



Clinical trial results:

Afatinib in pretreated patients with advanced NSCLC harbouring HER2 exon 20 mutations

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-005098-35 |
| Trial protocol | ES DE NL |
| Global end of trial date | 15 September 2017 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 07 February 2020 |
| First version publication date | 07 February 2020 |
| Summary attachment (see zip file) | Publication_Dziadziuszko et al__J Thorac Oncol_2019_DOI: 10.1016/j.jtho.2019.02.017 (ETOP NICHE Dziadziuszko et al_2019.pdf) |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | ETOP7-14 NICHE |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-----------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02369484 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Boehringer number: 1200.230 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | European Thoracic Oncology Platform (ETOP) |
| Sponsor organisation address | Effingerstrasse 40, Bern, Switzerland, 3008 |
| Public contact | ETOP Coordinating Office, ETOP, +41 315119400, NICHE@etop-eu.org |
| Scientific contact | ETOP Coordinating Office, ETOP, +41 315119400, NICHE@etop-eu.org |

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 | 15 September 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 September 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 September 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the ability of afatinib to control disease in pretreated patients with advanced NSCLC harbouring HER2 exon 20 mutations.

Protection of trial subjects:

Trial subjects are closely monitored during the entire duration of the trial by the participating investigators. For safety purposes any adverse events occurred from enrolment of a trial subject until 30 days after treatment discontinuation need to be reported.

In case of adverse events and treatment-related toxicities management guidance have been provided in the study protocol to treat trial subjects in adequately manner.

Precautions and warnings about the use of the study drug are provided in the trial subject information sheet to ensure that study drug is correctly used in order to avoid unnecessary adverse reactions and in addition to ensure that in case of an adverse event the study patient contacts the investigator for appropriate measures.

The safety and efficacy of the trial treatment have been regularly reviewed by the ETOP IDMC (independent data monitoring committee) at their semi-annual meetings to safeguard the interest and safety of the patients in the trial and to ensure the scientific integrity of the trial. Additionally, the risk/benefit ratio have been regularly evaluated by the ETOP Steering Committee on a semi-annual basis.

Technical and organisational controls (including physical, electronic and managerial measures) are in place to protect personal data and integrity of trial subjects.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 24 June 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Netherlands: 7 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | Germany: 3 |
| Worldwide total number of subjects | 13 |
| EEA total number of subjects | 13 |

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) | 8 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled to the ETOP/7-14 NICHE trial on 16.09.2015, while the last one on August 2016, before accrual was suspended in October 2016. Patients were enrolled in 3 centers (Netherlands Cancer Institute of Amsterdam, Vall d' Herbon Univesity Hospital (Spain) and Universitatsklinikum Koln (Germany)).

Pre-assignment

Screening details:

All 13 patients eligible for enrollment received treatment.

Period 1

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

Arms

| | |
|-----------|----------|
| Arm title | Afatinib |
|-----------|----------|

Arm description:

Afatinib 40 mg p.o./day until tumour progression or lack of tolerability

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

Dosage and administration details:

40mg daily p.o. until tumor progression or lack of tolerability.

Dose reduction to 30mg, reep 20mg, if required.

| | |
|---------------------------------------|----------|
| Number of subjects in period 1 | Afatinib |
| Started | 13 |
| Completed | 13 |

Period 2

| | |
|------------------------------|------------------|
| Period 2 title | Interim analysis |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|--|--------------------|
| Arm title | Afanitib (interim) |
| Arm description: Afatinib 40 mg p.o./day until tumour progression or lack of tolerability | |
| Arm type | Experimental |
| Investigational medicinal product name | Giotrif |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

40mg daily p.o. until tumor progression or lack of tolerability.
Dose reduction to 30mg, reep 20mg, if required.

| | |
|---|--------------------|
| Number of subjects in period 2^[1] | Afanitib (interim) |
| Started | 9 |
| Completed | 9 |

Notes:

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

Justification: A Simon's two-stage phase II design is adopted, with 9 patients in the 1st stage and 13 patients in the 2nd stage. The primary endpoint, disease control (DC), is evaluated at the 1st stage, after the first 9 patients have been followed for 12 weeks (interim analysis), and at the 2nd stage, approx. 40 months after inclusion of 1st patient (final analysis).

Baseline characteristics

Reporting groups

| | |
|--|---------------|
| Reporting group title | Overall study |
| Reporting group description: | |
| Afatinib 40 mg p.o./day until tumour progression or lack of tolerability | |

| Reporting group values | Overall study | Total | |
|---|---------------|-------|--|
| Number of subjects | 13 | 13 | |
| Age categorical | | | |
| Age as continuous characteristic only | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Age of patient at enrollment | | | |
| Units: years | | | |
| median | 59 | | |
| full range (min-max) | 39 to 82 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | 9 | |
| Male | 4 | 4 | |
| Smoking history | | | |
| Units: Subjects | | | |
| Current smoker | 1 | 1 | |
| Former smoker | 4 | 4 | |
| Never smoked | 8 | 8 | |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Netherlands | 7 | 7 | |
| Germany | 3 | 3 | |
| Spain | 3 | 3 | |
| ECOG Performance status | | | |
| PS 0: Fully active, able to carry on all pre-disease performance without restriction. PS 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. PS 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. PS 3: Capable of only limited self care, confined to bed or chair more than 50% of waking hours. PS 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | | | |
| Units: Subjects | | | |
| PS 0 | 7 | 7 | |
| PS 1 | 4 | 4 | |
| PS 2 | 2 | 2 | |
| T parameter | | | |
| Primary tumor (T) TX: Main tumor cannot be measured. T0: Main tumor cannot be found. T1, T2, T3, T4: Refers to the size and/or extent of the main tumor. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissues. T's may be further divided to provide more detail, such as T3a and T3b. | | | |
| Units: Subjects | | | |

| | | | |
|---|----|----|--|
| T1b | 1 | 1 | |
| T2a | 3 | 3 | |
| T3 | 3 | 3 | |
| T4 | 6 | 6 | |
| N parameter | | | |
| Regional lymph nodes (N) NX: Cancer in nearby lymph nodes cannot be measured. N0: There is no cancer in nearby lymph nodes. N1, N2, N3: Refers to the number and location of lymph nodes that contain cancer. The higher the number after the N, the more lymph nodes that contain cancer. | | | |
| Units: Subjects | | | |
| N0 | 5 | 5 | |
| N2 | 3 | 3 | |
| N3 | 5 | 5 | |
| M parameter | | | |
| Distant metastasis (M) MX: Metastasis cannot be measured. M0: Cancer has not spread to other parts of the body. M1: Cancer has spread to other parts of the body. | | | |
| Units: Subjects | | | |
| M0 | 1 | 1 | |
| M1a | 6 | 6 | |
| M1b | 6 | 6 | |
| TNM staging | | | |
| The TNM system is the most widely used cancer staging system. In the TNM system: The T refers to the size and extent of the main tumor. The main tumor is usually called the primary tumor. The N refers to the the number of nearby lymph nodes that have cancer. The M refers to whether the cancer has metastasized. This means that the cancer has spread from the primary tumor to other parts of the body. When your cancer is described by the TNM system, there will be numbers after each letter that give more details about the cancer—for example, T1N0MX or T3N1M0. | | | |
| Units: Subjects | | | |
| T1b-N3-M1b | 1 | 1 | |
| T2a-N0-M1a | 1 | 1 | |
| T2a-N2-M1b | 1 | 1 | |
| T2a-N3-M1b | 1 | 1 | |
| T3-N0-M1b | 1 | 1 | |
| T3-N2-M1a | 1 | 1 | |
| T3-N3-M1b | 1 | 1 | |
| T4-N0-M1a | 3 | 3 | |
| T4-N2-M0 | 1 | 1 | |
| T4-N3-M1a | 1 | 1 | |
| T4-N3-M1b | 1 | 1 | |
| Type of prior platinum treatment | | | |
| Units: Subjects | | | |
| Adjuvant | 2 | 2 | |
| Advanced disease | 11 | 11 | |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Afatinib |
| Reporting group description: | |
| Afatinib 40 mg p.o./day until tumour progression or lack of tolerability | |
| Reporting group title | Afatinib (interim) |
| Reporting group description: | |
| Afatinib 40 mg p.o./day until tumour progression or lack of tolerability | |

Primary: Disease control

| | |
|---|--------------------------------|
| End point title | Disease control ^[1] |
| End point description: | |
| Disease control (DC) is defined as complete or partial response, or disease stabilisation lasting at least 12 weeks. | |
| Disease control will be determined using RECIST 1.1 criteria: | |
| Complete Response (CR): Disappearance of all target lesions. | |
| Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters. | |
| Progression (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on the trial. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions denotes disease progression. | |
| Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters recorded on the trial. | |
| End point type | Primary |
| End point timeframe: | |
| At interim (after the first 9 pts have been followed for 12 weeks) & final analysis (approx. 40 months after inclusion of first pt) | |

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: In the interim analysis, evaluating the 12-week status of the first 9 patients according to the 1st stage of Simon's two-stage optimal design, 5 patients (55.6%) had progressed by 12 weeks, and thus, the stopping threshold of at most 3 patients not achieving DC by 12 weeks was crossed. Based on these results, the trial Steering Committee decided to stop recruitment into the trial. Treatment and follow-up for the enrolled patients continued as per protocol.

| End point values | Afatinib | Afatinib (interim) | | |
|-----------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 9 | | |
| Units: participants | | | | |
| DC at 12 weeks - "Yes" | 7 | 4 | | |
| DC at 12 weeks - "No" | 6 | 5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

| | |
|--|---------------------------|
| End point title | Progression-free Survival |
| End point description: Progression-free survival (PFS) is defined as the time from date of enrollment until documented progression or death, if progression is not documented. Censoring will occur at the last tumor assessment only if patients is lost to follow-up. | |
| End point type | Secondary |
| End point timeframe: Time assessed from the date of enrollment until documented progression or death (max 36 months). | |

| | | | | |
|----------------------------------|--------------------|--|--|--|
| End point values | Afatinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 15.9 (6.0 to 35.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|--|------------------|
| End point title | Overall Survival |
| End point description: Overall survival (OS) is defined as the time from the date of enrollment until death from any cause. Censoring will occur at the last follow-up. | |
| End point type | Secondary |
| End point timeframe: Time assessed from the date of enrollment until death (max 36 months). | |

| | | | | |
|----------------------------------|--------------------|--|--|--|
| End point values | Afatinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 ^[2] | | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 56.0 (16.3 to 100) | | | |

Notes:

[2] - Upper 95% limit is not reached, so we present the maximum value.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response

| | |
|-----------------|--------------------|
| End point title | Objective Response |
|-----------------|--------------------|

End point description:

Objective response is defined as best overall response (CR or PR) across all assessment time-points during the period from enrollment to termination of trial treatment. Objective response to afatinib treatment will be determined using RECIST 1.1 criteria:

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.

Progression (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on the trial. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions denotes disease progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters recorded on the trial.

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

End point timeframe:

Assessed across all time-points during the period from enrollment to termination of trial treatment (max. 36 months).

| | | | | |
|-------------------------------|-----------------|--|--|--|
| End point values | Afatinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: participants | | | | |
| Objective response (CR or PR) | 1 | | | |
| Stable disease | 6 | | | |
| Progressive disease | 5 | | | |
| Non-evaluable | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicities of Treatment

| | |
|-----------------|-------------------------|
| End point title | Toxicities of Treatment |
|-----------------|-------------------------|

End point description:

Adverse events classified according to NCI CTCAE version 4.

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

End point timeframe:

Assessed from the date of informed consent until 90 days after the final dose of afatinib (max 18 months).

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Afatinib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: participants | | | | |
| Experienced AE/SAE | 13 | | | |
| No AE/SAE | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of informed consent until 90 days after the final dose of afatinib (max 18 months).

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

Dictionary used

| | |
|-----------------|-----------|
| Dictionary name | NCI CTCAE |
|-----------------|-----------|

| | |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Afatinib |
|-----------------------|----------|

Reporting group description:

Afatinib: 40 mg p.o./day until tumour progression or lack of tolerability

| Serious adverse events | Afatinib | | |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 13 (38.46%) | | |
| number of deaths (all causes) | 8 | | |
| number of deaths resulting from adverse events | 1 | | |
| Cardiac disorders | | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhea | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnea | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle weakness lower limb | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| | | | |
|---|-------------------|--|--|
| Non-serious adverse events | Afatinib | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 13 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|---|---|--|--|
| Tumor pain subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Flu like symptoms subjects affected / exposed occurrences (all) Non-cardiac chest subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 3 2 / 13 (15.38%) 2 2 / 13 (15.38%) 2 1 / 13 (7.69%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Dyspnea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 3 2 / 13 (15.38%) 2 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 | | |
| Investigations GGT increased | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Asparate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Creatine increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Weight loss | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 1 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Other (paraplegia from Th4) | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Eye disorders | | | |

| | | | |
|---|------------------------|--|--|
| Dry eye subjects affected / exposed occurrences (all) | 2 / 13 (15.38%) 2 | | |
| Gastrointestinal disorders | | | |
| Diarrhea subjects affected / exposed occurrences (all) | 11 / 13 (84.62%) 11 | | |
| Mucositis oral subjects affected / exposed occurrences (all) | 4 / 13 (30.77%) 4 | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 3 | | |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 3 | | |
| Constipation subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Dry mouth subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema multiforme subjects affected / exposed occurrences (all) | 4 / 13 (30.77%) 4 | | |
| Rash acneiform subjects affected / exposed occurrences (all) | 4 / 13 (30.77%) 4 | | |
| Dry skin subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 3 | | |
| Other | | | |

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 13 (15.38%) 2 | | |
| Alopecia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Renal and urinary disorders Cystitis noninfective subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Urinary incontinence subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Urinary track obstruction subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Back pain subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Bone pain subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Myalgia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Infections and infestations Paronychia subjects affected / exposed occurrences (all) | 5 / 13 (38.46%) 5 | | |
| Bladder infection subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Eye infection | | | |

| | | | |
|------------------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Urinary track infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Nail infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Papulopustular rash | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Other (tonsillitis) | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Hyperkalemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hypermagnesemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hypoalbuminemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hypomagnesemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hyponatremia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported