



Clinical trial results:

A Phase Ib/II, multicenter, open-label study of EGF816 in combination with INC280 in adult subjects with EGFR mutated non-small cell lung cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-000726-37 |
| Trial protocol | DE ES FR IT |
| Global end of trial date | 11 May 2022 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 26 January 2023 |
| First version publication date | 26 January 2023 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CINC280X2105C |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02335944 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 November 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 11 May 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of nazartinib in combination with capmatinib and to estimate the preliminary anti-tumor activity of nazartinib in combination with capmatinib in participants with advanced non-small cell lung cancer with documented EGFR mutation.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 13 January 2015 |
| 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 | Australia: 8 |
| Country: Number of subjects enrolled | Canada: 5 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | Germany: 17 |
| Country: Number of subjects enrolled | Italy: 21 |
| Country: Number of subjects enrolled | Korea, Republic of: 14 |
| Country: Number of subjects enrolled | Norway: 4 |
| Country: Number of subjects enrolled | Singapore: 31 |
| Country: Number of subjects enrolled | Spain: 38 |
| Country: Number of subjects enrolled | Taiwan: 25 |
| Country: Number of subjects enrolled | United States: 6 |
| Worldwide total number of subjects | 177 |
| EEA total number of subjects | 88 |

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) | 112 |
| From 65 to 84 years | 65 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants took part in 19 investigative sites in 11 countries. Due to early study termination, Group 5 (Phase II part) was never opened

Pre-assignment

Screening details:

The screening period began once patients had signed the study informed consent. All screening/baseline evaluations were performed ≤ 28 days before Cycle 1 Day 1.

Period 1

| | |
|------------------------------|----------------------------------|
| Period 1 title | Treatment Phase (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Phase IB part- INC280 200mg BID/ EGF816 50mg QD |

Arm description:

Combination of INC280 200mg twice daily (BID) and EGF816 50mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Capmatinib |
| Investigational medicinal product code | INC280 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 200 mg, in fasted state.

| | |
|--|-----------------|
| Investigational medicinal product name | Nazartinib |
| Investigational medicinal product code | EGF816 |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 50 mg, in fasted state

| | |
|------------------|--|
| Arm title | Phase IB part- INC280 200mg BID/ EGF816 100mg QD |
|------------------|--|

Arm description:

Combination of INC280 200mg twice daily (BID) and EGF816 100mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Capmatinib |
| Investigational medicinal product code | INC280 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 200 mg, in fasted state.

| | |
|---|--|
| Investigational medicinal product name | Nazartinib |
| Investigational medicinal product code | EGF816 |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Nazartinib was administered orally, once a day, at a dose of 100 mg, in fasted state | |
| Arm title | Phase IB part- INC280 400mg BID/ EGF816 75mg QD |
| Arm description: | |
| Combination of INC280 400mg twice daily (BID) and EGF816 75mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Arm type | Experimental |
| Investigational medicinal product name | Nazartinib |
| Investigational medicinal product code | EGF816 |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Nazartinib was administered orally, once a day, at a dose of 75 mg, in fasted state | |
| Investigational medicinal product name | Capmatinib |
| Investigational medicinal product code | INC280 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state. | |
| Arm title | Phase IB part- INC280 400mg BID/ EGF816 100mg QD |
| Arm description: | |
| Combination of INC280 400mg twice daily (BID) and EGF816 100mg once daily (QD) in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Arm type | Experimental |
| Investigational medicinal product name | Capmatinib |
| Investigational medicinal product code | INC280 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state. | |
| Investigational medicinal product name | Nazartinib |
| Investigational medicinal product code | EGF816 |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Nazartinib was administered orally, once a day, at a dose of 100 mg, in fasted state | |
| Arm title | Phase IB part- INC280 400mg BID/ EGF816 150mg QD |
| Arm description: | |
| Combination of INC280 400mg twice daily (BID) and EGF816 150mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Arm type | Experimental |

| | |
|--|-----------------|
| Investigational medicinal product name | Nazartinib |
| Investigational medicinal product code | EGF816 |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 150 mg, in fasted state

| | |
|--|------------|
| Investigational medicinal product name | Capmatinib |
| Investigational medicinal product code | INC280 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state.

| | |
|------------------|-------------------|
| Arm title | Phase II- Group 1 |
|------------------|-------------------|

Arm description:

NSCLC participants with previously documented activating EGFR mutation, with any T790M and MET dysregulation status, who received 1 to 3 lines of systemic antineoplastic therapy prior to study entry including one line maximum of 1st or 2nd generation EGFR TKI. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nazartinib |
| Investigational medicinal product code | EGF816 |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 100 mg, in fasted state

| | |
|--|------------|
| Investigational medicinal product name | Capmatinib |
| Investigational medicinal product code | INC280 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state.

| | |
|------------------|-------------------|
| Arm title | Phase II- Group 2 |
|------------------|-------------------|

Arm description:

NSCLC participants harboring T790M mutation in de novo setting, irrespective of the activating mutation status who received none to 2 lines of systemic antineoplastic therapy prior to study entry, but no therapy known to inhibit EGFR. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nazartinib |
| Investigational medicinal product code | EGF816 |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 100 mg, in fasted state

| | |
|--|------------|
| Investigational medicinal product name | Capmatinib |
| Investigational medicinal product code | INC280 |
| Other name | |
| Pharmaceutical forms | Tablet |

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state.

| | |
|------------------|-------------------|
| Arm title | Phase II- Group 3 |
|------------------|-------------------|

Arm description:

NSCLC participants with previously documented EGFR activating mutation, T790M negative, and any MET status who never received any prior line of systemic antineoplastic therapy. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nazartinib |
| Investigational medicinal product code | EGF816 |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 100 mg, in fasted state

| | |
|--|------------|
| Investigational medicinal product name | Capmatinib |
| Investigational medicinal product code | INC280 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state.

| | |
|------------------|-------------------|
| Arm title | Phase II- Group 4 |
|------------------|-------------------|

Arm description:

NSCLC participants with previously documented EGFR activating mutations and any T790M and MET status who received none to 2 prior lines of systemic antineoplastic therapy prior to study entry. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fed state.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nazartinib |
| Investigational medicinal product code | EGF816 |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 100 mg, in fed state

| | |
|--|------------|
| Investigational medicinal product name | Capmatinib |
| Investigational medicinal product code | INC280 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fed state.

| Number of subjects in period 1 | Phase IB part- INC280 200mg BID/ EGF816 50mg QD | Phase IB part- INC280 200mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 75mg QD |
|--------------------------------|---|--|---|
| Started | 4 | 5 | 3 |
| Completed | 0 | 0 | 0 |
| Not completed | 4 | 5 | 3 |
| Physician decision | - | - | - |
| Adverse event, non-fatal | 2 | - | - |
| Study Terminated By Sponsor | - | - | - |
| Progressive Disease | 2 | 5 | 2 |
| Subject/Guardian Decision | - | - | 1 |

| Number of subjects in period 1 | Phase IB part- INC280 400mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 150mg QD | Phase II- Group 1 |
|--------------------------------|--|--|-------------------|
| Started | 16 | 5 | 52 |
| Completed | 1 | 0 | 2 |
| Not completed | 15 | 5 | 50 |
| Physician decision | 1 | - | 6 |
| Adverse event, non-fatal | 2 | 1 | 15 |
| Study Terminated By Sponsor | 1 | - | 3 |
| Progressive Disease | 11 | 4 | 25 |
| Subject/Guardian Decision | - | - | 1 |

| Number of subjects in period 1 | Phase II- Group 2 | Phase II- Group 3 | Phase II- Group 4 |
|--------------------------------|-------------------|-------------------|-------------------|
| Started | 3 | 47 | 42 |
| Completed | 0 | 5 | 6 |
| Not completed | 3 | 42 | 36 |
| Physician decision | 1 | 2 | 1 |
| Adverse event, non-fatal | - | 5 | 7 |
| Study Terminated By Sponsor | - | 1 | 1 |
| Progressive Disease | 2 | 30 | 27 |
| Subject/Guardian Decision | - | 4 | - |

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | Phase IB part- INC280 200mg BID/ EGF816 50mg QD |
| Reporting group description: Combination of INC280 200mg twice daily (BID) and EGF816 50mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Reporting group title | Phase IB part- INC280 200mg BID/ EGF816 100mg QD |
| Reporting group description: Combination of INC280 200mg twice daily (BID) and EGF816 100mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Reporting group title | Phase IB part- INC280 400mg BID/ EGF816 75mg QD |
| Reporting group description: Combination of INC280 400mg twice daily (BID) and EGF816 75mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Reporting group title | Phase IB part- INC280 400mg BID/ EGF816 100mg QD |
| Reporting group description: Combination of INC280 400mg twice daily (BID) and EGF816 100mg once daily (QD) in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Reporting group title | Phase IB part- INC280 400mg BID/ EGF816 150mg QD |
| Reporting group description: Combination of INC280 400mg twice daily (BID) and EGF816 150mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Reporting group title | Phase II- Group 1 |
| Reporting group description: NSCLC participants with previously documented activating EGFR mutation, with any T790M and MET dysregulation status, who received 1 to 3 lines of systemic antineoplastic therapy prior to study entry including one line maximum of 1st or 2nd generation EGFR TKI. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state | |
| Reporting group title | Phase II- Group 2 |
| Reporting group description: NSCLC participants harboring T790M mutation in de novo setting, irrespective of the activating mutation status who received none to 2 lines of systemic antineoplastic therapy prior to study entry, but no therapy known to inhibit EGFR. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state | |
| Reporting group title | Phase II- Group 3 |
| Reporting group description: NSCLC participants with previously documented EGFR activating mutation, T790M negative, and any MET status who never received any prior line of systemic antineoplastic therapy. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state | |
| Reporting group title | Phase II- Group 4 |
| Reporting group description: NSCLC participants with previously documented EGFR activating mutations and any T790M and MET status who received none to 2 prior lines of systemic antineoplastic therapy prior to study entry. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fed state. | |

| Reporting group values | Phase IB part- INC280 200mg BID/ EGF816 50mg QD | Phase IB part- INC280 200mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 75mg QD |
|--|---|--|---|
| Number of subjects | 4 | 5 | 3 |
| Age Categorical Units: Participants | | | |
| <=18 years | 0 | 0 | 0 |
| Between 18 and 65 years | 3 | 5 | 2 |

| | | | |
|------------|---|---|---|
| >=65 years | 1 | 0 | 1 |
|------------|---|---|---|

| | | | |
|---|---|---|---|
| Sex: Female, Male Units: Participants | | | |
| Female | 4 | 3 | 1 |
| Male | 0 | 2 | 2 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian | 2 | 3 | 1 |
| Caucasian | 2 | 2 | 1 |
| Missing | 0 | 0 | 1 |
| Black | 0 | 0 | 0 |

| Reporting group values | Phase IB part- INC280 400mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 150mg QD | Phase II- Group 1 |
|---|--|--|-------------------|
| Number of subjects | 16 | 5 | 52 |
| Age Categorical Units: Participants | | | |
| <=18 years | 0 | 0 | 0 |
| Between 18 and 65 years | 11 | 3 | 33 |
| >=65 years | 5 | 2 | 19 |
| Sex: Female, Male Units: Participants | | | |
| Female | 9 | 4 | 38 |
| Male | 7 | 1 | 14 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian | 10 | 4 | 26 |
| Caucasian | 4 | 1 | 22 |
| Missing | 2 | 0 | 3 |
| Black | 0 | 0 | 1 |

| Reporting group values | Phase II- Group 2 | Phase II- Group 3 | Phase II- Group 4 |
|---|-------------------|-------------------|-------------------|
| Number of subjects | 3 | 47 | 42 |
| Age Categorical Units: Participants | | | |
| <=18 years | 0 | 0 | 0 |
| Between 18 and 65 years | 1 | 30 | 24 |
| >=65 years | 2 | 17 | 18 |
| Sex: Female, Male Units: Participants | | | |
| Female | 2 | 33 | 24 |
| Male | 1 | 14 | 18 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian | 2 | 30 | 20 |
| Caucasian | 1 | 16 | 21 |
| Missing | 0 | 1 | 1 |
| Black | 0 | 0 | 0 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 177 | | |
| Age Categorical Units: Participants | | | |
| <=18 years | 0 | | |
| Between 18 and 65 years | 112 | | |
| >=65 years | 65 | | |
| Sex: Female, Male Units: Participants | | | |
| Female | 118 | | |
| Male | 59 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian | 98 | | |
| Caucasian | 70 | | |
| Missing | 8 | | |
| Black | 1 | | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Phase IB part- INC280 200mg BID/ EGF816 50mg QD |
| Reporting group description: Combination of INC280 200mg twice daily (BID) and EGF816 50mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Reporting group title | Phase IB part- INC280 200mg BID/ EGF816 100mg QD |
| Reporting group description: Combination of INC280 200mg twice daily (BID) and EGF816 100mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Reporting group title | Phase IB part- INC280 400mg BID/ EGF816 75mg QD |
| Reporting group description: Combination of INC280 400mg twice daily (BID) and EGF816 75mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Reporting group title | Phase IB part- INC280 400mg BID/ EGF816 100mg QD |
| Reporting group description: Combination of INC280 400mg twice daily (BID) and EGF816 100mg once daily (QD) in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Reporting group title | Phase IB part- INC280 400mg BID/ EGF816 150mg QD |
| Reporting group description: Combination of INC280 400mg twice daily (BID) and EGF816 150mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment | |
| Reporting group title | Phase II- Group 1 |
| Reporting group description: NSCLC participants with previously documented activating EGFR mutation, with any T790M and MET dysregulation status, who received 1 to 3 lines of systemic antineoplastic therapy prior to study entry including one line maximum of 1st or 2nd generation EGFR TKI. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state | |
| Reporting group title | Phase II- Group 2 |
| Reporting group description: NSCLC participants harboring T790M mutation in de novo setting, irrespective of the activating mutation status who received none to 2 lines of systemic antineoplastic therapy prior to study entry, but no therapy known to inhibit EGFR. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state | |
| Reporting group title | Phase II- Group 3 |
| Reporting group description: NSCLC participants with previously documented EGFR activating mutation, T790M negative, and any MET status who never received any prior line of systemic antineoplastic therapy. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state | |
| Reporting group title | Phase II- Group 4 |
| Reporting group description: NSCLC participants with previously documented EGFR activating mutations and any T790M and MET status who received none to 2 prior lines of systemic antineoplastic therapy prior to study entry. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fed state. | |

Primary: Phase Ib: Number of participants with dose limiting toxicities (DLTs)

| | |
|---|---|
| End point title | Phase Ib: Number of participants with dose limiting toxicities (DLTs) ^{[1][2]} |
| End point description: Number of participants with DLTs in the Phase Ib part. A DLT is defined as an AE or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with EGF816 in combination with INC280 | |

during the escalation part of the study (Phase Ib)

| | |
|----------------------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Up to first 28 days of treatment | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint is only applicable for Phase Ib arms

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| | | | | |
|-----------------------------|--|---|--|---|
| End point values | Phase IB part- INC280 200mg BID/ EGF816 50mg QD | Phase IB part- INC280 200mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 75mg QD | Phase IB part- INC280 400mg BID/ EGF816 100mg QD |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 1 | 13 |
| Units: Participants | 1 | 0 | 0 | 1 |

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | Phase IB part- INC280 400mg BID/ EGF816 150mg QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: Participants | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Group 1, 2 and 3: Overall Response Rate (ORR) by investigator's assessment per RECIST 1.1

| | |
|-----------------|--|
| End point title | Phase II Group 1, 2 and 3: Overall Response Rate (ORR) by investigator's assessment per RECIST 1.1 ^{[3][4]} |
|-----------------|--|

End point description:

ORR is defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) determined by investigator's assessment in accordance to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). ORR was assessed in Group 1, 2 and 3 (Phase II part).

CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

| | |
|-----------------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Up to approximately 4 years | |

Notes:

[3] - 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: This endpoint is only applicable for Phase II Groups 1, 2 and 3

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 1, 2 and 3

| End point values | Phase II-Group 1 | Phase II-Group 2 | Phase II-Group 3 | |
|-----------------------------------|----------------------|--------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 52 | 3 | 47 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 28.8 (17.1 to 43.10) | 33.3 (0.8 to 90.6) | 61.7 (46.4 to 75.5) | |

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Group 4: Number of participants with Adverse Events (AEs) and Serious AEs (SAEs)

| | |
|-----------------|---|
| End point title | Phase II Group 4: Number of participants with Adverse Events (AEs) and Serious AEs (SAEs) ^{[5][6]} |
|-----------------|---|

End point description:

Number of participants in Group 4 (Phase II part) with AEs and SAEs. An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. Any untoward event resulting in death, life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, congenital anomaly/birth defect or any other situation according to medical or scientific judgment is categorized as SAE.

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

End point timeframe:

From start of treatment up to 30 days after last dose of study treatment, assessed up to 3.7 years

Notes:

[5] - 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: This endpoint is only applicable for Phase II Group 4

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Group 4

| End point values | Phase II-Group 4 | | | |
|-----------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 42 | | | |
| Units: Participants | | | | |
| AEs | 42 | | | |
| SAEs | 26 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Group 4: Number of participants with dose reductions and dose interruptions of INC280 and EGF618

| | |
|-----------------|---|
| End point title | Phase II Group 4: Number of participants with dose reductions and dose interruptions of INC280 and EGF618 ^[7] ^[8] |
|-----------------|---|

End point description:

Number of participants with at least one dose reduction of INC280, at least one dose interruption of INC280, at least one dose reduction of EGF816 and at least one dose interruption of EGF816 in the Group 4 (Phase II part).

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

End point timeframe:

From start of treatment until end of treatment, assessed up to 3.6 years

Notes:

[7] - 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: This endpoint is only applicable for Phase II Group 4

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Group 4

| End point values | Phase II- Group 4 | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 42 | | | |
| Units: Participants | | | | |
| Dose Reduction of INC280 | 30 | | | |
| Dose Interruption of INC280 | 31 | | | |
| Dose Reduction of EGF816 | 12 | | | |
| Dose Interruption of EGF816 | 35 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Group 4: Dose intensity

| | |
|-----------------|---|
| End point title | Phase II Group 4: Dose intensity ^[9] ^[10] |
|-----------------|---|

End point description:

Dose intensity, defined as the ratio of total dose received and actual duration, for participants in Group 4 (Phase II part)

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

End point timeframe:

From start of treatment until end of treatment, assessed up to 3.6 years

Notes:

[9] - 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: This endpoint is only applicable for Phase II Group 4

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Group 4

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | Phase II-Group 4 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 42 | | | |
| Units: milligram/day | | | | |
| arithmetic mean (standard deviation) | | | | |
| INC280 | 666.2 (± 148.97) | | | |
| EGF816 | 87.4 (± 14.82) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Number of participants with dose reductions and dose interruptions of INC280 and EGF618

| | |
|-----------------|---|
| End point title | Phase Ib: Number of participants with dose reductions and dose interruptions of INC280 and EGF618 ^[11] |
|-----------------|---|

End point description:

Number of participants in Phase Ib with at least one dose reduction of INC280, at least one dose interruption of INC280, at least one dose reduction of EGF816 and at least one dose interruption of EGF816 .

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

End point timeframe:

From start of treatment until end of treatment, assessed up to approximately 5 years

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part-INC280 200mg BID/ EGF816 50mg QD | Phase IB part-INC280 200mg BID/ EGF816 100mg QD | Phase IB part-INC280 400mg BID/ EGF816 75mg QD | Phase IB part-INC280 400mg BID/ EGF816 100mg QD |
|-----------------------------|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 16 |
| Units: Participants | | | | |
| Dose Reduction of INC280 | 2 | 4 | 2 | 10 |
| Dose Interruption of INC280 | 2 | 2 | 2 | 12 |
| Dose Reduction of EGF816 | 2 | 1 | 1 | 5 |
| Dose Interruption of EGF816 | 2 | 2 | 2 | 11 |

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | Phase IB part-INC280 400mg BID/ EGF816 150mg QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: Participants | | | | |
| Dose Reduction of INC280 | 5 | | | |

| | | | | |
|-----------------------------|---|--|--|--|
| Dose Interruption of INC280 | 5 | | | |
| Dose Reduction of EGF816 | 3 | | | |
| Dose Interruption of EGF816 | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Group 1, 2 and 3: Number of participants with dose reductions and dose interruptions of INC280 and EGF618

| | |
|-----------------|--|
| End point title | Phase II Group 1, 2 and 3: Number of participants with dose reductions and dose interruptions of INC280 and EGF618 ^[12] |
|-----------------|--|

End point description:

Number of participants in Groups 1, 2 and 3 (Phase II part) with at least one dose reduction of INC280, at least one dose interruption of INC280, at least one dose reduction of EGF816 and at least one dose interruption of EGF816 .

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

End point timeframe:

From start of treatment until end of treatment, assessed up to approximately 4 years

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 1, 2 and 3

| End point values | Phase II- Group 1 | Phase II- Group 2 | Phase II- Group 3 | |
|-----------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 52 | 3 | 47 | |
| Units: Participants | | | | |
| Dose Reduction of INC280 | 33 | 3 | 34 | |
| Dose Interruption of INC280 | 31 | 3 | 39 | |
| Dose Reduction of EGF816 | 17 | 2 | 23 | |
| Dose Interruption of EGF816 | 34 | 3 | 40 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Dose intensity

| | |
|-----------------|--|
| End point title | Phase Ib: Dose intensity ^[13] |
|-----------------|--|

End point description:

Dose intensity, defined as the ratio of total dose received and actual duration, in Phase Ib participants

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

End point timeframe:

From start of treatment until end of treatment, assessed up to approximately 5 years

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part- INC280 200mg BID/ EGF816 50mg QD | Phase IB part- INC280 200mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 75mg QD | Phase IB part- INC280 400mg BID/ EGF816 100mg QD |
|--------------------------------------|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 16 |
| Units: milligram/day | | | | |
| arithmetic mean (standard deviation) | | | | |
| INC280 | 319.1 (± 101.09) | 356.9 (± 71.14) | 596.3 (± 200.24) | 658.2 (± 158.18) |
| EGF816 | 40.0 (± 12.60) | 89.6 (± 17.93) | 60.0 (± 13.36) | 85.2 (± 17.28) |

| End point values | Phase IB part- INC280 400mg BID/ EGF816 150mg QD | | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: milligram/day | | | | |
| arithmetic mean (standard deviation) | | | | |
| INC280 | 463.4 (± 212.52) | | | |
| EGF816 | 97.7 (± 36.43) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Group 1, 2 and 3: Dose intensity

| | |
|---|---|
| End point title | Phase II Group 1, 2 and 3: Dose intensity ^[14] |
| End point description: | |
| Dose intensity, defined as the ratio of total dose received and actual duration, in Group 1, 2 and 3 (Phase II) | |
| End point type | Secondary |
| End point timeframe: | |
| From start of treatment until end of treatment, assessed up to approximately 4 years | |

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 1, 2 and 3

| End point values | Phase II-Group 1 | Phase II-Group 2 | Phase II-Group 3 | |
|--------------------------------------|------------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 52 | 3 | 47 | |
| Units: milligram/day | | | | |
| arithmetic mean (standard deviation) | | | | |
| INC280 | 662.9 (± 160.73) | 562.9 (± 38.36) | 634.7 (± 172.33) | |
| EGF816 | 85.2 (± 18.21) | 76.3 (± 15.31) | 84.8 (± 15.53) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Overall Response Rate (ORR) per RECIST 1.1 based on investigator's assessment

| | |
|-----------------|---|
| End point title | Phase Ib: Overall Response Rate (ORR) per RECIST 1.1 based on investigator's assessment ^[15] |
|-----------------|---|

End point description:

ORR is defined as percentage of participants with best overall response of PR+CR determined by Investigator's assessment in accordance to RECIST 1.1. ORR was assessed in Phase Ib participants. CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

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

End point timeframe:

Up to approximately 5 years

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part-INC280 200mg BID/ EGF816 50mg QD | Phase IB part-INC280 200mg BID/ EGF816 100mg QD | Phase IB part-INC280 400mg BID/ EGF816 75mg QD | Phase IB part-INC280 400mg BID/ EGF816 100mg QD |
|-----------------------------------|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 16 |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 0 (0.0 to 60.2) | 40.0 (5.3 to 85.3) | 33.3 (0.8 to 90.6) | 50.0 (24.7 to 75.3) |

| End point values | Phase IB part-INC280 400mg BID/ EGF816 150mg QD | | | |
|-----------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 60.0 (14.7 to 94.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Group 4: Overall Response Rate (ORR) per RECIST 1.1 based on investigator's assessment

| | |
|-----------------|---|
| End point title | Phase II Group 4: Overall Response Rate (ORR) per RECIST 1.1 based on investigator's assessment ^[16] |
|-----------------|---|

End point description:

ORR is defined as percentage of participants with best overall response of PR+CR determined by Investigator's assessment in accordance to RECIST 1.1. ORR was assessed in Group 4 (Phase II) CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

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

End point timeframe:

Up to approximately 4 years

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Group 4

| | | | | |
|-----------------------------------|---------------------|--|--|--|
| End point values | Phase II-Group 4 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 42 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 42.9 (27.7 to 59.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Progression Free Survival (PFS) per RECIST 1.1 based on investigator's assessment

| | |
|-----------------|---|
| End point title | Phase Ib: Progression Free Survival (PFS) per RECIST 1.1 based on investigator's assessment ^[17] |
|-----------------|---|

End point description:

PFS is defined as time from date of first dose of study treatment to date of first documented disease progression determined by Investigator assessment in accordance to RECIST 1.1.or death due to any cause. The PFS distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, PFS is censored at the date of last adequate tumor assessment. PFS was assessed in Phase Ib participants

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

End point timeframe:

From date of first dose to first documented disease progression or death, assessed up to approximately 5 years

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part- INC280 200mg BID/ EGF816 50mg QD | Phase IB part- INC280 200mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 75mg QD | Phase IB part- INC280 400mg BID/ EGF816 100mg QD |
|----------------------------------|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 16 |
| Units: Months | | | | |
| median (confidence interval 95%) | 5.6 (3.5 to 999999) | 7.4 (1.6 to 999999) | 3.5 (0.8 to 999999) | 5.7 (1.9 to 42.1) |

| End point values | Phase IB part- INC280 400mg BID/ EGF816 150mg QD | | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 14.5 (7.3 to 999999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 1, 2, 3 and 4: Progression Free Survival (PFS) per RECIST 1.1 based on investigator's assessment

| | |
|-----------------|--|
| End point title | Phase II Groups 1, 2, 3 and 4: Progression Free Survival (PFS) per RECIST 1.1 based on investigator's assessment ^[18] |
|-----------------|--|

End point description:

PFS is defined as time from date of first dose of study treatment to date of first documented disease progression determined by Investigator assessment in accordance to RECIST 1.1 or death due to any cause. The PFS distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, PFS is censored at the date of last adequate tumor assessment. PFS was assessed in Group 1, 2, 3 and 4 (Phase II)

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

End point timeframe:

From date of first dose to first documented disease progression or death, assessed up to approximately 4 years

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 1, 2 3 and 4

| End point values | Phase II-Group 2 | Phase II-Group 3 | Phase II-Group 4 | |
|----------------------------------|---------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 47 | 42 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 3.8 (3.7 to 999999) | 10.1 (7.6 to 13.8) | 10.9 (5.6 to 19.2) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Time to Response (TTR) per RECIST 1.1 based on investigator's assessment

| | |
|-----------------|--|
| End point title | Phase Ib: Time to Response (TTR) per RECIST 1.1 based on investigator's assessment ^[19] |
|-----------------|--|

End point description:

TTR is defined as the time from the date of the first dose to the date of first documented response (CR or PR) determined by Investigator assessment in accordance to RECIST 1.1. The TTR distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, duration was censored at the date of last adequate tumor assessment. TTR was assessed in Phase Ib participants.

CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

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

End point timeframe:

From the date of the first dose to the date of first documented response, up to approximately 5 years

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part-INC280 200mg BID/ EGF816 50mg QD | Phase IB part-INC280 200mg BID/ EGF816 100mg QD | Phase IB part-INC280 400mg BID/ EGF816 75mg QD | Phase IB part-INC280 400mg BID/ EGF816 100mg QD |
|----------------------------------|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 16 |
| Units: Months | | | | |
| median (confidence interval 95%) | 999999 (999999 to 999999) | 999999 (1.8 to 999999) | 999999 (1.7 to 999999) | 3.5 (1.6 to 999999) |

| End point values | Phase IB part-INC280 400mg BID/ EGF816 150mg QD | | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 4.5 (1.9 to | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 1, 2, 3 and 4: Time to Response (TTR) per RECIST 1.1 based on investigator's assessment

| | |
|-----------------|---|
| End point title | Phase II Groups 1, 2, 3 and 4: Time to Response (TTR) per RECIST 1.1 based on investigator's assessment ^[20] |
|-----------------|---|

End point description:

TTR is defined as the time from the date of the first dose to the date of first documented response (CR or PR) determined by Investigator assessment in accordance to RECIST 1.1. The TTR distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, duration was censored at the date of last adequate tumor assessment. TTR was assessed in Group 1, 2, 3 and 4 (Phase II)

CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

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

End point timeframe:

From the date of the first dose to the date of first documented response, up to approximately 4 years

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 1, 2 3 and 4

| End point values | Phase II-Group 1 | Phase II-Group 2 | Phase II-Group 3 | Phase II-Group 4 |
|----------------------------------|----------------------|------------------------|------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 52 | 3 | 47 | 42 |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999 (5.4 to 999999) | 999999 (1.8 to 999999) | 1.9 (1.8 to 5.9) | 999999 (3.6 to 999999) |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Duration of Response (DOR) per RECIST 1.1 based on investigator's assessment

| | |
|-----------------|--|
| End point title | Phase Ib: Duration of Response (DOR) per RECIST 1.1 based on investigator's assessment ^[21] |
|-----------------|--|

End point description:

DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression determined by Investigator assessment in accordance to RECIST 1.1 or death due to underlying cancer. The DOR distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, duration was censored at the date of last adequate tumor assessment. DOR was assessed in Phase Ib participants

CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

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

End point timeframe:

From date of first documented response to first documented disease progression or death, assessed up to approximately 5 years

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part-INC280 200mg BID/ EGF816 50mg QD | Phase IB part-INC280 200mg BID/ EGF816 100mg QD | Phase IB part-INC280 400mg BID/ EGF816 75mg QD | Phase IB part-INC280 400mg BID/ EGF816 100mg QD |
|----------------------------------|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[22] | 2 | 1 | 8 |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | 8.8 (5.6 to 999999) | 14.8 (-999999 to 999999) | 25.3 (3.6 to 47.9) |

Notes:

[22] - No participants had a documented response (CR or PR)

| End point values | Phase IB part-INC280 400mg BID/ EGF816 150mg QD | | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.0 (5.4 to 999999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 1, 2, 3 and 4: Duration of Response (DOR) per RECIST 1.1 based on investigator's assessment

| | |
|-----------------|---|
| End point title | Phase II Groups 1, 2, 3 and 4: Duration of Response (DOR) per RECIST 1.1 based on investigator's assessment ^[23] |
|-----------------|---|

End point description:

DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression determined by Investigator assessment in accordance to RECIST 1.1 or death due to underlying cancer. The DOR distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, duration was censored at the date of last adequate tumor assessment. DOR was assessed in Group 1, 2, 3 and 4 (Phase II)

CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

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

End point timeframe:

From date of first documented response to first documented disease progression or deaths, assessed up to approximately 4 years

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 1, 2 3 and 4

| End point values | Phase II-Group 1 | Phase II-Group 2 | Phase II-Group 3 | Phase II-Group 4 |
|----------------------------------|-------------------|--------------------------|--------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 16 | 1 | 29 | 18 |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.5 (3.7 to 10.8) | 12.0 (-999999 to 999999) | 11.6 (6.6 to 17.5) | 14.5 (9.2 to 999999) |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Disease Control Rate (DCR) per RECIST 1.1 based on investigator's assessment

| | |
|-----------------|--|
| End point title | Phase Ib: Disease Control Rate (DCR) per RECIST 1.1 based on investigator's assessment ^[24] |
|-----------------|--|

End point description:

DCR is defined as the percentage of participants with best overall response of CR, PR, or stable disease (SD) determined by Investigator assessment in accordance to RECIST 1.1. DCR was assessed in Phase Ib participants

CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters; SD= Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progression.

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

End point timeframe:

Up to approximately 5 years

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part-INC280 200mg BID/ EGF816 50mg QD | Phase IB part-INC280 200mg BID/ EGF816 100mg QD | Phase IB part-INC280 400mg BID/ EGF816 75mg QD | Phase IB part-INC280 400mg BID/ EGF816 100mg QD |
|-----------------------------------|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 16 |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 100 (39.8 to 100) | 60.0 (14.7 to 94.7) | 33.3 (0.8 to 90.6) | 62.5 (35.4 to 84.8) |

| | | | | |
|-----------------------------------|---|--|--|--|
| End point values | Phase IB part- INC280 400mg BID/ EGF816 150mg QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 80.0 (28.4 to 99.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Group 1, 2 3 and 4: Disease Control Rate (DCR) per RECIST 1.1 based on investigator's assessment

| | |
|-----------------|---|
| End point title | Phase II Group 1, 2 3 and 4: Disease Control Rate (DCR) per RECIST 1.1 based on investigator's assessment ^[25] |
|-----------------|---|

End point description:

DCR is defined as the percentage of participants with best overall response of CR, PR, or SD determined by Investigator assessment in accordance to RECIST 1.1. DCR was assessed in Group 1, 2, 3 and 4 (Phase II)

CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters; SD= Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progression.

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

End point timeframe:

Up to approximately 4 years

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 1, 2 3 and 4

| | | | | |
|-----------------------------------|------------------------|----------------------|------------------------|------------------------|
| End point values | Phase II- Group 1 | Phase II- Group 2 | Phase II- Group 3 | Phase II- Group 4 |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 52 | 3 | 47 | 42 |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 59.6 (45.1 to 73.0) | 100 (29.2 to 100) | 93.6 (82.5 to 98.7) | 81.0 (65.9 to 91.4) |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Overall Survival (OS)

| | |
|-----------------|---|
| End point title | Phase Ib: Overall Survival (OS) ^[26] |
|-----------------|---|

End point description:

OS is defined as the time from first dose of the study treatment to the date of death due to any cause. The OS distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant was not known to have died, survival was censored at the date of last contact. OS was assessed in Phase Ib participants

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

End point timeframe:

From date of first dose to death, assessed up to approximately 5 years

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part-INC280 200mg BID/ EGF816 50mg QD | Phase IB part-INC280 200mg BID/ EGF816 100mg QD | Phase IB part-INC280 400mg BID/ EGF816 75mg QD | Phase IB part-INC280 400mg BID/ EGF816 100mg QD |
|----------------------------------|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 16 |
| Units: Months | | | | |
| median (confidence interval 95%) | 10.1 (8.1 to 999999) | 56.5 (6.5 to 999999) | 7.0 (1.1 to 999999) | 17.2 (5.7 to 58.7) |

| End point values | Phase IB part-INC280 400mg BID/ EGF816 150mg QD | | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 31.5 (16.6 to 999999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 1, 2, 3 and 4: Overall Survival (OS)

| | |
|-----------------|--|
| End point title | Phase II Groups 1, 2, 3 and 4: Overall Survival (OS) ^[27] |
|-----------------|--|

End point description:

OS is defined as the time from first dose of the study treatment to the date of death due to any cause. The OS distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant was not known to have died, survival was censored at the date of last contact. OS was assessed in Group 1, 2, 3 and 4

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

End point timeframe:

From date of first dose to death, assessed up to approximately 4 years

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 1, 2, 3 and 4

| End point values | Phase II-Group 1 | Phase II-Group 2 | Phase II-Group 3 | Phase II-Group 4 |
|----------------------------------|---------------------|---------------------|---------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 52 | 3 | 47 | 42 |
| Units: Months | | | | |
| median (confidence interval 95%) | 18.8 (14.9 to 26.0) | 5.6 (3.7 to 999999) | 25.6 (18.8 to 33.0) | 28.9 (20.5 to 999999) |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Area under the plasma concentration versus time curve from time 0 to 12 hours (AUC0-12) of INC280

| | |
|-----------------|---|
| End point title | Phase Ib: Area under the plasma concentration versus time curve from time 0 to 12 hours (AUC0-12) of INC280 ^[28] |
|-----------------|---|

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods.

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

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part-INC280 200mg BID/ EGF816 50mg QD | Phase IB part-INC280 200mg BID/ EGF816 100mg QD | Phase IB part-INC280 400mg BID/ EGF816 75mg QD | Phase IB part-INC280 400mg BID/ EGF816 100mg QD |
|--|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 1 | 12 |
| Units: hours*nanogram/mililiter (hr*ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 3 / 5 / 1 / 12 / 3) | 12300 (± 4710) | 10500 (± 4320) | 38300 (± 999999) | 22200 (± 10700) |
| Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2) | 11600 (± 3400) | 11800 (± 3360) | 48800 (± 999999) | 28900 (± 12700) |
| Cycle 2 Day 1 (n= 3 / 5 / 0 / 9 / 2) | 11300 (± 4050) | 11100 (± 1770) | 999999 (± 999999) | 21600 (± 7370) |

| | | | | |
|------------------|----------------|--|--|--|
| End point values | Phase IB part- | | | |
|------------------|----------------|--|--|--|

| | | | | |
|--|---|--|--|--|
| | INC280 400mg BID/ EGF816 150mg QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: hours*nanogram/mililiter (hr*ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 3 / 5 / 1 / 12 / 3) | 23000 (± 11600) | | | |
| Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2) | 23000 (± 3440) | | | |
| Cycle 2 Day 1 (n= 3 / 5 / 0 / 9 / 2) | 24900 (± 5190) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Peak plasma concentration (Cmax) of INC280

| | |
|---|--|
| End point title | Phase Ib: Peak plasma concentration (Cmax) of INC280 ^[29] |
| End point description: Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods. | |
| End point type | Secondary |
| End point timeframe: Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days) | |
| Notes: [29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only applicable for Phase Ib arms | |

| End point values | Phase IB part- INC280 200mg BID/ EGF816 50mg QD | Phase IB part- INC280 200mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 75mg QD | Phase IB part- INC280 400mg BID/ EGF816 100mg QD |
|--|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 1 | 12 |
| Units: nanogram/mililiter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 4 / 5 / 1 / 12 / 3) | 3630 (± 588) | 2530 (± 1080) | 8000 (± 999999) | 5100 (± 2550) |
| Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2) | 3070 (± 1120) | 2840 (± 1350) | 12000 (± 999999) | 5780 (± 2640) |
| Cycle 2 Day 1 (N= 3 / 5 / 0 / 10 / 2) | 3590 (± 1620) | 2800 (± 797) | 999999 (± 999999) | 4830 (± 1390) |

| | | | | |
|------------------|---|--|--|--|
| End point values | Phase IB part- INC280 400mg BID/ EGF816 | | | |
|------------------|---|--|--|--|

| | | | | |
|--|-----------------|--|--|--|
| | 150mg QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: nanogram/mililiter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 4 / 5 / 1 / 12 / 3) | 5930 (± 1330) | | | |
| Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2) | 4350 (± 933) | | | |
| Cycle 2 Day 1 (N= 3 / 5 / 0 / 10 / 2) | 6370 (± 1060) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Time to reach maximum concentration (Tmax) of INC280

| | |
|-----------------|--|
| End point title | Phase Ib: Time to reach maximum concentration (Tmax) of INC280 ^[30] |
|-----------------|--|

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods. Actual time of sample collection was used (not the nominal time point as per scheduled assessment)

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

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part-INC280 200mg BID/ EGF816 50mg QD | Phase IB part-INC280 200mg BID/ EGF816 100mg QD | Phase IB part-INC280 400mg BID/ EGF816 75mg QD | Phase IB part-INC280 400mg BID/ EGF816 100mg QD |
|--|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 1 | 12 |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 1 (n= 4 / 5 / 1 / 12 / 3) | 1.07 (1.00 to 2.00) | 2.00 (1.00 to 4.00) | 2.00 (2.00 to 2.00) | 2.01 (1.00 to 7.67) |
| Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2) | 1.12 (1.03 to 2.05) | 2.00 (0.883 to 7.98) | 1.17 (1.17 to 1.17) | 1.97 (0.950 to 4.00) |
| Cycle 2 Day 1 (n= 3 / 5 / 0 / 10 / 2) | 1.00 (1.00 to 2.00) | 2.00 (1.00 to 3.83) | 999999 (999999 to 999999) | 1.94 (0.983 to 4.00) |

| | | | | |
|------------------|---|--|--|--|
| End point values | Phase IB part-INC280 400mg BID/ EGF816 150mg QD | | | |
|------------------|---|--|--|--|

| | | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 1 (n= 4 / 5 / 1 / 12 / 3) | 2.00 (1.02 to 2.13) | | | |
| Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2) | 1.50 (1.00 to 2.00) | | | |
| Cycle 2 Day 1 (n= 3 / 5 / 0 / 10 / 2) | 1.51 (1.02 to 2.00) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Area under the plasma concentration versus time curve from time 0 to 12 hours (AUC0-12) of INC280

| | |
|-----------------|--|
| End point title | Phase II Groups 3 and 4: Area under the plasma concentration versus time curve from time 0 to 12 hours (AUC0-12) of INC280 ^[31] |
|-----------------|--|

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods.

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

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 3 and 4

| End point values | Phase II-Group 3 | Phase II-Group 4 | | |
|--|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 15 | | |
| Units: hours*nanogram/mililiter (hr*ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 8 / 12) | 22000 (± 8000) | 16900 (± 7360) | | |
| Cycle 2 Day 1 (n= 8 / 15) | 19700 (± 11200) | 20500 (± 7440) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Peak plasma concentration (Cmax) of INC280

| | |
|-----------------|--|
| End point title | Phase II Groups 3 and 4: Peak plasma concentration (Cmax) of |
|-----------------|--|

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods.

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

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 3 and 4

| End point values | Phase II-Group 3 | Phase II-Group 4 | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 15 | | |
| Units: nanogram/mililiter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 8 / 12) | 4770 (± 1460) | 3420 (± 1550) | | |
| Cycle 2 Day 1 (n= 8 / 15) | 4360 (± 2060) | 3940 (± 1660) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Time to reach maximum concentration (Tmax) of INC280

| | |
|-----------------|---|
| End point title | Phase II Groups 3 and 4: Time to reach maximum concentration (Tmax) of INC280 ^[33] |
|-----------------|---|

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods. Actual time of sample collection was used (not the nominal time point as per scheduled assessment)

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

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 3 and 4

| End point values | Phase II-Group 3 | Phase II-Group 4 | | |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 15 | | |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 1 (n= 8 / 12) | 1.99 (1.00 to 4.00) | 2.08 (1.85 to 8.00) | | |

| | | | | |
|---------------------------|---------------------|---------------------|--|--|
| Cycle 2 Day 1 (n= 8 / 15) | 1.47 (1.00 to 7.08) | 3.82 (1.00 to 4.10) | | |
|---------------------------|---------------------|---------------------|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Area under the plasma concentration versus time curve from time 0 to 24 hours (AUC0-24) of EGF816

| | |
|-----------------|---|
| End point title | Phase Ib: Area under the plasma concentration versus time curve from time 0 to 24 hours (AUC0-24) of EGF816 ^[34] |
|-----------------|---|

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods.

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

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part-INC280 200mg BID/ EGF816 50mg QD | Phase IB part-INC280 200mg BID/ EGF816 100mg QD | Phase IB part-INC280 400mg BID/ EGF816 75mg QD | Phase IB part-INC280 400mg BID/ EGF816 100mg QD |
|--|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 13 |
| Units: hours*nanogram/mililiter (hr*ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 3 / 5 / 2 / 11 / 2) | 3920 (± 1450) | 5850 (± 4380) | 4010 (± 534) | 5930 (± 3600) |
| Cycle 1 Day 15 (n= 4 / 5 / 2 / 12 / 2) | 5200 (± 2010) | 9630 (± 4060) | 7330 (± 108) | 11100 (± 5340) |
| Cycle 2 Day 1 (n= 3 / 4 / 0 / 11 / 2) | 4080 (± 1130) | 7460 (± 2340) | 999999 (± 999999) | 10500 (± 7480) |

| End point values | Phase IB part-INC280 400mg BID/ EGF816 150mg QD | | | |
|--|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: hours*nanogram/mililiter (hr*ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 3 / 5 / 2 / 11 / 2) | 10500 (± 3400) | | | |

| | | | | |
|--|----------------|--|--|--|
| Cycle 1 Day 15 (n= 4 / 5 / 2 / 12 / 2) | 16400 (± 5670) | | | |
| Cycle 2 Day 1 (n= 3 / 4 / 0 / 11 / 2) | 11400 (± 2360) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Peak plasma concentration (Cmax) of EGF816

| | |
|-----------------|--|
| End point title | Phase Ib: Peak plasma concentration (Cmax) of EGF816 ^[35] |
|-----------------|--|

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods.

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

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase IB part-INC280 200mg BID/ EGF816 50mg QD | Phase IB part-INC280 200mg BID/ EGF816 100mg QD | Phase IB part-INC280 400mg BID/ EGF816 75mg QD | Phase IB part-INC280 400mg BID/ EGF816 100mg QD |
|--|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 13 |
| Units: nanogram/mililiter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 4 / 5 / 2 / 13 / 3) | 258 (± 104) | 465 (± 323) | 302 (± 8.49) | 381 (± 231) |
| Cycle 1 Day 15 (n= 3 / 5 / 3 / 12 / 2) | 361 (± 165) | 677 (± 321) | 517 (± 180) | 595 (± 261) |
| Cycle 2 Day 1 (n= 3 / 5 / 0 / 11 / 2) | 269 (± 90.8) | 583 (± 261) | 999999 (± 999999) | 604 (± 365) |

| End point values | Phase IB part-INC280 400mg BID/ EGF816 150mg QD | | | |
|--|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: nanogram/mililiter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 4 / 5 / 2 / 13 / 3) | 777 (± 281) | | | |
| Cycle 1 Day 15 (n= 3 / 5 / 3 / 12 / 2) | 1010 (± 354) | | | |
| Cycle 2 Day 1 (n= 3 / 5 / 0 / 11 / 2) | 814 (± 137) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Time to reach maximum concentration (Tmax) of EGF816

| | |
|-----------------|--|
| End point title | Phase Ib: Time to reach maximum concentration (Tmax) of EGF816 ^[36] |
|-----------------|--|

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods. Actual time of sample collection was used (not the nominal time point as per scheduled assessment)

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

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase Ib arms

| End point values | Phase Ib part-INC280 200mg BID/ EGF816 50mg QD | Phase Ib part-INC280 200mg BID/ EGF816 100mg QD | Phase Ib part-INC280 400mg BID/ EGF816 75mg QD | Phase Ib part-INC280 400mg BID/ EGF816 100mg QD |
|--|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 13 |
| Units: Hours (hr) | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 1 (n= 4 / 5 / 2 / 13 / 3) | 3.03 (1.08 to 4.02) | 3.90 (2.00 to 4.00) | 3.00 (2.00 to 4.00) | 4.00 (2.00 to 8.99) |
| Cycle 1 Day 15 (n= 3 / 5 / 3 / 12 / 2) | 2.07 (2.00 to 4.05) | 3.95 (2.00 to 4.00) | 4.00 (2.17 to 4.05) | 5.90 (2.17 to 11.9) |
| Cycle 2 Day 1 (n= 3 / 5 / 0 / 11 / 2) | 4.00 (3.95 to 4.00) | 4.00 (2.00 to 4.00) | 999999 (999999 to 999999) | 4.00 (1.98 to 7.00) |

| End point values | Phase Ib part-INC280 400mg BID/ EGF816 150mg QD | | | |
|---------------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Hours (hr) | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 1 (n= 4 / 5 / 2 / 13 / 3) | 4.00 (2.03 to 4.02) | | | |

| | | | | |
|--|---------------------|--|--|--|
| Cycle 1 Day 15 (n= 3 / 5 / 3 / 12 / 2) | 3.93 (3.83 to 4.02) | | | |
| Cycle 2 Day 1 (n= 3 / 5 / 0 / 11 / 2) | 3.05 (2.10 to 4.00) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Area under the plasma concentration versus time curve from time 0 to 24 hours (AUC0-24) of EGF816

| | |
|-----------------|--|
| End point title | Phase II Groups 3 and 4: Area under the plasma concentration versus time curve from time 0 to 24 hours (AUC0-24) of EGF816 ^[37] |
|-----------------|--|

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods.

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

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 3 and 4

| End point values | Phase II-Group 3 | Phase II-Group 4 | | |
|--|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 15 | | |
| Units: hours*nanogram/mililiter (hr*ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 6 / 12) | 6390 (± 2460) | 3420 (± 1700) | | |
| Cycle 2 Day 1 (n= 5 / 15) | 11100 (± 2000) | 7670 (± 3330) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Peak plasma concentration (Cmax) of EGF816

| | |
|-----------------|---|
| End point title | Phase II Groups 3 and 4: Peak plasma concentration (Cmax) of EGF816 ^[38] |
|-----------------|---|

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods.

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

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1 and

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 3 and 4

| End point values | Phase II-Group 3 | Phase II-Group 4 | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 15 | | |
| Units: nanogram/mililiter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 6 / 12) | 448 (± 184) | 239 (± 107) | | |
| Cycle 2 Day 1 (n= 6 / 15) | 658 (± 117) | 447 (± 175) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Time to reach maximum concentration (Tmax) of EGF816

| | |
|-----------------|---|
| End point title | Phase II Groups 3 and 4: Time to reach maximum concentration (Tmax) of EGF816 ^[39] |
|-----------------|---|

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods. Actual time of sample collection was used (not the nominal time point as per scheduled assessment)

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

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Phase II Groups 3 and 4

| End point values | Phase II-Group 3 | Phase II-Group 4 | | |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 15 | | |
| Units: Hours (hr) | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 1 (n= 6 / 12) | 4.00 (1.12 to 8.00) | 4.00 (1.85 to 8.00) | | |
| Cycle 2 Day 1 (n= 6 / 15) | 4.00 (2.00 to 4.13) | 4.00 (3.82 to 8.00) | | |

Statistical analyses

Post-hoc: All collected deaths

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

| |
|------------------------|
| End point description: |
|------------------------|

On-treatment deaths were collected from first dose of study medication to 30 days after the last dose of study medication for a maximum duration of approximately 5 years (Phase Ib) and 4 years (Phase II).

Post-treatment deaths were collected after 30 days post-treatment, for a maximum duration of approximately 5 years (Phase Ib) and 4 years (Phase II).

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

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

| |
|----------------------|
| End point timeframe: |
|----------------------|

On-treatment: up to approximately 5 years (Phase Ib) and 4 years (Phase II). Post-treatment: Up to approximately 5 years (Phase Ib) and 4 years (Phase II).

| End point values | Phase IB part- INC280 200mg BID/ EGF816 50mg QD | Phase IB part- INC280 200mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 75mg QD | Phase IB part- INC280 400mg BID/ EGF816 100mg QD |
|-----------------------------|--|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 16 |
| Units: Participants | | | | |
| On-treatment deaths | 0 | 0 | 1 | 2 |
| Post-treatment deaths | 4 | 3 | 2 | 9 |
| All deaths | 4 | 3 | 3 | 11 |

| End point values | Phase IB part- INC280 400mg BID/ EGF816 150mg QD | Phase II- Group 1 | Phase II- Group 2 | Phase II- Group 3 |
|-----------------------------|---|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 52 | 3 | 47 |
| Units: Participants | | | | |
| On-treatment deaths | 0 | 9 | 2 | 5 |
| Post-treatment deaths | 3 | 26 | 1 | 25 |
| All deaths | 3 | 35 | 3 | 30 |

| End point values | Phase II- Group 4 | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 42 | | | |
| Units: Participants | | | | |
| On-treatment deaths | 1 | | | |
| Post-treatment deaths | 22 | | | |
| All deaths | 23 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment until last dose of study treatment plus 30 days, up to approximately 5 years (Phase Ib) and 4 years (Phase II).

Adverse event reporting additional description:

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

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Phase IB part- INC280 200mg BID/ EGF816 50mg QD |
|-----------------------|---|

Reporting group description:

Combination of INC280 200mg twice daily (BID) and EGF816 50mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

| | |
|-----------------------|--|
| Reporting group title | Phase IB part- INC280 200mg BID/ EGF816 100mg QD |
|-----------------------|--|

Reporting group description:

Combination of INC280 200mg twice daily (BID) and EGF816 100mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

| | |
|-----------------------|---|
| Reporting group title | Phase IB part- INC280 400mg BID/ EGF816 75mg QD |
|-----------------------|---|

Reporting group description:

Combination of INC280 400mg twice daily (BID) and EGF816 75mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

| | |
|-----------------------|--|
| Reporting group title | Phase IB part- INC280 400mg BID/ EGF816 100mg QD |
|-----------------------|--|

Reporting group description:

Combination of INC280 400mg twice daily (BID) and EGF816 100mg once daily (QD) in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

| | |
|-----------------------|--|
| Reporting group title | Phase IB part- INC280 400mg BID/ EGF816 150mg QD |
|-----------------------|--|

Reporting group description:

Combination of INC280 400mg twice daily (BID) and EGF816 150mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

| | |
|-----------------------|-------------------|
| Reporting group title | Phase II- Group 2 |
|-----------------------|-------------------|

Reporting group description:

NSCLC participants harboring T790M mutation in de novo setting, irrespective of the activating mutation status who received none to 2 lines of systemic antineoplastic therapy prior to study entry, but no therapy known to inhibit EGFR. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

| | |
|-----------------------|-------------------|
| Reporting group title | Phase II- Group 1 |
|-----------------------|-------------------|

Reporting group description:

NSCLC participants with previously documented activating EGFR mutation, with any T790M and MET dysregulation status, who received 1 to 3 lines of systemic antineoplastic therapy prior to study entry including one line maximum of 1st or 2nd generation EGFR TKI. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

| | |
|-----------------------|-------------------|
| Reporting group title | Phase II- Group 4 |
|-----------------------|-------------------|

Reporting group description:

NSCLC participants with previously documented EGFR activating mutations and any T790M and MET status who received none to 2 prior lines of systemic antineoplastic therapy prior to study entry. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fed state.

| | |
|-----------------------|-------------------|
| Reporting group title | Phase II- Group 3 |
|-----------------------|-------------------|

Reporting group description:

NSCLC participants with previously documented EGFR activating mutation, T790M negative, and any MET status who never received any prior line of systemic antineoplastic therapy. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

| | |
|-----------------------|------------------|
| Reporting group title | All Participants |
|-----------------------|------------------|

Reporting group description:

| |
|------------------|
| All Participants |
|------------------|

| Serious adverse events | Phase IB part- INC280 200mg BID/ EGF816 50mg QD | Phase IB part- INC280 200mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 75mg QD |
|---|---|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | 2 / 5 (40.00%) | 3 / 3 (100.00%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour associated fever | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |

| | | | |
|--|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |

| | | | |
|---|----------------|---------------|----------------|
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity pneumonitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|---------------|----------------|
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Apathy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|---------------|---------------|
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|---------------|---------------|
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|---------------|----------------|
| Epilepsy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive hydrocephalus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neurological decompensation | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Speech disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |

| | | | |
|---|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wernicke's encephalopathy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|---------------|---------------|
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Purpura | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash maculo-papular | | | |

| | | | |
|---|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|----------------|---------------|
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Empyema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster meningitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis | | | |

| | | | |
|---|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis aseptic | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia chlamydial | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|---|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |

| | | | |
|---|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Phase IB part- INC280 400mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 150mg QD | Phase II- Group 2 |
|---|--|--|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 16 (68.75%) | 4 / 5 (80.00%) | 2 / 3 (66.67%) |
| number of deaths (all causes) | 2 | 0 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |

| | | | |
|--|----------------|---------------|---------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |

| | | | |
|---|----------------|----------------|---------------|
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Aspiration | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity pneumonitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Psychiatric disorders | | | |
| Apathy | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|---------------|---------------|
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|---------------|---------------|
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|---------------|
| Epilepsy | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive hydrocephalus | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neurological decompensation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Speech disorder | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |

| | | | |
|---|----------------|---------------|---------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wernicke's encephalopathy | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|---------------|
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Purpura | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash maculo-papular | | | |

| | | | |
|---|----------------|----------------|---------------|
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|--|--|---|
| Infections and infestations Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 16 (6.25%) 1 / 1 0 / 0 | 1 / 5 (20.00%) 1 / 1 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 |
| Empyema subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 16 (6.25%) 0 / 1 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 |
| Enterocolitis infectious subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 16 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 |
| Erysipelas subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 16 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 |
| Herpes zoster subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 16 (6.25%) 1 / 1 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 |
| Herpes zoster meningitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 16 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 |
| Influenza subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 16 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 |
| Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 16 (6.25%) 0 / 1 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 |
| Meningitis | | | |

| | | | |
|---|----------------|---------------|---------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis aseptic | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia chlamydial | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|---|-----------------|---------------|---------------|
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |

| | | | |
|---|----------------|---------------|---------------|
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Phase II- Group 1 | Phase II- Group 4 | Phase II- Group 3 |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 29 / 52 (55.77%) | 26 / 42 (61.90%) | 33 / 47 (70.21%) |
| number of deaths (all causes) | 9 | 1 | 5 |
| number of deaths resulting from adverse events | 1 | 0 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 2 / 42 (4.76%) | 4 / 47 (8.51%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 2 / 42 (4.76%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity pneumonitis | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 3 / 42 (7.14%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 3 / 42 (7.14%) | 4 / 47 (8.51%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | 2 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| 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 | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| 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 failure | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 42 (0.00%) | 3 / 47 (6.38%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Psychiatric disorders | | | |
| Apathy | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Epilepsy | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 3 / 47 (6.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive hydrocephalus | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neurological decompensation | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Speech disorder | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wernicke's encephalopathy | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Purpura | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash maculo-papular | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 4 / 52 (7.69%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 3 / 47 (6.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 3 / 42 (7.14%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Empyema | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster meningitis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis aseptic | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural infection | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 52 (9.62%) | 4 / 42 (9.52%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia chlamydial | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Soft tissue infection | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | All Participants | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 113 / 177 (63.84%) | | |
| number of deaths (all causes) | 20 | | |
| number of deaths resulting from adverse events | 2 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour associated fever | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 177 (4.52%) | | |
| occurrences causally related to treatment / all | 4 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |

| | | | |
|---|------------------|--|--|
| Anaphylactic shock | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Aspiration | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 177 (4.52%) | | |
| occurrences causally related to treatment / all | 1 / 9 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypersensitivity pneumonitis | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences causally related to treatment / all | 5 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 10 / 177 (5.65%) | | |
| occurrences causally related to treatment / all | 3 / 12 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Pneumonitis | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 6 / 177 (3.39%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Psychiatric disorders | | | |
| Apathy | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Aspartate aminotransferase increased | | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood bilirubin increased | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood creatinine increased | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ejection fraction decreased | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Neutrophil count decreased | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Weight decreased | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Injury, poisoning and procedural complications | | | | |
| Procedural pain | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fall | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | |
|---|-----------------|--|--|
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Epilepsy | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Headache | | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hydrocephalus | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypertensive hydrocephalus | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Loss of consciousness | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neurological decompensation | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Seizure | | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | | |
| occurrences causally related to treatment / all | 0 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Speech disorder | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal cord compression | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tremor | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wernicke's encephalopathy | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Hypoacusis | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hiatus hernia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences causally related to treatment / all | 3 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Purpura | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash macular | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash maculo-papular | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences causally related to treatment / all | 7 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urticaria | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------------------------|--|--|
| Infections and infestations Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 9 / 177 (5.08%) 5 / 12 0 / 0 | | |
| Empyema subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 177 (0.56%) 0 / 1 0 / 0 | | |
| Enterocolitis infectious subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 177 (0.56%) 0 / 1 0 / 0 | | |
| Erysipelas subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 177 (1.13%) 3 / 3 0 / 0 | | |
| Herpes zoster subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 177 (0.56%) 1 / 1 0 / 0 | | |
| Herpes zoster meningitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 177 (0.56%) 0 / 1 0 / 0 | | |
| Influenza subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 177 (1.13%) 0 / 2 0 / 0 | | |
| Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 177 (0.56%) 0 / 1 0 / 0 | | |
| Meningitis | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Meningitis aseptic | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Necrotising fasciitis | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural infection | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 10 / 177 (5.65%) | | | |
| occurrences causally related to treatment / all | 0 / 10 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pneumonia aspiration | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia chlamydial | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Soft tissue infection | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Phase IB part- INC280 200mg BID/ EGF816 50mg QD | Phase IB part- INC280 200mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 75mg QD |
|---|---|--|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | 5 / 5 (100.00%) | 3 / 3 (100.00%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pallor | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 3 | 2 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chills | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Face oedema | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 5 (0.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 3 | 0 | 3 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 5 (20.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 3 | 5 | 2 |
| Pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Immune system disorders | | | |
| Anaphylactoid reaction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Reproductive system and breast disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Perineal pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Prostatomegaly | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal pruritus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 5 (40.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 1 | 2 | 2 |
| Dry throat | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 1 | 1 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoxia | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal discomfort | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|----------------|----------------|----------------|
| Depression | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Amylase increased | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 4 | 5 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood creatine increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 6 | 1 |
| Blood creatinine increased | | | |

| | | | |
|-------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 4 (50.00%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood uric acid increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---------------------|--------------------|---------------------|
| Protein total decreased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Weight increased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Traumatic haematoma subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Nervous system disorders Amnesia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 2 |
| Dysaesthesia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |

| | | | |
|--------------------------------------|---------------|----------------|----------------|
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Leukopenia | | | |

| | | | |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 1 | 3 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 2 | 4 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 3 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Deafness transitory | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Eye pruritus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye swelling | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eyelid oedema | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Vitreous floaters subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Abdominal distension subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 3 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 1 / 5 (20.00%) 1 | 1 / 3 (33.33%) 1 |
| Dry mouth subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Dysphagia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |

| | | | |
|--|---------------------|--------------------|---------------------|
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Lip blister subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Lip dry subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Mouth ulceration subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Nausea subjects affected / exposed occurrences (all) | 2 / 4 (50.00%) 2 | 0 / 5 (0.00%) 0 | 2 / 3 (66.67%) 3 |
| Odynophagia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Stomatitis subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Toothache subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Alopecia | | | |

| | | | |
|--|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eczema | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail discolouration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Rash papular subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Rash pruritic subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Skin hyperpigmentation subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Chronic kidney disease subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypertonic bladder subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Renal failure subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 2 / 4 (50.00%) 2 | 1 / 5 (20.00%) 2 | 1 / 3 (33.33%) 2 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Bone pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flank pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Joint stiffness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 0 | 1 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tendon pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |

| | | | |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |

| | | | |
|------------------------------------|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinobronchitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Hyperlipasaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|--------------------|---------------------|---------------------|
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 5 (20.00%) 1 | 1 / 3 (33.33%) 1 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 2 |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypophagia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 3 |
| Hypoproteinaemia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 3 |

| Non-serious adverse events | Phase IB part- INC280 400mg BID/ EGF816 100mg QD | Phase IB part- INC280 400mg BID/ EGF816 150mg QD | Phase II- Group 2 |
|--|--|--|--------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 16 / 16 (100.00%) | 5 / 5 (100.00%) | 3 / 3 (100.00%) |
| Vascular disorders Hot flush subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypotension | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 2 | 1 |
| Pallor | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 5 | 0 | 2 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Chills | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Face oedema | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 6 / 16 (37.50%) | 2 / 5 (40.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 10 | 2 | 3 |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Oedema peripheral | | | |

| | | | |
|--|-----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 8 / 16 (50.00%) 17 | 4 / 5 (80.00%) 8 | 3 / 3 (100.00%) 3 |
| Pain subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 3 | 1 / 5 (20.00%) 2 | 0 / 3 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 7 / 16 (43.75%) 11 | 3 / 5 (60.00%) 3 | 0 / 3 (0.00%) 0 |
| Immune system disorders Anaphylactoid reaction subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Perineal pain subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Prostatomegaly subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Vulvovaginal pruritus subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 5 / 16 (31.25%) 10 | 1 / 5 (20.00%) 1 | 1 / 3 (33.33%) 3 |
| Dry throat | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 8 | 1 | 1 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal discomfort | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Nasal dryness | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Productive cough | | | |

| | | | |
|--|-----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 3 / 16 (18.75%) 6 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Throat irritation subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Confusional state subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Depression subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 5 (20.00%) 2 | 0 / 3 (0.00%) 0 |
| Sleep disorder subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 2 | 2 / 5 (40.00%) 3 | 2 / 3 (66.67%) 2 |
| Amylase increased subjects affected / exposed occurrences (all) | 8 / 16 (50.00%) 13 | 2 / 5 (40.00%) 2 | 1 / 3 (33.33%) 3 |
| Aspartate aminotransferase increased | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 5 (20.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 2 | 2 | 2 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 8 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatine increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 8 / 16 (50.00%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 12 | 7 | 4 |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood uric acid increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|----------------------|---------------------|--------------------|
| C-reactive protein increased subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Electrocardiogram QT prolonged subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 3 | 1 / 5 (20.00%) 2 | 0 / 3 (0.00%) 0 |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Lipase increased subjects affected / exposed occurrences (all) | 4 / 16 (25.00%) 6 | 1 / 5 (20.00%) 2 | 0 / 3 (0.00%) 0 |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 6 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Protein total decreased subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 3 / 16 (18.75%) 3 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Weight increased subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 2 | 2 / 5 (40.00%) 2 | 0 / 3 (0.00%) 0 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 2 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural pain subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Traumatic haematoma | | | |

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|--|---------------------|---------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 7 | 1 | 0 |
| Dysaesthesia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Headache | | | |
| subjects affected / exposed | 7 / 16 (43.75%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 12 | 0 | 1 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Lethargy | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Neuropathy peripheral | | | |

| | | | |
|--------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 2 |
| Syncope | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 2 | 2 | 2 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Deafness transitory | | | |

| | | | |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hypoacusis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Eye pruritus | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye swelling | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eyelid oedema | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitreous floaters | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |

| | | | |
|----------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 2 / 5 (40.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 11 | 2 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 16 (37.50%) | 2 / 5 (40.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 18 | 3 | 2 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Lip blister | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Lip dry | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 11 / 16 (68.75%) | 5 / 5 (100.00%) | 3 / 3 (100.00%) |
| occurrences (all) | 27 | 5 | 3 |
| Odynophagia | | | |

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|--|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 8 | 3 | 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 6 / 16 (37.50%) | 3 / 5 (60.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 20 | 6 | 1 |
| Hepatobiliary disorders | | | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 7 | 4 | 0 |
| Eczema | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ingrowing nail | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nail discolouration | | | |

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| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 6 | 2 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 4 / 5 (80.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 5 | 4 | 1 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash pruritic | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

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| subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Chronic kidney disease subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypertonic bladder subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Renal failure subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 3 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Bone pain subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Flank pain subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Joint stiffness subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 3 | 2 / 5 (40.00%) 2 | 0 / 3 (0.00%) 0 |
| Muscular weakness | | | |

| | | | |
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| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 3 / 5 (60.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 6 | 0 |
| Tendon pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
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| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 2 / 5 (40.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 6 | 3 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Sinobronchitis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|------------------------|---------------------|---------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 16 (25.00%) 5 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Viral infection subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 10 / 16 (62.50%) 17 | 1 / 5 (20.00%) 2 | 1 / 3 (33.33%) 1 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 2 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hyperlipasaemia subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 2 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 5 / 16 (31.25%) 8 | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 2 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 5 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 3 | 1 / 5 (20.00%) 1 | 1 / 3 (33.33%) 1 |
| Hypomagnesaemia | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 3 / 16 (18.75%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 16 | 1 | 1 |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |
| Hypophagia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 5 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 15 | 1 | 0 |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| Non-serious adverse events | Phase II- Group 1 | Phase II- Group 4 | Phase II- Group 3 |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 51 / 52 (98.08%) | 42 / 42 (100.00%) | 47 / 47 (100.00%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 4 / 47 (8.51%) |
| occurrences (all) | 1 | 2 | 5 |
| Pallor | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 6 / 52 (11.54%) | 10 / 42 (23.81%) | 18 / 47 (38.30%) |
| occurrences (all) | 12 | 14 | 22 |
| Chest pain | | | |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chills | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 0 / 42 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 3 | 0 | 3 |
| Face oedema | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 1 / 42 (2.38%) | 2 / 47 (4.26%) |
| occurrences (all) | 2 | 1 | 2 |
| Fatigue | | | |
| subjects affected / exposed | 14 / 52 (26.92%) | 9 / 42 (21.43%) | 9 / 47 (19.15%) |
| occurrences (all) | 15 | 11 | 10 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 5 / 42 (11.90%) | 2 / 47 (4.26%) |
| occurrences (all) | 4 | 8 | 3 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 8 / 52 (15.38%) | 6 / 42 (14.29%) | 6 / 47 (12.77%) |
| occurrences (all) | 9 | 6 | 8 |
| Oedema peripheral | | | |
| subjects affected / exposed | 27 / 52 (51.92%) | 26 / 42 (61.90%) | 31 / 47 (65.96%) |
| occurrences (all) | 53 | 42 | 93 |
| Pain | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 1 / 42 (2.38%) | 2 / 47 (4.26%) |
| occurrences (all) | 3 | 1 | 3 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 3 / 42 (7.14%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 4 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 52 (15.38%) | 12 / 42 (28.57%) | 11 / 47 (23.40%) |
| occurrences (all) | 12 | 14 | 13 |
| Immune system disorders | | | |
| Anaphylactoid reaction | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|------------------------|------------------------|------------------------|
| Hypersensitivity subjects affected / exposed occurrences (all) | 2 / 52 (3.85%) 3 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Reproductive system and breast disorders | | | |
| Pelvic pain subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Perineal pain subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Prostatomegaly subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Vulvovaginal pruritus subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 10 / 52 (19.23%) 20 | 14 / 42 (33.33%) 23 | 11 / 47 (23.40%) 13 |
| Dry throat subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Dysphonia subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 1 / 42 (2.38%) 1 | 1 / 47 (2.13%) 1 |
| Dyspnoea subjects affected / exposed occurrences (all) | 11 / 52 (21.15%) 14 | 7 / 42 (16.67%) 7 | 13 / 47 (27.66%) 13 |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 0 / 42 (0.00%) 0 | 4 / 47 (8.51%) 4 |
| Haemoptysis | | | |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 52 (1.92%) | 2 / 42 (4.76%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Hypoxia | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Nasal discomfort | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 5 / 42 (11.90%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 5 | 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 3 / 42 (7.14%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 3 | 2 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 0 | 5 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 5 / 42 (11.90%) | 2 / 47 (4.26%) |
| occurrences (all) | 3 | 5 | 2 |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 42 (0.00%) | 4 / 47 (8.51%) |
| occurrences (all) | 2 | 0 | 4 |

| | | | |
|--|------------------|------------------|------------------|
| Confusional state | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 0 | 2 |
| Depression | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 4 / 42 (9.52%) | 3 / 47 (6.38%) |
| occurrences (all) | 4 | 5 | 3 |
| Sleep disorder | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 7 / 52 (13.46%) | 13 / 42 (30.95%) | 13 / 47 (27.66%) |
| occurrences (all) | 7 | 17 | 19 |
| Amylase increased | | | |
| subjects affected / exposed | 11 / 52 (21.15%) | 7 / 42 (16.67%) | 11 / 47 (23.40%) |
| occurrences (all) | 35 | 17 | 23 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 11 / 42 (26.19%) | 13 / 47 (27.66%) |
| occurrences (all) | 4 | 15 | 20 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 1 | 1 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 2 / 42 (4.76%) | 6 / 47 (12.77%) |
| occurrences (all) | 1 | 2 | 10 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 3 / 47 (6.38%) |
| occurrences (all) | 2 | 1 | 6 |
| Blood creatine increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood creatine phosphokinase increased | | | |

| | | | |
|-------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 5 / 52 (9.62%) | 6 / 42 (14.29%) | 5 / 47 (10.64%) |
| occurrences (all) | 12 | 10 | 6 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 10 / 52 (19.23%) | 15 / 42 (35.71%) | 16 / 47 (34.04%) |
| occurrences (all) | 14 | 35 | 30 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 2 / 42 (4.76%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 2 | 1 |
| Blood uric acid increased | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 3 / 42 (7.14%) | 1 / 47 (2.13%) |
| occurrences (all) | 2 | 9 | 1 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 5 / 42 (11.90%) | 5 / 47 (10.64%) |
| occurrences (all) | 2 | 9 | 6 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 12 / 52 (23.08%) | 8 / 42 (19.05%) | 7 / 47 (14.89%) |
| occurrences (all) | 40 | 11 | 19 |

| | | | |
|---|-----------------------|------------------------|------------------------|
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 1 / 42 (2.38%) 1 | 0 / 47 (0.00%) 0 |
| Protein total decreased subjects affected / exposed occurrences (all) | 4 / 52 (7.69%) 4 | 3 / 42 (7.14%) 3 | 0 / 47 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 2 / 42 (4.76%) 2 | 1 / 47 (2.13%) 1 |
| Weight increased subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 2 / 42 (4.76%) 2 | 4 / 47 (8.51%) 4 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 2 / 47 (4.26%) 2 |
| Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 47 (2.13%) 1 |
| Traumatic haematoma subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 47 (2.13%) 1 |
| Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 1 / 42 (2.38%) 1 | 0 / 47 (0.00%) 0 |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 1 / 42 (2.38%) 1 | 0 / 47 (0.00%) 0 |
| Nervous system disorders Amnesia subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 47 (2.13%) 1 |
| Dizziness subjects affected / exposed occurrences (all) | 9 / 52 (17.31%) 10 | 10 / 42 (23.81%) 13 | 11 / 47 (23.40%) 12 |

| | | | |
|--------------------------------------|-----------------|------------------|------------------|
| Dysaesthesia | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 4 / 47 (8.51%) |
| occurrences (all) | 0 | 1 | 4 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 7 / 52 (13.46%) | 12 / 42 (28.57%) | 17 / 47 (36.17%) |
| occurrences (all) | 8 | 14 | 23 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 2 / 42 (4.76%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 2 | 3 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 1 | 1 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 1 | 4 |
| Syncope | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 9 / 52 (17.31%) | 4 / 42 (9.52%) | 11 / 47 (23.40%) |
| occurrences (all) | 10 | 4 | 17 |
| Febrile neutropenia | | | |

| | | | |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 0 | 2 |
| Lymphopenia | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences (all) | 4 | 3 | 2 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 2 / 42 (4.76%) | 3 / 47 (6.38%) |
| occurrences (all) | 4 | 2 | 3 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 0 | 2 |
| Deafness transitory | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoacusis | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 3 / 42 (7.14%) | 3 / 47 (6.38%) |
| occurrences (all) | 2 | 3 | 3 |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 6 / 47 (12.77%) |
| occurrences (all) | 1 | 0 | 6 |
| Eye disorders | | | |
| Eye pruritus | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 1 | 3 |
| Eye swelling | | | |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitreous floaters | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 3 / 42 (7.14%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 4 / 42 (9.52%) | 7 / 47 (14.89%) |
| occurrences (all) | 1 | 4 | 7 |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 2 / 42 (4.76%) | 5 / 47 (10.64%) |
| occurrences (all) | 6 | 3 | 5 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 7 / 42 (16.67%) | 6 / 47 (12.77%) |
| occurrences (all) | 4 | 7 | 7 |
| Constipation | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 8 / 42 (19.05%) | 6 / 47 (12.77%) |
| occurrences (all) | 6 | 9 | 9 |
| Diarrhoea | | | |
| subjects affected / exposed | 20 / 52 (38.46%) | 20 / 42 (47.62%) | 26 / 47 (55.32%) |
| occurrences (all) | 39 | 30 | 37 |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 3 / 42 (7.14%) | 1 / 47 (2.13%) |
| occurrences (all) | 2 | 3 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 10 / 52 (19.23%) | 6 / 42 (14.29%) | 9 / 47 (19.15%) |
| occurrences (all) | 11 | 6 | 9 |

| | | | |
|--|------------------|------------------|------------------|
| Dysphagia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 3 / 42 (7.14%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 3 | 2 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 6 / 42 (14.29%) | 2 / 47 (4.26%) |
| occurrences (all) | 2 | 7 | 2 |
| Lip blister | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lip dry | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 4 / 42 (9.52%) | 4 / 47 (8.51%) |
| occurrences (all) | 0 | 4 | 4 |
| Nausea | | | |
| subjects affected / exposed | 28 / 52 (53.85%) | 19 / 42 (45.24%) | 27 / 47 (57.45%) |
| occurrences (all) | 41 | 31 | 38 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 1 | 1 |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 52 (9.62%) | 3 / 42 (7.14%) | 12 / 47 (25.53%) |
| occurrences (all) | 5 | 13 | 20 |
| Toothache | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 0 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 20 / 52 (38.46%) | 11 / 42 (26.19%) | 22 / 47 (46.81%) |
| occurrences (all) | 33 | 12 | 33 |
| Hepatobiliary disorders | | | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 42 (2.38%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 1 | 3 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|------------------|------------------|
| Acne | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 0 | 5 |
| Alopecia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 4 / 47 (8.51%) |
| occurrences (all) | 0 | 0 | 4 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 4 / 42 (9.52%) | 10 / 47 (21.28%) |
| occurrences (all) | 3 | 5 | 11 |
| Dry skin | | | |
| subjects affected / exposed | 5 / 52 (9.62%) | 5 / 42 (11.90%) | 7 / 47 (14.89%) |
| occurrences (all) | 5 | 5 | 11 |
| Eczema | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 6 / 42 (14.29%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 8 | 1 |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Nail discolouration | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 6 / 52 (11.54%) | 14 / 42 (33.33%) | 9 / 47 (19.15%) |
| occurrences (all) | 8 | 19 | 14 |
| Rash | | | |
| subjects affected / exposed | 7 / 52 (13.46%) | 9 / 42 (21.43%) | 11 / 47 (23.40%) |
| occurrences (all) | 8 | 10 | 13 |
| Rash macular | | | |

| | | | |
|--|------------------------|-----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 1 / 42 (2.38%) 1 | 3 / 47 (6.38%) 4 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 10 / 52 (19.23%) 10 | 9 / 42 (21.43%) 13 | 14 / 47 (29.79%) 21 |
| Rash papular subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 2 / 42 (4.76%) 3 | 2 / 47 (4.26%) 2 |
| Rash pruritic subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 1 / 42 (2.38%) 1 | 3 / 47 (6.38%) 4 |
| Skin hyperpigmentation subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 47 (2.13%) 1 |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 2 / 42 (4.76%) 2 | 2 / 47 (4.26%) 2 |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Chronic kidney disease subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Hypertonic bladder subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Renal failure subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 0 / 42 (0.00%) 0 | 1 / 47 (2.13%) 1 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|----------------|------------------|------------------|
| Arthralgia | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 6 / 42 (14.29%) | 10 / 47 (21.28%) |
| occurrences (all) | 3 | 6 | 13 |
| Back pain | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 8 / 42 (19.05%) | 7 / 47 (14.89%) |
| occurrences (all) | 2 | 9 | 8 |
| Bone pain | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 1 / 42 (2.38%) | 3 / 47 (6.38%) |
| occurrences (all) | 2 | 1 | 8 |
| Flank pain | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| Joint stiffness | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 14 / 42 (33.33%) | 12 / 47 (25.53%) |
| occurrences (all) | 4 | 19 | 15 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 2 / 42 (4.76%) | 3 / 47 (6.38%) |
| occurrences (all) | 2 | 2 | 4 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 4 / 47 (8.51%) |
| occurrences (all) | 0 | 0 | 4 |
| Myalgia | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 42 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 3 | 0 | 3 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 7 / 42 (16.67%) | 7 / 47 (14.89%) |
| occurrences (all) | 4 | 8 | 8 |

| | | | |
|---|---------------------|----------------------|----------------------|
| Tendon pain subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 2 / 52 (3.85%) 2 | 2 / 42 (4.76%) 2 | 2 / 47 (4.26%) 4 |
| Cellulitis subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 5 / 42 (11.90%) 8 | 3 / 47 (6.38%) 4 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 1 / 42 (2.38%) 1 | 0 / 47 (0.00%) 0 |
| Cystitis subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 1 / 42 (2.38%) 1 | 0 / 47 (0.00%) 0 |
| Folliculitis subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 1 / 42 (2.38%) 1 | 3 / 47 (6.38%) 3 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 1 / 42 (2.38%) 1 | 0 / 47 (0.00%) 0 |
| Herpes zoster subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 3 / 42 (7.14%) 4 | 0 / 47 (0.00%) 0 |
| Infection subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 5 / 52 (9.62%) 6 | 5 / 42 (11.90%) 5 | 5 / 47 (10.64%) 7 |
| Paronychia subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 7 | 7 / 42 (16.67%) 8 | 7 / 47 (14.89%) 8 |
| Pharyngitis | | | |

| | | | |
|------------------------------------|------------------|-----------------|------------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 2 / 42 (4.76%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 2 / 42 (4.76%) | 2 / 47 (4.26%) |
| occurrences (all) | 2 | 2 | 2 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 42 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 0 | 4 |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 1 / 42 (2.38%) | 2 / 47 (4.26%) |
| occurrences (all) | 5 | 1 | 2 |
| Sinobronchitis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 1 | 2 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 52 (17.31%) | 6 / 42 (14.29%) | 6 / 47 (12.77%) |
| occurrences (all) | 11 | 10 | 8 |
| Urinary tract infection | | | |
| subjects affected / exposed | 5 / 52 (9.62%) | 8 / 42 (19.05%) | 4 / 47 (8.51%) |
| occurrences (all) | 7 | 19 | 4 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 14 / 52 (26.92%) | 9 / 42 (21.43%) | 14 / 47 (29.79%) |
| occurrences (all) | 16 | 11 | 15 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 1 / 42 (2.38%) | 0 / 47 (0.00%) |
| occurrences (all) | 8 | 1 | 0 |

| | | | |
|-----------------------------|-----------------|-----------------|------------------|
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 2 / 42 (4.76%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 2 | 4 |
| Hyperlipasaemia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 9 / 52 (17.31%) | 7 / 42 (16.67%) | 10 / 47 (21.28%) |
| occurrences (all) | 17 | 9 | 15 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 42 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 2 | 0 | 4 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 1 | 2 |
| Hypokalaemia | | | |
| subjects affected / exposed | 5 / 52 (9.62%) | 2 / 42 (4.76%) | 4 / 47 (8.51%) |
| occurrences (all) | 8 | 2 | 5 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 3 / 42 (7.14%) | 3 / 47 (6.38%) |
| occurrences (all) | 7 | 3 | 5 |
| Hyponatraemia | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 2 / 42 (4.76%) | 1 / 47 (2.13%) |
| occurrences (all) | 6 | 3 | 1 |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 42 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 2 / 42 (4.76%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 2 | 1 |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 42 (2.38%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 1 | 1 |

| | | | |
|---|------------------|--|--|
| Non-serious adverse events | All Participants | | |
| Total subjects affected by non-serious adverse events | | | |

| | | | |
|--|--------------------|--|--|
| subjects affected / exposed | 176 / 177 (99.44%) | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences (all) | 3 | | |
| Hypotension | | | |
| subjects affected / exposed | 10 / 177 (5.65%) | | |
| occurrences (all) | 12 | | |
| Pallor | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 2 | | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 44 / 177 (24.86%) | | |
| occurrences (all) | 62 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Chills | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences (all) | 8 | | |
| Face oedema | | | |
| subjects affected / exposed | 9 / 177 (5.08%) | | |
| occurrences (all) | 9 | | |
| Fatigue | | | |
| subjects affected / exposed | 46 / 177 (25.99%) | | |
| occurrences (all) | 57 | | |
| Gait disturbance | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 2 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 10 / 177 (5.65%) | | |
| occurrences (all) | 15 | | |

| | | | |
|---|---------------------------|--|--|
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 23 / 177 (12.99%) 26 | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 103 / 177 (58.19%) 226 | | |
| Pain subjects affected / exposed occurrences (all) | 6 / 177 (3.39%) 7 | | |
| Peripheral swelling subjects affected / exposed occurrences (all) | 7 / 177 (3.95%) 10 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 43 / 177 (24.29%) 55 | | |
| Immune system disorders Anaphylactoid reaction subjects affected / exposed occurrences (all) | 1 / 177 (0.56%) 1 | | |
| Hypersensitivity subjects affected / exposed occurrences (all) | 3 / 177 (1.69%) 5 | | |
| Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all) | 1 / 177 (0.56%) 1 | | |
| Perineal pain subjects affected / exposed occurrences (all) | 1 / 177 (0.56%) 1 | | |
| Prostatomegaly subjects affected / exposed occurrences (all) | 1 / 177 (0.56%) 1 | | |
| Vulvovaginal pruritus subjects affected / exposed occurrences (all) | 1 / 177 (0.56%) 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|-----------------------------|-------------------|--|--|
| Cough | | | |
| subjects affected / exposed | 47 / 177 (26.55%) | | |
| occurrences (all) | 75 | | |
| Dry throat | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Dysphonia | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences (all) | 5 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 40 / 177 (22.60%) | | |
| occurrences (all) | 48 | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 2 | | |
| Epistaxis | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences (all) | 5 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences (all) | 5 | | |
| Hypoxia | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences (all) | 4 | | |
| Nasal discomfort | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 2 | | |
| Nasal dryness | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 8 / 177 (4.52%) | | |
| occurrences (all) | 8 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 9 / 177 (5.08%) | | |
| occurrences (all) | 9 | | |

| | | | |
|--|-------------------------|--|--|
| Pneumothorax subjects affected / exposed occurrences (all) | 3 / 177 (1.69%) 3 | | |
| Productive cough subjects affected / exposed occurrences (all) | 5 / 177 (2.82%) 7 | | |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 3 / 177 (1.69%) 3 | | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 13 / 177 (7.34%) 17 | | |
| Throat irritation subjects affected / exposed occurrences (all) | 1 / 177 (0.56%) 1 | | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 6 / 177 (3.39%) 6 | | |
| Confusional state subjects affected / exposed occurrences (all) | 3 / 177 (1.69%) 3 | | |
| Depression subjects affected / exposed occurrences (all) | 2 / 177 (1.13%) 2 | | |
| Insomnia subjects affected / exposed occurrences (all) | 12 / 177 (6.78%) 14 | | |
| Sleep disorder subjects affected / exposed occurrences (all) | 3 / 177 (1.69%) 3 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 41 / 177 (23.16%) 54 | | |
| Amylase increased | | | |

| | | | |
|--|-------------------|--|--|
| subjects affected / exposed | 45 / 177 (25.42%) | | |
| occurrences (all) | 103 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 34 / 177 (19.21%) | | |
| occurrences (all) | 47 | | |
| Blood albumin decreased | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences (all) | 12 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 12 / 177 (6.78%) | | |
| occurrences (all) | 18 | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 6 / 177 (3.39%) | | |
| occurrences (all) | 10 | | |
| Blood creatine increased | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 3 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 22 / 177 (12.43%) | | |
| occurrences (all) | 42 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 56 / 177 (31.64%) | | |
| occurrences (all) | 108 | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 2 | | |
| Blood potassium increased | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Blood urea increased | | | |

| | | | |
|-------------------------------------|-------------------|--|--|
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences (all) | 4 | | |
| Blood uric acid increased | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 2 | | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences (all) | 13 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 16 / 177 (9.04%) | | |
| occurrences (all) | 23 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 4 | | |
| Lipase increased | | | |
| subjects affected / exposed | 33 / 177 (18.64%) | | |
| occurrences (all) | 81 | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 7 | | |
| Protein total decreased | | | |
| subjects affected / exposed | 8 / 177 (4.52%) | | |
| occurrences (all) | 8 | | |
| Weight decreased | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences (all) | 7 | | |
| Weight increased | | | |
| subjects affected / exposed | 13 / 177 (7.34%) | | |
| occurrences (all) | 13 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences (all) | 4 | | |

| | | | |
|--|-------------------|--|--|
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 2 | | |
| Traumatic haematoma | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 2 | | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences (all) | 3 | | |
| Bradycardia | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 2 | | |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 3 | | |
| Dizziness | | | |
| subjects affected / exposed | 36 / 177 (20.34%) | | |
| occurrences (all) | 45 | | |
| Dysaesthesia | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 3 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 6 / 177 (3.39%) | | |
| occurrences (all) | 6 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 45 / 177 (25.42%) | | |
| occurrences (all) | 59 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 8 / 177 (4.52%) | | |
| occurrences (all) | 9 | | |

| | | | |
|--------------------------------------|-------------------|--|--|
| Lethargy | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences (all) | 4 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences (all) | 3 | | |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Seizure | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences (all) | 9 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 30 / 177 (16.95%) | | |
| occurrences (all) | 39 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 2 | | |
| Leukopenia | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences (all) | 6 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences (all) | 11 | | |
| Neutropenia | | | |
| subjects affected / exposed | 6 / 177 (3.39%) | | |
| occurrences (all) | 10 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 10 / 177 (5.65%) | | |
| occurrences (all) | 12 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Deafness | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences (all) | 7 | | |
| Deafness transitory | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Ear pain | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 3 | | |
| Hypoacusis | | | |
| subjects affected / exposed | 9 / 177 (5.08%) | | |
| occurrences (all) | 9 | | |
| Tinnitus | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences (all) | 7 | | |
| Eye disorders | | | |
| Eye pruritus | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences (all) | 5 | | |
| Eye swelling | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences (all) | 3 | | |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Vitreous floaters | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences (all) | 4 | | |
| Abdominal distension | | | |

| | | | |
|----------------------------------|-------------------|--|--|
| subjects affected / exposed | 13 / 177 (7.34%) | | |
| occurrences (all) | 13 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 14 / 177 (7.91%) | | |
| occurrences (all) | 17 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 20 / 177 (11.30%) | | |
| occurrences (all) | 22 | | |
| Constipation | | | |
| subjects affected / exposed | 28 / 177 (15.82%) | | |
| occurrences (all) | 42 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 79 / 177 (44.63%) | | |
| occurrences (all) | 132 | | |
| Dry mouth | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences (all) | 7 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 30 / 177 (16.95%) | | |
| occurrences (all) | 33 | | |
| Dysphagia | | | |
| subjects affected / exposed | 8 / 177 (4.52%) | | |
| occurrences (all) | 8 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 12 / 177 (6.78%) | | |
| occurrences (all) | 13 | | |
| Lip blister | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 2 | | |
| Lip dry | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Mouth ulceration | | | |
| subjects affected / exposed | 9 / 177 (5.08%) | | |
| occurrences (all) | 9 | | |
| Nausea | | | |

| | | | |
|--|-------------------|--|--|
| subjects affected / exposed | 97 / 177 (54.80%) | | |
| occurrences (all) | 150 | | |
| Odynophagia | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences (all) | 3 | | |
| Stomatitis | | | |
| subjects affected / exposed | 25 / 177 (14.12%) | | |
| occurrences (all) | 49 | | |
| Toothache | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences (all) | 5 | | |
| Vomiting | | | |
| subjects affected / exposed | 64 / 177 (36.16%) | | |
| occurrences (all) | 106 | | |
| Hepatobiliary disorders | | | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences (all) | 5 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences (all) | 6 | | |
| Alopecia | | | |
| subjects affected / exposed | 8 / 177 (4.52%) | | |
| occurrences (all) | 11 | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 21 / 177 (11.86%) | | |
| occurrences (all) | 26 | | |
| Dry skin | | | |
| subjects affected / exposed | 23 / 177 (12.99%) | | |
| occurrences (all) | 32 | | |
| Eczema | | | |
| subjects affected / exposed | 9 / 177 (5.08%) | | |
| occurrences (all) | 11 | | |
| Ingrowing nail | | | |

| | | | |
|--|-------------------|--|--|
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 2 | | |
| Nail discolouration | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Night sweats | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 2 | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 36 / 177 (20.34%) | | |
| occurrences (all) | 50 | | |
| Rash | | | |
| subjects affected / exposed | 28 / 177 (15.82%) | | |
| occurrences (all) | 32 | | |
| Rash macular | | | |
| subjects affected / exposed | 9 / 177 (5.08%) | | |
| occurrences (all) | 10 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 43 / 177 (24.29%) | | |
| occurrences (all) | 56 | | |
| Rash papular | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences (all) | 6 | | |
| Rash pruritic | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences (all) | 9 | | |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 2 | | |
| Urticaria | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences (all) | 5 | | |

| | | | |
|---|-------------------|--|--|
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 177 (1.13%) | | |
| occurrences (all) | 2 | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Hypertonic bladder | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences (all) | 3 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 26 / 177 (14.69%) | | |
| occurrences (all) | 32 | | |
| Back pain | | | |
| subjects affected / exposed | 18 / 177 (10.17%) | | |
| occurrences (all) | 20 | | |
| Bone pain | | | |
| subjects affected / exposed | 6 / 177 (3.39%) | | |
| occurrences (all) | 11 | | |
| Flank pain | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences (all) | 4 | | |
| Joint stiffness | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 35 / 177 (19.77%) | | |
| occurrences (all) | 45 | | |

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|--|-------------------------|--|--|
| Muscular weakness subjects affected / exposed occurrences (all) | 1 / 177 (0.56%) 1 | | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 7 / 177 (3.95%) 8 | | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 4 / 177 (2.26%) 4 | | |
| Myalgia subjects affected / exposed occurrences (all) | 10 / 177 (5.65%) 12 | | |
| Neck pain subjects affected / exposed occurrences (all) | 2 / 177 (1.13%) 2 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 23 / 177 (12.99%) 28 | | |
| Tendon pain subjects affected / exposed occurrences (all) | 1 / 177 (0.56%) 1 | | |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 7 / 177 (3.95%) 10 | | |
| Cellulitis subjects affected / exposed occurrences (all) | 12 / 177 (6.78%) 17 | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 4 / 177 (2.26%) 4 | | |
| Cystitis subjects affected / exposed occurrences (all) | 2 / 177 (1.13%) 2 | | |
| Folliculitis | | | |

| | | | |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences (all) | 5 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences (all) | 3 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences (all) | 6 | | |
| Infection | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 16 / 177 (9.04%) | | |
| occurrences (all) | 19 | | |
| Paronychia | | | |
| subjects affected / exposed | 25 / 177 (14.12%) | | |
| occurrences (all) | 33 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 177 (1.69%) | | |
| occurrences (all) | 3 | | |
| Pneumonia | | | |
| subjects affected / exposed | 9 / 177 (5.08%) | | |
| occurrences (all) | 9 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences (all) | 5 | | |
| Rhinitis | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences (all) | 10 | | |
| Sinobronchitis | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Skin infection | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences (all) | 5 | | |
| Tooth infection | | | |

| | | | |
|------------------------------------|-------------------|--|--|
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 25 / 177 (14.12%) | | |
| occurrences (all) | 34 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 18 / 177 (10.17%) | | |
| occurrences (all) | 31 | | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 50 / 177 (28.25%) | | |
| occurrences (all) | 63 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 8 / 177 (4.52%) | | |
| occurrences (all) | 14 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 6 / 177 (3.39%) | | |
| occurrences (all) | 8 | | |
| Hyperlipasaemia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 2 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 34 / 177 (19.21%) | | |
| occurrences (all) | 52 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences (all) | 10 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 4 / 177 (2.26%) | | |
| occurrences (all) | 5 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 15 / 177 (8.47%) | | |
| occurrences (all) | 20 | | |

| | | | |
|-----------------------------|------------------|--|--|
| Hypomagnesaemia | | | |
| subjects affected / exposed | 15 / 177 (8.47%) | | |
| occurrences (all) | 33 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 10 / 177 (5.65%) | | |
| occurrences (all) | 19 | | |
| Hypophagia | | | |
| subjects affected / exposed | 1 / 177 (0.56%) | | |
| occurrences (all) | 1 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 7 / 177 (3.95%) | | |
| occurrences (all) | 22 | | |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 5 / 177 (2.82%) | | |
| occurrences (all) | 7 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 28 November 2014 | <p>Reduced nazartinib starting dose to 50 mg qd.</p> <p>Clarified the subsequent escalation of nazartinib and capmatinib doses.</p> <p>Revised the DLT definitions by adding Grade 2 pneumonitis as dose-limiting toxicity.</p> <p>Provided the latest available clinical safety and PK data for nazartinib and capmatinib tablet formulation.</p> <p>Provided updated hypothetical scenarios in reflection of the reduced starting dose of nazartinib and the updated priors based on the updated safety information.</p> |
| 24 July 2015 | <p>Introduced a formulation change for nazartinib from capsules to tablets (viable formulation for commercialization).</p> <p>Recommended guidelines for management and dose modification of rash/skin toxicities were provided for the nazartinib treatment.</p> <p>For capmatinib treatment, updated the dose modifications guideline for hepatotoxicity in regard to discontinuing study medication(s) with concurrent elevation of ALT and/or AST > 3×ULN and total bilirubin > 2×ULN with ALP < 2×ULN, in the absence of signs of cholestasis, hemolysis, and alternative causes of the liver injury (e.g., concomitant use of hepatotoxic drug(s), alcoholic hepatitis, etc.). Specific work-up for potential Hy's law cases had been added to the protocol.</p> <p>The dose modification rules and the dose limiting toxicity for liver toxicity as well as the follow-up evaluations for hepatic toxicities had also been updated accordingly.</p> <p>Included precautionary measures against ultraviolet exposure as capmatinib had photosensitization potential.</p> <p>Additionally, updated the exclusion criteria and few new exclusion criteria were added.</p> <p>Updated concomitant therapies, criteria for interruption and re-initiation of nazartinib and capmatinib.</p> |
| 01 September 2015 | <p>Provided detailed information about an urgent safety measure related to nazartinib.</p> <p>Excluded subjects with other malignancies, who underwent a bone marrow or solid organ transplant, with a known history of human immunodeficiency virus infection, or receiving immunosuppressive agents or chronic corticosteroids at study entry.</p> <p>Allowed subjects with either HBV surface antigen positive or HBV-DNA positive to enroll into the study if willing to take antiviral therapy 1-2 weeks prior to first dose of study treatment and continue antiviral therapy for at least 4 weeks after the last dose of study treatment.</p> <p>Allowed new subjects with negative hepatitis C antibody (HC Ab) or who were HC Ab positive but with an undetectable level of HCV-RNA into the study. Subjects with detectable HCV-RNA were not eligible to enroll into the study.</p> |

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| 02 November 2015 | <p>Implemented a centralization of analysis for the resistance mutations EGFR T790M and MET oncogene amplification at a Novartis designated central laboratory for all subjects entering into Phase II.</p> <p>Introduced 50 mg dose strength of nazartinib tablets for better compliance.</p> <p>Optimized the subject safety and the toxicity monitoring as well as to align Novartis study protocols, the QTcF eligibility criterion and the management guidelines for pancreatic toxicity were revised.</p> <p>Updated the definition of the end of study to detail study continuation conditions after completion of the primary analysis until all subjects discontinued, or until another clinical trial was available for all ongoing subjects to be transferred to that clinical study and continue to receive capmatinib + nazartinib.</p> <p>Clarified the possibility of using bisphosphonates during the study.</p> <p>Detailed the use of an Interactive Response Technology system in the Phase II part of the study to specify the enrollment and the study drug dispensation tracking via the application.</p> <p>Modalities and conditions for subject re-screening after screen failure was introduced, together with screening assessments to be performed again during the new screening phase.</p> |
| 29 July 2016 | <p>Better defined the subject population to be enrolled in the Phase II part of the study (expansion phase). A new group was added (Group 3), and the sample size of Group 2 was revised.</p> <p>Implemented a requirement of ECOG performance status of 0-1 for all subjects to be enrolled in the study to ensure that subjects would be able to receive potential benefit from study treatment.</p> <p>Removed the exclusion criterion on fasting plasma glucose ≥ 160 mg/dL (≥ 8.9 mmol/L) in the absence of evidence of impact on the glycemia in light of the most recent available clinical data and according to the latest versions of capmatinib and nazartinib Investigator Brochures</p> <p>Introduced a new dose strength (150 mg) for capmatinib tablets.</p> <p>Introduced other rare EGFR activating sensitizing mutations that were also considered for enrollment onto the Phase II. These rare mutations, L861Q, G719X, and S768I, account for almost 10% of the cases whereas L858R point mutation and exon 19 deletions accounted for approximately 90% of the cases.</p> <p>Updated the overview of capmatinib and nazartinib according to last Investigator Brochure versions.</p> <p>Removed the restriction of proton pump inhibitors use during the course of the study.</p> <p>Clarified the conditions in which local laboratory assessments should be reported in the Case Report Form during the Phase 2 part of the trial.</p> <p>Clarified the time window for post-dose ECG during the visits with PK sampling.</p> <p>Clarified the definition of acquired resistance mechanisms and the definition of the 4 subgroups of subjects being enrolled in the Phase II Group 1.</p> <p>Clarified the biosample requirements for the optional biomarker assessments.</p> <p>Introduced the RP2D and the dose reduction steps starting from the RP2D.</p> |
| 11 April 2017 | <p>Added in Phase II a new group 4 of subjects (N=30) with EGFRmut, any T790M, any MET, in order to assess the safety and tolerability of the combination therapy when taken with food (unrestricted meal type).</p> <p>Proposed a new group 4 to administer study medication with food to improve the tolerability profile of the combination therapy, as dosing with food had been shown to improve the GI tolerability of some multi-kinase inhibitors such as imatinib (Gleevec®) and bosutinib (Bosulif®).</p> <p>Corrected the exclusion criterion for subjects with asymptomatic serum amylase and lipase > Grade 2, to clarify that subject now met exclusion criterion even if only one of the two parameters (asymptomatic serum amylase or lipase) was > Grade 2.</p> <p>Added the collection of an optional on-treatment biopsy with paired cfDNA sample to identify emergence of potential resistance markers during treatment as well as understand the correlation between tissue and plasma biomarker status.</p> <p>Clarified the exclusion criterion for subjects with brain metastases.</p> <p>Clarified the interpretation of study discontinuation after dose interruption.</p> |

| | |
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| 20 October 2021 | <p>A new group 5 added per protocol amendment 7 will not be opened as Novartis made the decision to discontinue the study on 11-May-2022. Below are the key changes in amendment 7.</p> <p>As of 20-Oct-2021, a total of 177 participants have been enrolled in the study: 33 participants in Phase Ib and 144 in Phase II (Group 1 to Group 4). All participants from Phase Ib and Phase II Groups 1 to 4 had met one of the end of study completion criteria as considered under protocol amendment 6 and there were no participants receiving treatment.</p> <p>The main purpose of this amendment is to implement a new subject group, Phase II Group 5, to determine the efficacy and safety of capmatinib monotherapy. The rationale for this addition is based on the following: Based on evidence suggesting that MET gene amplification plays an important role as a mechanism of resistance to treatment with EGFR-TKIs in NSCLC patients carrying mutated EGFR. Furthermore, the fact that there are reports showing significant clinical antitumor activity in this subpopulation of patients when combining an EGFR-TKI with a specific cMET inhibitor (such as Capmatinib). Therefore, the contribution of capmatinib as a monodrug needs to be established. This information will pave the way for the optimal use of the combination in future trials.</p> |
|-----------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com> for complete trial results.

Notes: