



Clinical trial results:

A randomized phase III study of imatinib dose optimization compared with nilotinib in patients with Chronic Myelogenous Leukemia and suboptimal response to standard-dose imatinib

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2008-007054-35 |
| Trial protocol | DE FI |
| Global end of trial date | 25 July 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 06 July 2018 |
| First version publication date | 06 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CAMN107A2404 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00802841 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

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 | 25 July 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 July 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the comparative efficacy between imatinib dose escalation and nilotinib, in terms of CCyR after 6 months, for patients with CML in chronic phase with suboptimal response to imatinib standard dose.

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 | 25 May 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 | Argentina: 10 |
| Country: Number of subjects enrolled | Brazil: 34 |
| Country: Number of subjects enrolled | China: 34 |
| Country: Number of subjects enrolled | Colombia: 3 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | Guatemala: 2 |
| Country: Number of subjects enrolled | India: 41 |
| Country: Number of subjects enrolled | Mexico: 10 |
| Country: Number of subjects enrolled | Panama: 1 |
| Country: Number of subjects enrolled | Poland: 4 |
| Country: Number of subjects enrolled | Russian Federation: 47 |
| Country: Number of subjects enrolled | Venezuela, Bolivarian Republic of: 3 |
| Worldwide total number of subjects | 191 |
| EEA total number of subjects | 6 |

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) | 174 |
| From 65 to 84 years | 17 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were randomized in 1:1 ratio to imatinib 600 mg QD or nilotinib 400 mg BID for a 2 year study period.

Pre-assignment

Screening details:

Cross-over from one arm to the other was allowed for intolerant patients anytime during treatment, patients who failed to achieve CCyR after 6 months of treatment, loss of response, loss of CHR, loss of best achieved cytogenetic response any time during treatment, or other reason approved by the Study Management Committee.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Nilotinib |

Arm description:

Participants received 400 mg nilotinib twice daily (BID).

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nilotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

400 mg b.i.d.

| | |
|------------------|----------|
| Arm title | Imatinib |
|------------------|----------|

Arm description:

Participants received 600 mg imatinib once daily (QD).

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

Dosage and administration details:

600 mg qd

| Number of subjects in period 1 | Nilotinib | Imatinib |
|---------------------------------------|-----------|----------|
| Started | 96 | 95 |
| Full Analysis Set | 96 | 95 |
| Cross-over set | 13 | 56 |
| Safety Set | 96 | 93 |
| Completed | 0 | 0 |
| Not completed | 96 | 95 |
| Adverse event, serious fatal | 1 | 2 |
| Treatment duration completed | 66 | 76 |
| Consent withdrawn by subject | 9 | 5 |
| Disease progression | 7 | 3 |
| Adverse event, non-fatal | 8 | 2 |
| Protocol deviation | 2 | 6 |
| Administrative problems | 1 | - |
| Lost to follow-up | 2 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Nilotinib |
|-----------------------|-----------|

Reporting group description:

Participants received 400 mg nilotinib twice daily (BID).

| | |
|-----------------------|----------|
| Reporting group title | Imatinib |
|-----------------------|----------|

Reporting group description:

Participants received 600 mg imatinib once daily (QD).

| Reporting group values | Nilotinib | Imatinib | Total |
|---|-----------|----------|-------|
| Number of subjects | 96 | 95 | 191 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 89 | 85 | 174 |
| From 65-84 years | 7 | 10 | 17 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 44.6 | 44.2 | |
| standard deviation | ± 14.47 | ± 15.02 | - |
| Gender, Male/Female Units: Participants | | | |
| Female | 42 | 37 | 79 |
| Male | 54 | 58 | 112 |

End points

End points reporting groups

| | |
|---|-----------|
| Reporting group title | Nilotinib |
| Reporting group description: | |
| Participants received 400 mg nilotinib twice daily (BID). | |
| Reporting group title | Imatinib |
| Reporting group description: | |
| Participants received 600 mg imatinib once daily (QD). | |

Primary: Percentage of participants with Complete Cytogenetic Response (CCyR)

| | |
|---|--|
| End point title | Percentage of participants with Complete Cytogenetic Response (CCyR) |
| End point description: | |
| CCyR was assessed from bone marrow samples. CCyR was defined as having 0% Philadelphia positive (Ph+) chromosome metaphases in bone marrow. | |
| End point type | Primary |
| End point timeframe: | |
| 6 months | |

| End point values | Nilotinib | Imatinib | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 95 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 50 | 42.1 | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Complete cytogenetic response |
| Comparison groups | Imatinib v Nilotinib |
| Number of subjects included in analysis | 191 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3106 |
| Method | Fisher exact |

Secondary: Percentage of participants with Major Molecular Response (MMR)

| | |
|---|--|
| End point title | Percentage of participants with Major Molecular Response (MMR) |
| End point description: | |
| MMR was defined as having a fusion gene of the Bcr and Abl genes of (BCR-ABL) less than or equal to | |

0.1% on the International Scale (IS).

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 12 and 24 months | |

| End point values | Nilotinib | Imatinib | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 95 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| 12 months | 36.5 | 25.3 | | |
| 24 months | 37.5 | 35.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with CCyR

| | |
|---|--------------------------------------|
| End point title | Percentage of participants with CCyR |
| End point description: | |
| CCyR was assessed from bone marrow samples. CCyR was defined as having 0% Philadelphia positive (Ph+) chromosome metaphases in bone marrow. | |
| End point type | Secondary |
| End point timeframe: | |
| 12 and 24 months | |

| End point values | Nilotinib | Imatinib | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 95 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| 12 months | 53.1 | 55.8 | | |
| 24 months | 51 | 61.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to CCyR

| | |
|-----------------|--------------|
| End point title | Time to CCyR |
|-----------------|--------------|

| | |
|---|-----------|
| End point description: | |
| Time to CCyR was defined as time from date of randomization to date of first documented CCyR. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| End point values | Nilotinib | Imatinib | | |
|------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 95 | | |
| Units: Months | | | | |
| median (confidence interval) | 5.55 (5.52 to 5.98) | 5.85 (5.59 to 11.04) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CCyR

| | |
|---|------------------|
| End point title | Duration of CCyR |
| End point description: | |
| Duration of CCyR was defined as time from the date of randomization to the date of first loss of CCyR or death, whichever came first. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| End point values | Nilotinib | Imatinib | | |
|------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 95 | | |
| Units: Months | | | | |
| median (confidence interval) | 9999 (999 to 99999) | 17.2 (17.2 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

| | |
|--|---------------------------------|
| End point title | Progression-Free Survival (PFS) |
| End point description: | |
| PFS was defined as the time from the date of randomization to the date of documented disease | |

progression to accelerated phase or blast crisis (AP/BC), or death due to any cause.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| End point values | Nilotinib | Imatinib | | |
|------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 95 | | |
| Units: Months | | | | |
| median (confidence interval) | 9999 (999 to 99999) | 9999 (999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS)

| | |
|---|---------------------------|
| End point title | Event-Free Survival (EFS) |
| End point description: | |
| EFS was defined as the time from the date of randomization to the date of the first occurrence of any of the following: loss of Complete Hematological Response (CHR), loss of Partial Cytogenetic Response (PCyR), loss of CCyR, death on treatment or progression to AP/BC. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| End point values | Nilotinib | Imatinib | | |
|------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 95 | | |
| Units: Months | | | | |
| median (confidence interval) | 9999 (999 to 99999) | 24.3 (23.8 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

| | |
|---|-----------------------|
| End point title | Overall survival (OS) |
| End point description: | |
| OS was defined as time from date of randomization to the date of the death. | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| End point values | Nilotinib | Imatinib | | |
|------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 95 | | |
| Units: Months | | | | |
| median (confidence interval) | 9999 (999 to 99999) | 25.7 (9 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

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

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Nilotinib 400 mg BID |
|-----------------------|----------------------|

Reporting group description:

Nilotinib 400 mg BID

| | |
|-----------------------|------------------------------------|
| Reporting group title | Cross-over to nilotinib 400 mg BID |
|-----------------------|------------------------------------|

Reporting group description:

Cross-over to nilotinib 400 mg BID

| | |
|-----------------------|----------------------------------|
| Reporting group title | Cross-over to imatinib 600 mg QD |
|-----------------------|----------------------------------|

Reporting group description:

Cross-over to imatinib 600 mg QD

| | |
|-----------------------|--------------------|
| Reporting group title | Imatinib 600 mg QD |
|-----------------------|--------------------|

Reporting group description:

Imatinib 600 mg QD

| Serious adverse events | Nilotinib 400 mg BID | Cross-over to nilotinib 400 mg BID | Cross-over to imatinib 600 mg QD |
|---|----------------------|------------------------------------|----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 96 (11.46%) | 4 / 56 (7.14%) | 1 / 13 (7.69%) |
| number of deaths (all causes) | 1 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Blast cell crisis | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 1 / 56 (1.79%) | 0 / 13 (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 |
| Endometrial cancer | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 96 (0.00%) | 0 / 56 (0.00%) | 0 / 13 (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 | | | |
| Arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 0 / 13 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 1 / 56 (1.79%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 0 / 56 (0.00%) | 0 / 13 (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 |
| Malaria antibody test positive | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 0 / 56 (0.00%) | 0 / 13 (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 | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 0 / 13 (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 |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 96 (2.08%) | 0 / 56 (0.00%) | 0 / 13 (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 |
| Angina unstable | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 0 / 13 (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 |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 0 / 56 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 0 / 13 (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 |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 0 / 13 (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 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 1 / 56 (1.79%) | 0 / 13 (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 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 96 (2.08%) | 1 / 56 (1.79%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 0 / 56 (0.00%) | 0 / 13 (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 | | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 0 / 13 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 0 / 56 (0.00%) | 0 / 13 (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 | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 1 / 56 (1.79%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 0 / 56 (0.00%) | 0 / 13 (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 |
| Endocrine disorders | | | |
| Autoimmune thyroiditis | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 0 / 13 (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 |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 0 / 13 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 0 / 13 (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 | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 0 / 56 (0.00%) | 0 / 13 (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 |
| Hepatitis B | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 96 (0.00%) | 0 / 56 (0.00%) | 0 / 13 (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 / 96 (0.00%) | 1 / 56 (1.79%) | 0 / 13 (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 |

| Serious adverse events | Imatinib 600 mg QD | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 93 (9.68%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Blast cell crisis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometrial cancer | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Haemoglobin decreased | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Malaria antibody test positive | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphadenopathy | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Endocrine disorders | | | |
| Autoimmune thyroiditis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis B | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Nilotinib 400 mg BID | Cross-over to nilotinib 400 mg BID | Cross-over to imatinib 600 mg QD |
|---|----------------------|------------------------------------|----------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 80 / 96 (83.33%) | 44 / 56 (78.57%) | 11 / 13 (84.62%) |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 5 / 96 (5.21%) 5 | 2 / 56 (3.57%) 2 | 1 / 13 (7.69%) 1 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 96 (6.25%) | 0 / 56 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 4 | 0 | 3 |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 0 / 56 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 96 (5.21%) | 1 / 56 (1.79%) | 0 / 13 (0.00%) |
| occurrences (all) | 7 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 12 / 96 (12.50%) | 6 / 56 (10.71%) | 2 / 13 (15.38%) |
| occurrences (all) | 14 | 6 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 96 (5.21%) | 0 / 56 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 5 | 0 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 96 (3.13%) | 1 / 56 (1.79%) | 1 / 13 (7.69%) |
| occurrences (all) | 4 | 1 | 1 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 0 / 56 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 20 / 96 (20.83%) | 9 / 56 (16.07%) | 0 / 13 (0.00%) |
| occurrences (all) | 30 | 15 | 0 |
| Aspartate aminotransferase increased | | | |

| | | | |
|--|------------------|------------------|----------------|
| subjects affected / exposed | 7 / 96 (7.29%) | 4 / 56 (7.14%) | 0 / 13 (0.00%) |
| occurrences (all) | 12 | 5 | 0 |
| Bilirubin conjugated increased | | | |
| subjects affected / exposed | 8 / 96 (8.33%) | 5 / 56 (8.93%) | 0 / 13 (0.00%) |
| occurrences (all) | 17 | 8 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 13 / 96 (13.54%) | 11 / 56 (19.64%) | 0 / 13 (0.00%) |
| occurrences (all) | 35 | 20 | 0 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 0 | 1 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 8 / 96 (8.33%) | 3 / 56 (5.36%) | 0 / 13 (0.00%) |
| occurrences (all) | 12 | 3 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 3 / 96 (3.13%) | 3 / 56 (5.36%) | 0 / 13 (0.00%) |
| occurrences (all) | 5 | 3 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 96 (2.08%) | 4 / 56 (7.14%) | 1 / 13 (7.69%) |
| occurrences (all) | 4 | 7 | 1 |
| Weight increased | | | |
| subjects affected / exposed | 3 / 96 (3.13%) | 4 / 56 (7.14%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 4 | 1 |
| White blood cell count increased | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 0 / 56 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Animal bite | | | |
| subjects affected / exposed | 0 / 96 (0.00%) | 1 / 56 (1.79%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 96 (2.08%) | 0 / 56 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 0 | 1 |
| Nervous system disorders | | | |

| | | | |
|--|------------------------|------------------------|----------------------|
| Dizziness subjects affected / exposed occurrences (all) | 3 / 96 (3.13%) 3 | 3 / 56 (5.36%) 3 | 1 / 13 (7.69%) 1 |
| Headache subjects affected / exposed occurrences (all) | 14 / 96 (14.58%) 18 | 8 / 56 (14.29%) 9 | 4 / 13 (30.77%) 4 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 11 / 96 (11.46%) 15 | 10 / 56 (17.86%) 14 | 4 / 13 (30.77%) 4 |
| Leukocytosis subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | 1 / 56 (1.79%) 1 | 1 / 13 (7.69%) 1 |
| Leukopenia subjects affected / exposed occurrences (all) | 10 / 96 (10.42%) 17 | 9 / 56 (16.07%) 15 | 0 / 13 (0.00%) 0 |
| Lymphopenia subjects affected / exposed occurrences (all) | 3 / 96 (3.13%) 6 | 3 / 56 (5.36%) 6 | 1 / 13 (7.69%) 1 |
| Neutropenia subjects affected / exposed occurrences (all) | 11 / 96 (11.46%) 28 | 13 / 56 (23.21%) 18 | 1 / 13 (7.69%) 1 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 19 / 96 (19.79%) 33 | 13 / 56 (23.21%) 30 | 3 / 13 (23.08%) 4 |
| Eye disorders | | | |
| Eyelid oedema subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | 0 / 56 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Papilloedema subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | 0 / 56 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Periorbital oedema subjects affected / exposed occurrences (all) | 2 / 96 (2.08%) 2 | 1 / 56 (1.79%) 1 | 2 / 13 (15.38%) 2 |
| Gastrointestinal disorders | | | |

| | | | |
|--|------------------------|-----------------------|----------------------|
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 96 (1.04%) 1 | 0 / 56 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 6 / 96 (6.25%) 6 | 0 / 56 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Anal fissure subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | 0 / 56 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 6 / 96 (6.25%) 7 | 1 / 56 (1.79%) 1 | 1 / 13 (7.69%) 1 |
| Dyspepsia subjects affected / exposed occurrences (all) | 2 / 96 (2.08%) 2 | 0 / 56 (0.00%) 0 | 2 / 13 (15.38%) 2 |
| Nausea subjects affected / exposed occurrences (all) | 5 / 96 (5.21%) 5 | 4 / 56 (7.14%) 5 | 2 / 13 (15.38%) 3 |
| Proctalgia subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | 0 / 56 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Stomatitis subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | 0 / 56 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Tongue haematoma subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | 0 / 56 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Vomiting subjects affected / exposed occurrences (all) | 4 / 96 (4.17%) 5 | 5 / 56 (8.93%) 6 | 3 / 13 (23.08%) 7 |
| Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 14 / 96 (14.58%) 30 | 9 / 56 (16.07%) 10 | 0 / 13 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|------------------------|-----------------------|---------------------|
| Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | 1 / 56 (1.79%) 1 | 1 / 13 (7.69%) 1 |
| Rash subjects affected / exposed occurrences (all) | 22 / 96 (22.92%) 24 | 9 / 56 (16.07%) 11 | 1 / 13 (7.69%) 1 |
| Pruritus subjects affected / exposed occurrences (all) | 8 / 96 (8.33%) 11 | 3 / 56 (5.36%) 5 | 0 / 13 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 9 / 96 (9.38%) 11 | 2 / 56 (3.57%) 4 | 1 / 13 (7.69%) 1 |
| Myalgia subjects affected / exposed occurrences (all) | 8 / 96 (8.33%) 8 | 2 / 56 (3.57%) 2 | 0 / 13 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 3 / 96 (3.13%) 3 | 3 / 56 (5.36%) 3 | 0 / 13 (0.00%) 0 |
| Infections and infestations | | | |
| Influenza subjects affected / exposed occurrences (all) | 0 / 96 (0.00%) 0 | 0 / 56 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 5 / 96 (5.21%) 7 | 1 / 56 (1.79%) 1 | 0 / 13 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 4 / 96 (4.17%) 4 | 3 / 56 (5.36%) 3 | 0 / 13 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 11 / 96 (11.46%) 18 | 2 / 56 (3.57%) 4 | 0 / 13 (0.00%) 0 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 5 / 96 (5.21%) 6 | 1 / 56 (1.79%) 1 | 0 / 13 (0.00%) 0 |

| | | | |
|-----------------------------|------------------|----------------|----------------|
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 96 (1.04%) | 1 / 56 (1.79%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 1 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 10 / 96 (10.42%) | 1 / 56 (1.79%) | 1 / 13 (7.69%) |
| occurrences (all) | 22 | 1 | 4 |

| | | | |
|---|--------------------|--|--|
| Non-serious adverse events | Imatinib 600 mg QD | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 61 / 93 (65.59%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | | |
| occurrences (all) | 3 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences (all) | 0 | | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 93 (8.60%) | | |
| occurrences (all) | 8 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | | |
| occurrences (all) | 2 | | |
| Oropharyngeal pain | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 2 | | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 93 (0.00%) 0 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 5 / 93 (5.38%) 7 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 4 | | |
| Bilirubin conjugated increased subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 3 | | |
| Blood phosphorus decreased subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 2 | | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 0 / 93 (0.00%) 0 | | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 8 / 93 (8.60%) 10 | | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 3 | | |
| Weight increased subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 3 | | |
| White blood cell count increased | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 0 / 93 (0.00%) 0 | | |
| Injury, poisoning and procedural complications Animal bite subjects affected / exposed occurrences (all) | 0 / 93 (0.00%) 0 | | |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 0 / 93 (0.00%) 0 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 4 / 93 (4.30%) 5 6 / 93 (6.45%) 7 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) | 18 / 93 (19.35%) 22 0 / 93 (0.00%) 0 22 / 93 (23.66%) 39 6 / 93 (6.45%) 8 23 / 93 (24.73%) 49 24 / 93 (25.81%) 47 | | |

| | | | |
|-----------------------------|------------------|--|--|
| Eye disorders | | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 10 / 93 (10.75%) | | |
| occurrences (all) | 13 | | |
| Papilloedema | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences (all) | 0 | | |
| Periorbital oedema | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | | |
| occurrences (all) | 2 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | | |
| occurrences (all) | 2 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | | |
| occurrences (all) | 4 | | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences (all) | 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 15 / 93 (16.13%) | | |
| occurrences (all) | 17 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | | |
| occurrences (all) | 2 | | |
| Nausea | | | |
| subjects affected / exposed | 14 / 93 (15.05%) | | |
| occurrences (all) | 27 | | |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tongue haematoma | | | |

| | | | |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>0 / 93 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Vomiting</p> <p>subjects affected / exposed</p> <p>10 / 93 (10.75%)</p> <p>occurrences (all)</p> <p>20</p> | | | |
| <p>Hepatobiliary disorders</p> <p>Hyperbilirubinaemia</p> <p>subjects affected / exposed</p> <p>1 / 93 (1.08%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Hyperhidrosis</p> <p>subjects affected / exposed</p> <p>0 / 93 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>4 / 93 (4.30%)</p> <p>occurrences (all)</p> <p>6</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>0 / 93 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>3 / 93 (3.23%)</p> <p>occurrences (all)</p> <p>3</p> <p>Myalgia</p> <p>subjects affected / exposed</p> <p>1 / 93 (1.08%)</p> <p>occurrences (all)</p> <p>1</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>1 / 93 (1.08%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Infections and infestations</p> <p>Influenza</p> <p>subjects affected / exposed</p> <p>0 / 93 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Upper respiratory tract infection</p> <p>subjects affected / exposed</p> <p>5 / 93 (5.38%)</p> <p>occurrences (all)</p> <p>8</p> | | | |

| | | | |
|------------------------------------|----------------|--|--|
| Metabolism and nutrition disorders | | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | | |
| occurrences (all) | 3 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | | |
| occurrences (all) | 4 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | | |
| occurrences (all) | 6 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 17 February 2009 | The primary reason for Amendment 1 was to include European sites as participants. The secondary reason was to clarify the timing of the interim analysis and to incorporate the Independent Data Monitoring Committee that would monitor safety throughout the study and review safety and efficacy data during the interim analysis. The number of interim analyses was updated from two to one. |
| 17 June 2009 | Amendment 2 was implemented to add the EU-DRACT number for European sites. This amendment only applied to Europe and was not applicable to Latin America. |
| 03 May 2010 | Amendment 3: The protocol has been revised to modify certain inclusion and exclusion criteria such as primarily INF-a usage and Bone Marrow testing for confirmation of study inclusion. The changes were implemented following thorough analysis of reasons for screening failure of patients considered for the protocol under previous amendment. These changes will not affect the study endpoints or objectives but merely allow for patient that would otherwise be eligible for this study to be included. Also addressed in this amendment is the change in ELN 2009 recommendations to allow for patients at 3 months of treatment with imatinib to be evaluated for suboptimal response. |
| 20 December 2010 | Amendment 4 was issued to revise the Case Report Forms (CRFs) and Data Management section as well as to update the language in the IVRS/IWRS section in accordance with Novartis SOPs. In addition, this amendment clarified the Visit Assessment Schedule and OS follow up. |
| 15 March 2012 | Amendment 5 was issued to update safety information and to clarify patient eligibility criteria. The safety update included pregnancy language, cardiac, death and sudden cardiac death and CYP34a inhibitors/inducers. The pregnancy language was updated since the reproductive-developmental toxicity profiles of nilotinib and imatinib do not indicate genotoxicity, pregnancy outcomes from female partners of male patients participating in this study were collected. The main eligibility criteria clarifications were to prior therapy, definition of intolerance and definition of chronic phase CML. An additional change was made to the secondary endpoints. The rate of CHR was removed as a secondary endpoint. Patients with no CHR at baseline are considered treatment failures and were thus not eligible for the study. All patients were expected to be in CHR at baseline. However, it was possible for patients to have loss of CHR on study. Loss of CHR, which needed to be confirmed, was retained as a study endpoint CHR as it was one of the events included in the definition of EFS. |
| 16 January 2014 | The major reason for amendment 6 was to ensure alignment and consistency of pregnancy prevention language with the nilotinib program language, nilotinib label, and Novartis internal pregnancy guidelines. These changes have also been incorporated into the consent form. In addition, the risks associated with nilotinib in the consent form have been updated to reflect the current investigators brochure. |

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 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: