17.60%) |
| Rash erythematous | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Rash generalised | 5 (6.58%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 5 (4.00%) |
| Rash maculo-papular | 0 (0.00%) | 1 (6.25%) | 1 (6.25%) | 0 (0.00%) | 2 (1.60%) |
| Seborrhoeic dermatitis | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Skin exfoliation | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Skin fissures | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Skin hyperplasia | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |
| Skin lesion | 1 (1.32%) | 0 (0.00%) | 1 (6.25%) | 1 (5.88%) | 3 (2.40%) |
| Skin mass | 1 (1.32%) | 1 (6.25%) | 0 (0.00%) | 0 (0.00%) | 2 (1.60%) |
| Skin striae | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| **Vascular disorders** | | | | | |
| Deep vein thrombosis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (5.88%) | 1 (0.80%) |
| Flushing | 1 (1.32%) | 0 (0.00%) | 2 (12.50%) | 0 (0.00%) | 3 (2.40%) |
| Hot flush | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |
| Hypertension | 6 (7.89%) | 3 (18.75%) | 3 (18.75%) | 0 (0.00%) | 12 (9.60%) |
| Hypotension | 1 (1.32%) | 2 (12.50%) | 0 (0.00%) | 1 (5.88%) | 4 (3.20%) |
| Lymphoedema | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (5.88%) | 2 (1.60%) |

| | | | | | |
|---|---|---|---|---|---|
| Peripheral venous disease | 0 (0.00%) | 0 (0.00%) | 1 (6.25%) | 0 (0.00%) | 1 (0.80%) |

## Other Relevant Findings

None

## Conclusion:

DRB436B2204 (COMBI-MB) study demonstrated that dabrafenib and trametinib combination therapy is effective in BRAF V600 mutant melanoma subjects with brain metastases.

- Treatment with the dabrafenib and trametinib combination led to clinical significant reductions in tumor size and extended PFS and overall survival in this population with poor prognosis. However, the duration of overall response and progression-free survival in all cohorts in this study were shorter than those observed in randomized trials evaluating dabrafenib and trametinib in patients with metastatic melanoma without brain metastases.
- Clinical activity was observed in all cohorts and regardless of prior treatment, BRAF V600 mutation sub-type, symptoms, and performance status.
- The adverse event profile of the combination therapy in this subject population is consistent to other studies of this combination in unresectable or metastatic melanoma subjects without brain metastases.
- Permanent discontinuations of study treatment due to adverse events were low and overall exposure to both dabrafenib and trametinib was high indicating good tolerability to study treatments.
- Overall, data from this study provides favorable benefit-risk profile justifying treatment with dabrafenib and trametinib combination in subjects with melanoma with brain metastases

## Date of Clinical Trial Report

10-Sep-2018