



Clinical trial results:

A Phase 1b/2, Open-Label, Multi-Center, Dose Escalation Study of Binimetinib In Combination with Panitumumab in Adult Patients with Mutant RAS or Wild-Type RAS Metastatic Colorectal Cancer

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-001986-18 |
| Trial protocol | ES BE IT NL DE FR |
| Global end of trial date | 25 January 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 25 November 2017 |
| First version publication date | 25 November 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CMEK162X2116 |
|-----------------------|--------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Array BioPharma Inc. |
| Sponsor organisation address | 3200 Walnut Street, Boulder, United States, 80301 Colorado |
| Public contact | Victor Sandor, MD Chief Medical Officer , Array BioPharma Inc., +34 900353036, info@arraybiopharma.com |
| Scientific contact | Victor Sandor, MD Chief Medical Officer, Array BioPharma Inc., +34 900353036, info@arraybiopharma.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 | 11 August 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 January 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Phase Ib: To estimate the MTD and/or RP2D of MEK162 in combination with panitumumab

Phase II: To assess clinical efficacy of the MEK162 and panitumumab combination

Protection of trial subjects:

In both study phases, doses of study drug were adjusted or interrupted as appropriate based on protocol-defined treatment modifications. If an infusion reaction occurred while panitumumab was being administered, the infusion was stopped immediately, and the patient was closely monitored and treated according to institutional standards.

Background therapy:

Patients who took concomitant medication chronically were advised to maintain the same dose and dose schedule throughout the study period, as medically feasible

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 19 November 2013 |
| 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 | Netherlands: 10 |
| Country: Number of subjects enrolled | Spain: 7 |
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | Canada: 8 |
| Country: Number of subjects enrolled | United States: 16 |
| Worldwide total number of subjects | 53 |
| EEA total number of subjects | 29 |

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) | 40 |
| From 65 to 84 years | 13 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at a total of 8 sites: 2 sites in the United States, and 1 site each in Belgium, Canada, France, Italy, The Netherlands, and Spain. The patient population consisted of adult patients with mutant RAS or WT RAS mCRC. A total of 10 patients were enrolled in Phase 1b and 43 patients were enrolled in Phase 2.

Pre-assignment

Screening details:

Four patients were screened but not enrolled in Phase 1b and 35 patients were screened but not enrolled in Phase 2. Patients were male or female, at least 18 years of age with a histological or cytological confirmation of mCRC, with evidence of measurable disease as determined by RECIST v1.1.

Period 1

| | |
|------------------------------|----------------------------------|
| Period 1 title | Dose-escalation Phase (Phase 1b) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable, this clinical trial was open-label.

Arms

| | |
|------------------|---------------------------------------|
| Arm title | Binimetinib (MEK162) plus Panitumumab |
|------------------|---------------------------------------|

Arm description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Binimetinib |
| Investigational medicinal product code | MEK162 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The tablets were yellow to dark yellow and supplied in dosage strengths of 15 mg. Binimetinib tablets were to be taken orally BID, 12 ± 2 hours apart at approximately the same time each day, 2 hours before and 1 hour after food intake.

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

Dosage and administration details:

Panitumumab was dosed based on patient body weight and the starting dose selected for Panitumumab was 6 mg/kg Q2W. Each dose of panitumumab dose was administered intravenously at the study site Q2W on Days 1 and 15 of every 28-day cycle according to institutional standards. The panitumumab dose was calculated based on the patient's actual body weight at baseline and was recalculated for subsequent doses per institutional guidelines.

| Number of subjects in period 1 | Binimetinib (MEK162) plus Panitumumab |
|--------------------------------|---------------------------------------|
| Started | 10 |
| Completed | 53 |

| | |
|-------------------------|--|
| Joined | 43 |
| Late recruitment | 43 |
| Late recruitment reason | based on Mutant / WT RAS and anti-EGFR/- Naïve |

Period 2

| | |
|------------------------------|--------------------------|
| Period 2 title | Efficacy Phase (Phase 2) |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable, this study was open-label.

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFR/- Naïve |

Arm description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Binimetinib |
| Investigational medicinal product code | MEK162 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The tablets were yellow to dark yellow and supplied in dosage strengths of 15 mg. Binimetinib tablets were to be taken orally BID, 12 ± 2 hours apart at approximately the same time each day, 2 hours before and 1 hour after food intake.

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

Dosage and administration details:

Panitumumab was dosed based on patient body weight and the starting dose selected for panitumumab was 6 mg/kg Q2W. Each dose of panitumumab dose was administered intravenously at the study site Q2W on Days 1 and 15 of every 28-day cycle according to institutional standards. The panitumumab dose was calculated based on the patient's actual body weight at baseline and was recalculated for

subsequent doses per institutional guidelines.

| | |
|------------------|---|
| Arm title | Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi |
|------------------|---|

Arm description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Binimetinib |
| Investigational medicinal product code | MEK162 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The tablets were yellow to dark yellow and supplied in dosage strengths of 15 mg. Binimetinib tablets were to be taken orally BID, 12 ± 2 hours apart at approximately the same time each day, 2 hours before and 1 hour after food intake.

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

Dosage and administration details:

Panitumumab was dosed based on patient body weight and the starting dose selected for panitumumab was 6 mg/kg Q2W. Each dose of panitumumab dose was administered intravenously at the study site Q2W on Days 1 and 15 of every 28-day cycle according to institutional standards. The panitumumab dose was calculated based on the patient's actual body weight at baseline and was recalculated for subsequent doses per institutional guidelines.

| | |
|------------------|--|
| Arm title | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve |
|------------------|--|

Arm description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Binimetinib |
| Investigational medicinal product code | MEK162 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The tablets were yellow to dark yellow and supplied in dosage strengths of 15 mg. Binimetinib tablets were to be taken orally BID, 12 ± 2 hours apart at approximately the same time each day, 2 hours before and 1 hour after food intake.

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

Dosage and administration details:

Panitumumab was dosed based on patient body weight and the starting dose selected for panitumumab was 6 mg/kg Q2W. Each dose of panitumumab dose was administered intravenously at the study site Q2W on Days 1 and 15 of every 28-day cycle according to institutional standards. The panitumumab dose was calculated based on the patient's actual body weight at baseline and was recalculated for subsequent doses per institutional guidelines.

| | |
|------------------|--|
| Arm title | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve |
|------------------|--|

Arm description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Binimetinib |
| Investigational medicinal product code | MEK162 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The tablets were yellow to dark yellow and supplied in dosage strengths of 15 mg. Binimetinib tablets were to be taken orally BID, 12 ± 2 hours apart at approximately the same time each day, 2 hours before and 1 hour after food intake.

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

Dosage and administration details:

Panitumumab was dosed based on patient body weight and the starting dose selected for panitumumab was 6 mg/kg Q2W. Each dose of panitumumab dose was administered intravenously at the study site Q2W on Days 1 and 15 of every 28-day cycle according to institutional standards. The panitumumab dose was calculated based on the patient's actual body weight at baseline and was recalculated for subsequent doses per institutional guidelines.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is dose escalation part only (10 patients enrolled) to estimate the maximum tolerated dose (MTD) and/or RP2D of binimetinib in combination with panitumumab. Phase 2 began after the declaration of the MTD/RP2D. For this phase of the study, additional patients were enrolled, based on previous anti-EGFR monoclonal antibody therapy and RAS mutational status, into 1 of 4 different Phase 2 patient groups.

| Number of subjects in period 2^[2][3] | Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve | Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve |
|--|--|---|--|
| Started | 15 | 5 | 15 |
| Completed | 15 | 5 | 15 |

| Number of subjects in period 2^[2][3] | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve |
|--|--|
| Started | 8 |
| Completed | 8 |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: This study was a multi-center, open-label, dose-finding escalation study comprising 2 parts: Phase 1b was the dose escalation part, and it was followed by a Phase 2 clinical efficacy evaluation. In the first part 10 patients have been enrolled and subsequently 43 patients in the second part have been enrolled to a total of 53 patients globally included.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: This study was a multi-center, open-label, dose-finding escalation study comprising 2 parts: Phase 1b was the dose escalation part, and it was followed by a Phase 2 clinical efficacy evaluation. In the first part 10 patients have been enrolled and subsequently 43 patients in the second part have been enrolled to a total of 53 patients globally included.

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve |
|-----------------------|--|

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|-----------------------|---|
| Reporting group title | Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi |
|-----------------------|---|

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|-----------------------|--|
| Reporting group title | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve |
|-----------------------|--|

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|-----------------------|--|
| Reporting group title | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve |
|-----------------------|--|

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| Reporting group values | Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve | Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve |
|---------------------------------------|--|---|--|
| Number of subjects | 15 | 5 | 15 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 13 | 3 | 10 |
| From 65-84 years | 2 | 2 | 5 |
| Age continuous Units: years | | | |
| median | 56 | 55 | 58 |
| full range (min-max) | 36 to 71 | 49 to 75 | 30 to 79 |
| Gender categorical Units: Subjects | | | |
| Female | 9 | 4 | 9 |

| | | | |
|------|---|---|---|
| Male | 6 | 1 | 6 |
|------|---|---|---|

| Reporting group values | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve | Total | |
|---------------------------------------|--|-------|--|
| Number of subjects | 8 | 43 | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 6 | 32 | |
| From 65-84 years | 2 | 11 | |
| Age continuous Units: years | | | |
| median | 55 | | |
| full range (min-max) | 30 to 79 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 5 | 27 | |
| Male | 3 | 16 | |

Subject analysis sets

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Full analysis set (FAS) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All 53 patients were included in the full analysis set (FAS). The FAS included all patients who received at least 1 full or partial dose of binimetinib or panitumumab.

| Reporting group values | Full analysis set (FAS) | | |
|---------------------------------------|-------------------------|--|--|
| Number of subjects | 53 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 40 | | |
| From 65-84 years | 13 | | |
| Age continuous Units: years | | | |
| median | 55 | | |
| full range (min-max) | 30 to 79 | | |
| Gender categorical Units: Subjects | | | |
| Female | 31 | | |
| Male | 22 | | |

End points

End points reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Binimetinib (MEK162) plus Panitumumab |
|-----------------------|---------------------------------------|

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|-----------------------|--|
| Reporting group title | Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve |
|-----------------------|--|

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|-----------------------|---|
| Reporting group title | Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi |
|-----------------------|---|

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|-----------------------|--|
| Reporting group title | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve |
|-----------------------|--|

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|-----------------------|--|
| Reporting group title | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve |
|-----------------------|--|

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Full analysis set (FAS) |
|----------------------------|-------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

All 53 patients were included in the full analysis set (FAS). The FAS included all patients who received at least 1 full or partial dose of binimetinib or panitumumab.

Primary: Overall Response Rate (ORR) as per RECIST version 1.1

| | |
|-----------------|---|
| End point title | Overall Response Rate (ORR) as per RECIST version 1.1 |
|-----------------|---|

End point description:

Overall response rate is the sum of patients with complete response and partial response. The best overall response (BOR) was recorded from the start of the treatment until disease progression.

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

End point timeframe:

All patients considered for enrollment in Phase 2. Patients continued treatment with the combination therapy of binimetinib and panitumumab until progression of disease, development of unacceptable toxicity.

| End point values | Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve | Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 5 | 15 | 8 |
| Units: number of patients | | | | |
| complete response (confirmed) | 0 | 0 | 0 | 0 |
| partial response (confirmed) | 0 | 0 | 1 | 0 |

| End point values | Full analysis set (FAS) | | | |
|-------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 53 | | | |
| Units: number of patients | | | | |
| complete response (confirmed) | 0 | | | |
| partial response (confirmed) | 1 | | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis version 9.2 |
|--|--|
| Statistical analysis description: | |
| The clinical study data were analyzed by Array BioPharma Inc. and/or a designated contract research organization. For Bayesian modeling, programs were compiled using R (version 2.13.2) and WinBUGS (version 1.4.3) available in the production environment from MODESIM. | |
| Comparison groups | Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi v Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve v Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve v Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve |
| Number of subjects included in analysis | 43 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 2.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 12.3 |
| Variability estimate | Standard deviation |

Notes:

[1] - Clopper-Pearson method

Primary: Incidence of dose-limiting toxicities (DLTs) in Cycle 1

| | |
|-----------------|--|
| End point title | Incidence of dose-limiting toxicities (DLTs) in Cycle 1 ^[2] |
|-----------------|--|

End point description:

At least 21 out of the 28 planned daily doses of binimetinib [BID] and both doses of panitumumab [Q2W] in the first 28 days of dosing. A DLT was defined as an AE or clinically significant abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurred within the first 28 days of treatment with binimetinib and panitumumab and met the specified criteria for the type of toxicity.

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

End point timeframe:

Patients had been observed for ≥ 28 days following the first dose.

Notes:

[2] - 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: An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control principle was used to guide the dose escalation of the combination treatment to its maximum tolerated dose/recommended Phase 2 dose.

| End point values | Full analysis set (FAS) | | | |
|------------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 53 | | | |
| Units: number of patients with DLT | | | | |
| Dose Limiting Toxicity (all) | 5 | | | |
| DLTs leading to discontinuation | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

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

End point description:

Kaplan-Meier Estimates of Overall Survival Rate – % [95% CI]. Analysis of OS was performed if at least 50% of the patients died.

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

End point timeframe:

Overall survival is defined as the time from the start of treatment to the date of death due to any cause. If it was not known whether a patient had died, survival was censored at the date of last contact.

| End point values | Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve | Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve | Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve |
|----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 5 | 15 | 8 |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| 50th Percentile Events | 3.5 (2.1 to 8) | 5.5 (3.9 to 9.6) | 5.8 (3.1 to 8) | 11.2 (2.1 to 13.3) |

| End point values | Full analysis set (FAS) | | | |
|----------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 53 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| 50th Percentile Events | 5.5 (3.9 to 8) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing antineoplastic treatments was to be collected for 30 days after the last dose of study treatment.

Adverse event reporting additional description:

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (RECIST version 1.1 criteria), were not to be reported as a SAE. Adverse events separate from the progression of malignancy were reported as per the usual guidelines used for such events.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | All Phase 2 Patients |
|-----------------------|----------------------|

Reporting group description:

All Phase 2 Patients (N=43) included

| | |
|-----------------------|----------|
| Reporting group title | Phase 1b |
|-----------------------|----------|

Reporting group description:

Phase 1b (N=10) patients

| | |
|-----------------------|-------------------------------------|
| Reporting group title | All Patients (Phase 1b and Phase 2) |
|-----------------------|-------------------------------------|

Reporting group description:

All Patients (N=53) included in both Phase 1b and 2 phases

| Serious adverse events | All Phase 2 Patients | Phase 1b | All Patients (Phase 1b and Phase 2) |
|---|----------------------|-----------------|-------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 22 / 43 (51.16%) | 3 / 10 (30.00%) | 25 / 53 (47.17%) |
| number of deaths (all causes) | 5 | 2 | 7 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood CPK increased | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Troponin T increased | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Abdominal distension | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | 0 / 10 (0.00%) | 4 / 53 (7.55%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | 1 / 10 (10.00%) | 3 / 53 (5.66%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Small intestinal obstruction | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | 1 / 10 (10.00%) | 3 / 53 (5.66%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 1 / 10 (10.00%) | 2 / 53 (3.77%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 1 / 10 (10.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 1 / 10 (10.00%) | 2 / 53 (3.77%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Pneumomediastinum | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 1 / 10 (10.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 1 / 10 (10.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin infection | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 1 / 10 (10.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 10 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 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 | All Phase 2 Patients | Phase 1b | All Patients (Phase 1b and Phase 2) |
|---|----------------------|-------------------|-------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 43 / 43 (100.00%) | 10 / 10 (100.00%) | 53 / 53 (100.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | 2 / 10 (20.00%) | 5 / 53 (9.43%) |
| occurrences (all) | 3 | 2 | 5 |
| Hypotension | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | 1 / 10 (10.00%) | 3 / 53 (5.66%) |
| occurrences (all) | 2 | 1 | 3 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 16 / 43 (37.21%) | 9 / 10 (90.00%) | 25 / 53 (47.17%) |
| occurrences (all) | 16 | 9 | 25 |
| Chills | | | |
| subjects affected / exposed | 7 / 43 (16.28%) | 3 / 10 (30.00%) | 10 / 53 (18.87%) |
| occurrences (all) | 7 | 3 | 10 |
| Oedema Peripheral | | | |
| subjects affected / exposed | 8 / 43 (18.60%) | 2 / 10 (20.00%) | 10 / 53 (18.87%) |
| occurrences (all) | 8 | 2 | 10 |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 43 (18.60%) | 2 / 10 (20.00%) | 10 / 53 (18.87%) |
| occurrences (all) | 8 | 2 | 10 |
| Asthenia | | | |
| subjects affected / exposed | 8 / 43 (18.60%) | 0 / 10 (0.00%) | 8 / 53 (15.09%) |
| occurrences (all) | 8 | 0 | 8 |
| Feeling Cold | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 3 / 10 (30.00%) | 3 / 53 (5.66%) |
| occurrences (all) | 0 | 3 | 3 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | 1 / 10 (10.00%) | 4 / 53 (7.55%) |
| occurrences (all) | 3 | 1 | 4 |
| Cough | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | 1 / 10 (10.00%) | 3 / 53 (5.66%) |
| occurrences (all) | 2 | 1 | 3 |

| | | | |
|--|------------------------|----------------------|------------------------|
| Dysphonia subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | 2 / 10 (20.00%) 2 | 3 / 53 (5.66%) 3 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | 3 / 10 (30.00%) 3 | 4 / 53 (7.55%) 4 |
| Anxiety subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | 0 / 10 (0.00%) 0 | 3 / 53 (5.66%) 3 |
| Investigations | | | |
| Blood Creatine Phosphokinase Increased subjects affected / exposed occurrences (all) | 12 / 43 (27.91%) 12 | 5 / 10 (50.00%) 5 | 17 / 53 (32.08%) 17 |
| Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all) | 8 / 43 (18.60%) 8 | 0 / 10 (0.00%) 0 | 8 / 53 (15.09%) 8 |
| Ejection Fraction Decreased subjects affected / exposed occurrences (all) | 6 / 43 (13.95%) 6 | 1 / 10 (10.00%) 1 | 7 / 53 (13.21%) 7 |
| Blood Creatinine Increased subjects affected / exposed occurrences (all) | 6 / 43 (13.95%) 6 | 0 / 10 (0.00%) 0 | 6 / 53 (11.32%) 6 |
| Lipase Increased subjects affected / exposed occurrences (all) | 5 / 43 (11.63%) 5 | 1 / 10 (10.00%) 1 | 6 / 53 (11.32%) 6 |
| Alanine Aminotransferase Increased subjects affected / exposed occurrences (all) | 5 / 43 (11.63%) 5 | 0 / 10 (0.00%) 0 | 5 / 53 (9.43%) 5 |
| Blood Bilirubin Increased subjects affected / exposed occurrences (all) | 4 / 43 (9.30%) 4 | 0 / 10 (0.00%) 0 | 4 / 53 (7.55%) 4 |
| Weight Decreased subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | 3 / 10 (30.00%) 3 | 4 / 53 (7.55%) 4 |
| Blood Alkaline Phosphatase | | | |

| | | | |
|--|---|--|--|
| Increased subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | 0 / 10 (0.00%) 0 | 3 / 53 (5.66%) 3 |
| Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | 3 / 10 (30.00%) 3 | 6 / 53 (11.32%) 6 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all) | 9 / 43 (20.93%) 9 4 / 43 (9.30%) 4 | 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 | 9 / 53 (16.98%) 9 4 / 53 (7.55%) 4 |
| Eye disorders Vision Blurred subjects affected / exposed occurrences (all) Chorioretinopathy subjects affected / exposed occurrences (all) Retinal Detachment subjects affected / exposed occurrences (all) Retinopathy subjects affected / exposed occurrences (all) Periorbital Oedema subjects affected / exposed occurrences (all) Vitreous Floaters subjects affected / exposed occurrences (all) | 5 / 43 (11.63%) 5 4 / 43 (9.30%) 4 4 / 43 (9.30%) 4 3 / 43 (6.98%) 3 1 / 43 (2.33%) 1 2 / 43 (4.65%) 2 | 2 / 10 (20.00%) 2 2 / 10 (20.00%) 2 1 / 10 (10.00%) 1 2 / 10 (20.00%) 2 2 / 10 (20.00%) 2 1 / 10 (10.00%) 1 | 7 / 53 (13.21%) 7 6 / 53 (11.32%) 6 5 / 53 (9.43%) 5 5 / 53 (9.43%) 5 3 / 53 (5.66%) 3 3 / 53 (5.66%) 3 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 31 / 43 (72.09%) 31 | 7 / 10 (70.00%) 7 | 38 / 53 (71.70%) 38 |

| | | | |
|--|------------------|-----------------|------------------|
| Vomiting | | | |
| subjects affected / exposed | 24 / 43 (55.81%) | 4 / 10 (40.00%) | 28 / 53 (52.83%) |
| occurrences (all) | 24 | 4 | 28 |
| Nausea | | | |
| subjects affected / exposed | 22 / 43 (51.16%) | 5 / 10 (50.00%) | 27 / 53 (50.94%) |
| occurrences (all) | 22 | 5 | 27 |
| Abdominal Pain | | | |
| subjects affected / exposed | 13 / 43 (30.23%) | 1 / 10 (10.00%) | 14 / 53 (26.42%) |
| occurrences (all) | 13 | 1 | 14 |
| Stomatitis | | | |
| subjects affected / exposed | 10 / 43 (23.26%) | 3 / 10 (30.00%) | 13 / 53 (24.53%) |
| occurrences (all) | 10 | 3 | 13 |
| Constipation | | | |
| subjects affected / exposed | 10 / 43 (23.26%) | 2 / 10 (20.00%) | 12 / 53 (22.64%) |
| occurrences (all) | 10 | 2 | 12 |
| Dry Mouth | | | |
| subjects affected / exposed | 5 / 43 (11.63%) | 1 / 10 (10.00%) | 6 / 53 (11.32%) |
| occurrences (all) | 5 | 1 | 6 |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | 2 / 10 (20.00%) | 6 / 53 (11.32%) |
| occurrences (all) | 4 | 2 | 6 |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | 0 / 10 (0.00%) | 4 / 53 (7.55%) |
| occurrences (all) | 4 | 0 | 4 |
| Oral Pain | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | 0 / 10 (0.00%) | 4 / 53 (7.55%) |
| occurrences (all) | 4 | 0 | 4 |
| Gastrooesophageal Reflux Disease | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 2 / 10 (20.00%) | 3 / 53 (5.66%) |
| occurrences (all) | 1 | 2 | 3 |
| Glossodynia | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | 0 / 10 (0.00%) | 3 / 53 (5.66%) |
| occurrences (all) | 3 | 0 | 3 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis Acneiform | | | |

| | | | |
|---|------------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 15 / 43 (34.88%) 15 | 8 / 10 (80.00%) 8 | 23 / 53 (43.40%) 23 |
| Rash subjects affected / exposed occurrences (all) | 20 / 43 (46.51%) 20 | 2 / 10 (20.00%) 2 | 22 / 53 (41.51%) 22 |
| Dry Skin subjects affected / exposed occurrences (all) | 11 / 43 (25.58%) 11 | 6 / 10 (60.00%) 6 | 17 / 53 (32.08%) 17 |
| Rash Maculo-Papular subjects affected / exposed occurrences (all) | 7 / 43 (16.28%) 7 | 5 / 10 (50.00%) 5 | 12 / 53 (22.64%) 12 |
| Skin Fissures subjects affected / exposed occurrences (all) | 5 / 43 (11.63%) 5 | 3 / 10 (30.00%) 3 | 8 / 53 (15.09%) 8 |
| Pruritus subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | 1 / 10 (10.00%) 1 | 4 / 53 (7.55%) 4 |
| Erythema subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 | 1 / 10 (10.00%) 1 | 3 / 53 (5.66%) 3 |
| Musculoskeletal and connective tissue disorders | | | |
| Back Pain subjects affected / exposed occurrences (all) | 5 / 43 (11.63%) 5 | 3 / 10 (30.00%) 3 | 8 / 53 (15.09%) 8 |
| Arthralgia subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 | 3 / 10 (30.00%) 3 | 5 / 53 (9.43%) 5 |
| Pain In Extremity subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | 2 / 10 (20.00%) 2 | 3 / 53 (5.66%) 3 |
| Infections and infestations | | | |
| Paronychia subjects affected / exposed occurrences (all) | 5 / 43 (11.63%) 5 | 3 / 10 (30.00%) 3 | 8 / 53 (15.09%) 8 |
| Folliculitis | | | |

| | | | |
|---|----------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 5 / 43 (11.63%) 5 | 3 / 10 (30.00%) 3 | 8 / 53 (15.09%) 8 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | 1 / 10 (10.00%) 1 | 4 / 53 (7.55%) 4 |
| Sepsis subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | 0 / 10 (0.00%) 0 | 3 / 53 (5.66%) 3 |
| Urinary Tract Infection subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 | 1 / 10 (10.00%) 1 | 3 / 53 (5.66%) 3 |
| Metabolism and nutrition disorders | | | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 6 / 43 (13.95%) 6 | 6 / 10 (60.00%) 6 | 12 / 53 (22.64%) 12 |
| Decreased Appetite subjects affected / exposed occurrences (all) | 6 / 43 (13.95%) 6 | 5 / 10 (50.00%) 5 | 11 / 53 (20.75%) 11 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 9 / 43 (20.93%) 9 | 0 / 10 (0.00%) 0 | 9 / 53 (16.98%) 9 |
| Dehydration subjects affected / exposed occurrences (all) | 5 / 43 (11.63%) 5 | 2 / 10 (20.00%) 2 | 7 / 53 (13.21%) 7 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 4 / 43 (9.30%) 4 | 1 / 10 (10.00%) 1 | 5 / 53 (9.43%) 5 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | 2 / 10 (20.00%) 2 | 5 / 53 (9.43%) 5 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | 0 / 10 (0.00%) 0 | 3 / 53 (5.66%) 3 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | 0 / 10 (0.00%) 0 | 3 / 53 (5.66%) 3 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 02 April 2014 | Protocol Version 01, dated 02 April 2014 |
| 18 September 2015 | Protocol Version 02, dated 18 September 2015 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported