



Clinical trial results:

Phase III Trial Evaluating the Effectiveness of a Dose Adjustment of Imatinib Mesylate on the Molecular Response (MIM)

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2008-007094-20 |
| Trial protocol | FR |
| Global end of trial date | 01 January 2017 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 20 January 2022 |
| First version publication date | 20 January 2022 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | IB 2009-07 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01827930 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Institut Bergonié |
| Sponsor organisation address | 229 cours de l'Argonne, Bordeaux, France, 33076 |
| Public contact | Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.unicancer.fr |
| Scientific contact | Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.unicancer.fr |

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 | 01 January 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 January 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 January 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Phase III Trial to Evaluate the Effectiveness of a Dose Adjustment of Imatinib Mesylate on the Molecular Response in Patients With chronic myeloid leukemia (CML) in Chronic Phase Treated With IM 400 mg / Day for at Least Two Years, Complete Cytogenetic Response for at Least One Year

Protection of trial subjects:

A supervisory committee is constituted to evaluate the benefit/risk ratio along the study period.

Background therapy:

The Imatinib Mesylate at a dose of 400 mg / day is the standard treatment for patients with CML-CP. Recent studies show that the quality of response rate (complete cytogenetic response and major molecular response rate) is dependent on the residual plasma Imatinib.

Evidence for comparator:

The Imatinib Mesylate at a dose of 400 mg / day is the standard treatment for patients with CML-CP. Recent studies show that the quality of response rate (complete cytogenetic response and major molecular response rate) is dependent on the residual plasma Imatinib. This study aims to evaluate the effectiveness of a strategy for dose adjustment of Imatinib Mesylate based on the measurement of the residual plasma imatinib in patients treated for at least 2 years Imatinib 400 mg / d in complete cytogenetic response for at least 1 year.

| | |
|---|------------------|
| Actual start date of recruitment | 14 December 2009 |
| 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 | France: 68 |
| Worldwide total number of subjects | 68 |
| EEA total number of subjects | 68 |

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 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 65 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Criteria

Inclusion Criteria:

Patients with CML-CP treated for at least two years by Imatinib Mesylate 400 mg / d,
Patients in complete cytogenetic response for at least 1 year
Patients with residual disease detectable by quantitative RT-PCR (RQ-PCR)
ECOG \leq 2,
Age \geq 18 years
Signed informed consent,
Membership of a social security system

Period 1

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

Blinding implementation details:

not blinded

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--|
| Arm title | Randomized trial / Control Arm: Imatinib 400 |
|------------------|--|

Arm description:

Patients with IM concentration < 1000ng/mL are randomized between :

(1) Experimental Arm : adapted strategy (up to 600 MG IM)

(2) Control Arm : standard strategy (400 MG IM)

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Imatinib Mesylate |
| Investigational medicinal product code | |
| Other name | Glivec |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Drug: Imatinib Mesylate 600 MG Oral Tablet

| | |
|------------------|---|
| Arm title | Randomized trial / Experimental Arm: Imatinib 600 |
|------------------|---|

Arm description:

Patients with IM concentration < 1000ng/mL are randomized between :

(1) Experimental Arm : adapted strategy (up to 600 MG IM)

(2) Control Arm : standard strategy (400 MG IM)

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

Dosage and administration details:

Imatinib Mesylate 600 MG Oral Tablet:

| | |
|--|-------------------------------|
| Arm title | Parallel cohort: Imatinib 400 |
| Arm description: Patients with IM concentration > 1000ng/mL are included in a parallel cohort and receive standard strategy (400 MG IM) | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Randomized trial / Control Arm: Imatinib 400 | Randomized trial / Experimental Arm: Imatinib 600 | Parallel cohort: Imatinib 400 |
|---------------------------------------|--|---|----------------------------------|
| Started | 25 | 24 | 19 |
| Completed | 25 | 24 | 19 |

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Randomized trial / Control Arm: Imatinib 400 |
| Reporting group description: | |
| Patients with IM concentration < 1000ng/mL are randomized between : | |
| (1) Experimental Arm : adapted strategy (up to 600 MG IM) | |
| (2) Control Arm : standard strategy (400 MG IM) | |
| Reporting group title | Randomized trial / Experimental Arm: Imatinib 600 |
| Reporting group description: | |
| Patients with IM concentration < 1000ng/mL are randomized between : | |
| (1) Experimental Arm : adapted strategy (up to 600 MG IM) | |
| (2) Control Arm : standard strategy (400 MG IM) | |
| Reporting group title | Parallel cohort: Imatinib 400 |
| Reporting group description: | |
| Patients with IM concentration > 1000ng/mL are included in a parallel cohort and receive standard strategy (400 MG IM) | |

| Reporting group values | Randomized trial / Control Arm: Imatinib 400 | Randomized trial / Experimental Arm: Imatinib 600 | Parallel cohort: Imatinib 400 |
|--|--|---|----------------------------------|
| Number of subjects | 25 | 24 | 19 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| median | 52.7 | 50.6 | 65.3 |
| full range (min-max) | 25.1 to 79.1 | 27.2 to 72.0 | 34.3 to 80.4 |
| Gender categorical Units: Subjects | | | |
| Female | 6 | 4 | 6 |
| Male | 19 | 20 | 13 |

| Reporting group values | Total | | |
|---|-------------|--|--|
| Number of subjects | 68 | | |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) | 0 0 0 | | |

| | | | |
|--|----|--|--|
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| median | | | |
| full range (min-max) | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 16 | | |
| Male | 52 | | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Randomized trial / Control Arm: Imatinib 400 |
| Reporting group description: Patients with IM concentration < 1000ng/mL are randomized between : (1) Experimental Arm : adapted strategy (up to 600 MG IM) (2) Control Arm : standard strategy (400 MG IM) | |
| Reporting group title | Randomized trial / Experimental Arm: Imatinib 600 |
| Reporting group description: Patients with IM concentration < 1000ng/mL are randomized between : (1) Experimental Arm : adapted strategy (up to 600 MG IM) (2) Control Arm : standard strategy (400 MG IM) | |
| Reporting group title | Parallel cohort: Imatinib 400 |
| Reporting group description: Patients with IM concentration > 1000ng/mL are included in a parallel cohort and receive standard strategy (400 MG IM) | |

Primary: Percentage of Patients Presenting a Decline of the BCR-ABL Transcript Rate at 12 Months From Baseline

| | |
|--|---|
| End point title | Percentage of Patients Presenting a Decline of the BCR-ABL Transcript Rate at 12 Months From Baseline |
| End point description: The BCR-ABL transcript rate was analysed by molecular biology by RQ-PCR at study entry, 3 months, 6 months, 9 months and 12 months. Treatment is considered effective at 12 months if: for patients with an inclusion transcript rate less than 0.1%: the transcript rate at 12 months is less or equal to 0.001% or undetectable. for patients with an inclusion transcript rate greater than 0.1% : the transcript rate at 12 months is less or equal to 0.1% or undetectable. If BCR-ABL transcript level was unavailable at M12, the treatment was considered ineffective. | |
| End point type | Primary |
| End point timeframe: 12 Months From Baseline | |

| End point values | Randomized trial / Control Arm: Imatinib 400 | Randomized trial / Experimental Arm: Imatinib 600 | Parallel cohort: Imatinib 400 | |
|-----------------------------|--|---|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 24 | 19 | |
| Units: subjects | 8 | 7 | 2 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis for primary outcome |
| Statistical analysis description: The proportion of Patients Presenting a Decline of the BCR-ABL Transcript Rate at 12 Months From Baseline was estimated as the number of patients with a Decline of the BCR-ABL Transcript Rate at 12 Months From Baseline divided by the number of all patients. The 95% confidence interval is reported (binomial law) | |
| Comparison groups | Randomized trial / Experimental Arm: Imatinib 600 v Randomized trial / Control Arm: Imatinib 400 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.05 ^[2] |
| Method | t-test, 2-sided |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.34 |
| upper limit | 3.86 |
| Variability estimate | Standard error of the mean |

Notes:

[1] - Rates are reported for each arm. no comparison was performed.

[2] - not applicable.

Secondary: Molecular Response at 12 Months

| | |
|--|---------------------------------|
| End point title | Molecular Response at 12 Months |
| End point description: The molecular response is defined by the measurement of BCR-ABL transcript rate by quantitative RT-PCR (RQ-PCR) on peripheral venous blood according to international standards. It is defined as: - Major Molecular Response (MMR): BCR-ABL transcript rate \leq 0.1% - Complete Molecular Response (CMR): transcript BCR-ABL undetectable and non quantifiable. | |
| End point type | Secondary |
| End point timeframe: 12 months from baseline | |

| End point values | Randomized trial / Control Arm: Imatinib 400 | Randomized trial / Experimental Arm: Imatinib 600 | Parallel cohort: Imatinib 400 | |
|-----------------------------|--|---|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 24 | 19 | |
| Units: Subjects | 19 | 20 | 12 | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

throughout the follow-up of the patient, up to 1 year

Adverse event reporting additional description:

All adverse event (related and unrelated to treatment) were reported.

All serious adverse event (related and unrelated to treatment) were reported.

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

Dictionary used

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

| | |
|--------------------|---|
| Dictionary version | 2 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Randomized trial / Control Arm: Imatinib 400 |
|-----------------------|--|

Reporting group description:

Patients with IM concentration < 1000ng/mL are randomized between :

(1) Experimental Arm : adapted strategy (up to 600 MG IM)

(2) Control Arm : standard strategy (400 MG IM)

| | |
|-----------------------|---|
| Reporting group title | Randomized trial / Experimental Arm: Imatinib 600 |
|-----------------------|---|

Reporting group description:

Patients with IM concentration < 1000ng/mL are randomized between :

(1) Experimental Arm : adapted strategy (up to 600 MG IM)

(2) Control Arm : standard strategy (400 MG IM)

| | |
|-----------------------|-------------------------------|
| Reporting group title | Parallel cohort: Imatinib 400 |
|-----------------------|-------------------------------|

Reporting group description:

Patients with IM concentration > 1000ng/mL are included in a parallel cohort and receive standard strategy (400 MG IM)

| Serious adverse events | Randomized trial / Control Arm: Imatinib 400 | Randomized trial / Experimental Arm: Imatinib 600 | Parallel cohort: Imatinib 400 |
|---|--|---|----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | 3 / 24 (12.50%) | 0 / 19 (0.00%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | 1 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gastrointestinal - Other | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 24 (0.00%) | 0 / 19 (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 |
| Renal/Genitourinary - Other | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 24 (0.00%) | 0 / 19 (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 | | | |
| Fracture | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | 0 / 19 (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 |
| Cardiac disorders | | | |
| Cardiac General - Other (Specify, ___) | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 24 (0.00%) | 0 / 19 (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 ischemia/infarction | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | 0 / 19 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal/Soft Tissue - Other | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 24 (0.00%) | 0 / 19 (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 |
| Pulmonary/Upper Respiratory - Other | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 24 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infection - Other | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | 0 / 19 (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 |

| Non-serious adverse events | Randomized trial / Control Arm: Imatinib 400 | Randomized trial / Experimental Arm: Imatinib 600 | Parallel cohort: Imatinib 400 |
|--|--|---|----------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 25 (48.00%) | 24 / 24 (100.00%) | 15 / 19 (78.95%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 24 (4.17%) | 1 / 19 (5.26%) |
| occurrences (all) | 2 | 1 | 1 |
| Carotid | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 24 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Fatigue (asthenia, lethargy, malaise) | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | 9 / 24 (37.50%) | 2 / 19 (10.53%) |
| occurrences (all) | 4 | 10 | 2 |
| Edema:head and neck | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 3 / 24 (12.50%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 6 | 1 |
| Edema:limb | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 24 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 0 | 1 |
| Lymphatics - Other | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 24 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Immune system disorders | | | |
| Allergic reaction/hypersensitivity (including drug fever) | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip) | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 24 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 2 |
| Nose | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|--|---------------------|----------------------|----------------------|
| Cough subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | 2 / 19 (10.53%) 2 |
| Dyspnea (shortness of breath) subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | 1 / 19 (5.26%) 1 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Depression subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 2 / 24 (8.33%) 2 | 1 / 19 (5.26%) 1 |
| Investigations | | | |
| Leukocytes (total WBC) subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 3 | 3 / 24 (12.50%) 3 | 1 / 19 (5.26%) 2 |
| Lymphopenia subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 3 | 1 / 24 (4.17%) 1 | 1 / 19 (5.26%) 1 |
| Neutrophils/granulocytes (ANC/AGC) subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 2 | 4 / 24 (16.67%) 4 | 1 / 19 (5.26%) 1 |
| Cardiac disorders | | | |
| Cardiac General - Other subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Nervous system disorders | | | |
| Head/headache subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 24 (4.17%) 1 | 2 / 19 (10.53%) 2 |
| Blood and lymphatic system disorders | | | |
| Hemoglobin subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 2 / 24 (8.33%) 2 | 2 / 19 (10.53%) 2 |
| Eye disorders | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| Cataract | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 24 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Ocular/Visual - Other | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 2 / 24 (8.33%) | 2 / 19 (10.53%) |
| occurrences (all) | 2 | 2 | 2 |
| Watery eye (epiphora, tearing) † 1 [3] | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 24 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Diarrhea | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 6 / 24 (25.00%) | 4 / 19 (21.05%) |
| occurrences (all) | 0 | 7 | 4 |
| Dry mouth/salivary gland (xerostomia) | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 24 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal - Other | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 2 / 24 (8.33%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 7 | 1 |
| Stomach | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 2 / 24 (8.33%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 2 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatology/Skin - Other | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 3 / 24 (12.50%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 4 | 1 |
| Induration/fibrosis (skin and subcutaneous tissue) | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 24 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus/itching | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 2 / 24 (8.33%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 2 | 1 |
| Renal and urinary disorders | | | |
| Renal failure | | | |

| | | | |
|--|----------------------|-----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Renal/Genitourinary - Other subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 0 / 19 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Musculoskeletal/Soft Tissue - Other subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 4 | 9 / 24 (37.50%) 12 | 2 / 19 (10.53%) 2 |
| Joint subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | 2 / 19 (10.53%) 2 |
| Infections and infestations Infection - Other subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 6 / 24 (25.00%) 8 | 4 / 19 (21.05%) 5 |
| Metabolism and nutrition disorders Phosphate, serum-low (hypophosphatemia) subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 2 / 24 (8.33%) 2 | 1 / 19 (5.26%) 1 |
| Triglyceride, serum-high (hypertriglyceridemia) subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 2 | 0 / 24 (0.00%) 0 | 1 / 19 (5.26%) 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---------------------------------|
| 02 October 2009 | Protocol V2.1 dated 22-sep-2009 |
| 18 June 2012 | Protocol V3 dated 02-jan-2012 |
| 16 May 2014 | Protocol V4 dated 28-feb-2014 |
| 30 August 2016 | Protocol V6 dated 06-jul-2016 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported