



Clinical trial results:

A multi-center, open-label, non-comparative, phase II trial on efficacy and safety of ICL670 given for 1 year with dose adjustments based on serum ferritin in patients with chronic anemia and transfusional hemosiderosis

A one-year extension to a multi-center, open-label, non-comparative, phase II trial on efficacy and safety of ICL670 given for 1 year with dose adjustments based on serum ferritin in patients with chronic anemia and transfusional hemosiderosis

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2006-003337-32 |
| Trial protocol | ES |
| Global end of trial date | 02 February 2012 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 22 July 2016 |
| First version publication date | 22 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CICL670A2204 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00631163 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 02 February 2012 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 February 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of deferasirox, based on liver iron concentration (LIC) decrease over one year in paediatric and adult subjects with chronic anemias and transfusional hemosiderosis other than β -thalassemia or sickle cell disease.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH), Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed. Rescue medication was not allowed during the course of the study. The investigator provided follow-up medical care for all subjects who were prematurely withdrawn from the study, or referred them for appropriate ongoing care.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 22 October 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Spain: 4 |
| Country: Number of subjects enrolled | Japan: 53 |
| Country: Number of subjects enrolled | Poland: 20 |
| Country: Number of subjects enrolled | Singapore: 3 |
| Country: Number of subjects enrolled | Turkey: 22 |
| Worldwide total number of subjects | 102 |
| EEA total number of subjects | 24 |

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) | 16 |
| Adolescents (12-17 years) | 8 |
| Adults (18-64 years) | 41 |
| From 65 to 84 years | 36 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 31 centres in 5 countries.

Pre-assignment

Screening details:

A total of 144 subjects were screened, of which only 102 subjects enrolled in the study. Remaining 42 subjects were considered as screen failures.

Period 1

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

Blinding implementation details:

This was an open-label study, hence no blinding was implemented.

Arms

| | |
|-----------|--------------------------|
| Arm title | Deferasirox (Core Study) |
|-----------|--------------------------|

Arm description:

The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Deferasirox |
| Investigational medicinal product code | ICL670 |
| Other name | |
| Pharmaceutical forms | Dispersible tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Deferasirox 20 mg/kg was administered once daily. The dose of deferasirox was adjusted to either 10 mg/kg or 30 mg/kg based on the volumes of blood transfusions being administered in a month.

| Number of subjects in period 1 | Deferasirox (Core Study) |
|---|--------------------------|
| Started | 102 |
| Completed | 68 |
| Not completed | 34 |
| Consent withdrawn by subject | 8 |
| Adverse event, non-fatal | 12 |
| Death | 6 |
| Subject's condition no longer required study drug | 1 |
| Administrative problems | 6 |

| | |
|-------------------|---|
| Lost to follow-up | 1 |
|-------------------|---|

Period 2

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

Blinding implementation details:

The study was open-label, hence no blinding was implemented.

Arms

| | |
|------------------|-------------------------------|
| Arm title | Deferasirox (Extension study) |
|------------------|-------------------------------|

Arm description:

The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Deferasirox |
| Investigational medicinal product code | ICL670 |
| Other name | |
| Pharmaceutical forms | Dispersible tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Deferasirox 20 mg/kg was administered once daily. The dose of deferasirox was adjusted to either 10 mg/kg or 30 mg/kg based on the volumes of blood transfusions being administered in a month.

| Number of subjects in period 2^[1] | Deferasirox (Extension study) |
|---|-------------------------------|
| Started | 57 |
| Completed | 52 |
| Not completed | 5 |
| Consent withdrawn by subject | 2 |
| Adverse event, non-fatal | 1 |
| Abnormal laboratory values | 1 |
| Protocol deviation | 1 |

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: Of 68 subjects who completed the preceding period, only 57 subjects opted to enroll in extension study.

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Deferasirox (Core Study) |
|-----------------------|--------------------------|

Reporting group description:

The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level.

| Reporting group values | Deferasirox (Core Study) | Total | |
|------------------------|--------------------------|-------|--|
| Number of subjects | 102 | 102 | |
| Age categorical | | | |
| Units: Subjects | | | |
| 2 years to < 6years | 11 | 11 | |
| 6 years to <12 years | 5 | 5 | |
| 12 years to <18 years | 8 | 8 | |
| 18 years to < 65 years | 41 | 41 | |
| >= 65 years | 37 | 37 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 47.8 | | |
| standard deviation | ± 25.9 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 49 | 49 | |
| Male | 53 | 53 | |

End points

End points reporting groups

| | |
|--|-------------------------------|
| Reporting group title | Deferasirox (Core Study) |
| Reporting group description: The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level. | |
| Reporting group title | Deferasirox (Extension study) |
| Reporting group description: The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level. | |
| Subject analysis set title | All randomised subjects |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level. | |
| Subject analysis set title | Japanese subjects |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: All subjects who were enrolled in Japan and received deferasirox as per the study protocol. | |

Primary: Absolute change from baseline in liver iron concentration (LIC) to Year 1

| | |
|---|--|
| End point title | Absolute change from baseline in liver iron concentration (LIC) to Year 1 ^[1] |
| End point description: LIC, a predictor of iron burden, was measured using relaxation rate magnetic resonance imaging (R2-MRI) technique. Relaxation rate was determined as $R2 = 1/\text{relaxation time (T2)}$. The baseline value of LIC of subjects was categorized as < 7, ≥ 7 to < 15, and ≥ 15 milligram of iron/tissue dry weight (mg Fe/g dw). A negative change from baseline favored study treatment in reducing LIC. The analysis was performed in per-protocol population in core study (PP1 Set), comprising of all enrolled subjects who had LIC assessments at baseline and Year 1. | |
| End point type | Primary |
| End point timeframe: Baseline, Year 1 (End of core study) | |
| 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: only summary results available, no comparative statistics available | |

| | | | | |
|--------------------------------------|--------------------------|--|--|--|
| End point values | Deferasirox (Core Study) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: mg Fe/g dw | | | | |
| arithmetic mean (standard deviation) | -10.9 (± 11.86) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in liver iron concentration (LIC) to end of Year 2

| | |
|---|--|
| End point title | Absolute change from baseline in liver iron concentration (LIC) to end of Year 2 |
| End point description: LIC, a predictor of iron burden, was measured using R2-MRI technique. Relaxation rate was determined as $R2 = 1/T2$. The baseline value of LIC of subjects was categorized as < 7 , ≥ 7 to < 15 , and ≥ 15 mg Fe/g dw. A negative change from baseline favoured study treatment in reducing LIC. The analysis was performed in per-protocol population in core study (PP2 Set), comprising of all enrolled subjects who had LIC assessments at baseline and at end of the extension phase. | |
| End point type | Secondary |
| End point timeframe: Baseline to End of Year 2 (End of extension study) | |

| | | | | |
|--------------------------------------|-------------------------------|--|--|--|
| End point values | Deferasirox (Extension study) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: mg Fe/g dw | | | | |
| arithmetic mean (standard deviation) | -13.5 (± 14.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in LIC in Japanese subgroup

| | |
|--|---|
| End point title | Absolute change from baseline in LIC in Japanese subgroup |
| End point description: | |
| LIC, a predictor of iron burden, was measured using R2-MRI technique. Relaxation rate was determined as $R2 = 1/T2$. The baseline value of LIC was < 7 , ≥ 7 to < 15 , and ≥ 15 mg Fe/g dw. A negative change from baseline favoured study treatment in reducing LIC. The analysis was performed in PP1 set in Japanese subgroup defined as all subjects who were enrolled in Japan for core study (Year 1) and PP2 set in Japanese subgroup for extension study (Year 2). Here, 'n' signifies the subjects assessed for LIC in Japanese subgroup for each group, respectively. | |
| End point type | Secondary |

End point timeframe:

Baseline, End of Year 1 (End of core study), End of Year 2 (End of extension study)

| End point values | Japanese subjects | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 31 | | | |
| Units: mg Fe/g dw | | | | |
| arithmetic mean (standard deviation) | | | | |
| Year 1 (n= 31) | -13.9 (± 10.21) | | | |
| Year 2 (n= 26) | -18.4 (± 12.48) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in serum ferritin levels to Year 2

| | |
|-----------------|--|
| End point title | Absolute change from baseline in serum ferritin levels to Year 2 |
|-----------------|--|

End point description:

Serum ferritin was a marker for the monitoring of chelation therapy. Ferritin protein stores iron and provides overall iron levels, higher ferritin in blood showed more iron content. The analysis was performed in PP2 Set population and Japanese subgroup. Here, "Number of subjects analysed" signifies the subjects assessed for serum ferritin during the study for each arm, respectively.

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

End point timeframe:

Baseline up to Year 2 (End of extension study)

| End point values | All randomised subjects | Japanese subjects | | |
|--------------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 98 | 51 | | |
| Units: nanogram(s)/millilitre | | | | |
| arithmetic mean (standard deviation) | -677.9 (± 4462.11) | -892.8 (± 5724.89) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute serum ferritin levels over 2 years

| | |
|-----------------|---|
| End point title | Absolute serum ferritin levels over 2 years |
|-----------------|---|

End point description:

Serum ferritin was a marker for the monitoring of chelation therapy. Ferritin protein stores iron and provides overall iron levels, higher ferritin in blood showed more iron content. The analysis was performed in PP1 set population for core study (Year 1) and PP2 set population for extension study (Year 2) and Japanese subgroup. Here, "Number of subjects analysed" signifies the subjects assessed for serum ferritin during the study for each arm, respectively.

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

End point timeframe:

Baseline, Year 1 (End of core study), Year 2 (End of extension study)

| End point values | All randomised subjects | Japanese subjects | | |
|--------------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 50 | 31 | | |
| Units: nanogram(s)/millilitre | | | | |
| arithmetic mean (standard deviation) | | | | |
| Year 1 | 2653.3 (± 5281.3) | 2903.5 (± 3376) | | |
| Year 2 | 2092.4 (± 2287.11) | 2114.8 (± 2391.31) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total body iron elimination rate (TBIE), Iron intake, Iron excretion/iron intake and chelation efficiency after 2 years

| | |
|-----------------|---|
| End point title | Total body iron elimination rate (TBIE), Iron intake, Iron excretion/iron intake and chelation efficiency after 2 years |
|-----------------|---|

End point description:

Total body iron excretion (TBIE) was used to investigate the chelation efficacy of deferasirox therapy. TBIE rate was estimated based on the iron influx as determined by the amount of red cells transfused and the change in total body iron (TBI) stores. The analysis was performed in PP2 set population and Japanese subgroup. Here, "Number of subjects analysed" signifies the subjects assessed for TBIE in the study arm. Total body iron elimination rate (TBIE), Iron intake, Iron excretion/iron intake and chelation efficiency

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

End point timeframe:

Baseline, Year 2 (End of extension study)

| End point values | Deferasirox (Extension study) | Japanese subjects | | |
|--------------------------------------|-------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 41 | 26 | | |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| TBIE | 0.46 (± 0.252) | 0.54 (± 0.215) | | |

| | | | | |
|----------------------------|--------------------|---------------------|--|--|
| Iron intake | 0.27 (\pm 0.15) | 0.27 (\pm 0.16) | | |
| Iron excretion/iron intake | 2 (\pm 1.368) | 2.44 (\pm 1.417) | | |
| Chelation efficiency | 0.4 (\pm 0.221) | 0.5 (\pm 0.177) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of LIC and serum ferritin at core and extension study

| | |
|-----------------|---|
| End point title | Correlation of LIC and serum ferritin at core and extension study |
|-----------------|---|

End point description:

LIC, a predictor of iron burden, was measured using R2-MRI technique. Relaxation rate was determined as $R2 = 1/T2$. The baseline value of LIC was < 7 , ≥ 7 to < 15 , and ≥ 15 mg Fe/g dw. Serum ferritin was a marker for the monitoring of chelation therapy. Ferritin protein stores iron and provides overall iron levels, higher ferritin in blood showed more iron content. The correlation between absolute change in LIC and absolute change in serum ferritin was determined. The analysis was performed in PP1 set for core study (Year 1) and PP2 set for extension study (Year 2). Here, "Number of subjects analysed" signifies the subjects assessed for LIC and serum ferritin during the study for each arm, respectively.

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

End point timeframe:

Baseline, Year 1 (End of core study), Year 2 (End of extension study)

| End point values | Deferasirox (Core Study) | Deferasirox (Extension study) | | |
|--------------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 50 | 40 | | |
| Units: Correlation coefficient | | | | |
| number (not applicable) | 0.291 | 0.325 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs), serious adverse events (SAEs), adverse event of special interest (AESI), discontinuation and interruption

| | |
|-----------------|---|
| End point title | Number of subjects with adverse events (AEs), serious adverse events (SAEs), adverse event of special interest (AESI), discontinuation and interruption |
|-----------------|---|

End point description:

Adverse events (AEs) were defined as any unfavourable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events (SAEs) were defined as any untoward medical occurrences that result in death, are life threatening, require hospitalisation, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgement of investigators represent significant hazards. Death was defined as a fatal event leading to permanent cessation of all vital functions of the body. The analysis was performed in the safety set (SAF) population, defined as subjects who received

at least one dose of study drug, which was defined as at least one administration record with a valid date and an actual total daily dose administrated above zero, and Japanese sub-group.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Year 2 (End of extension study) | |

| End point values | All randomised subjects | Japanese subjects | | |
|--|-------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 102 | 53 | | |
| Units: Subjects | | | | |
| AEs | 97 | 53 | | |
| SAEs | 46 | 25 | | |
| Death | 5 | 4 | | |
| Mild AEs | 17 | 5 | | |
| Moderate AEs | 39 | 25 | | |
| Severe AEs | 41 | 23 | | |
| AEs suspected to study drug | 65 | 43 | | |
| SAEs suspected to study drug | 10 | 6 | | |
| AEs leading to discontinuation of study drug | 14 | 7 | | |
| AEs leading to dose adjustment/interruption | 67 | 42 | | |
| AESI | 62 | 39 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant ophthalmological abnormalities

| | |
|--|---|
| End point title | Number of subjects with clinically significant ophthalmological abnormalities |
| End point description: | |
| Clinically significant changes in left eye and right eye were assessed by the investigator based on methods like visual acuity, slit lamp examination, tonometry and fundus oculi. The analysis was performed in the SAF population and Japanese subgroup. These patients comprise 2 year completer groups | |
| End point type | Secondary |
| End point timeframe: | |
| 2 years (End of extension study) | |

| End point values | All randomised subjects | Japanese subjects | | |
|-----------------------------|-------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 50 ^[2] | 28 ^[3] | | |
| Units: Subjects | | | | |
| Normal | 25 | 12 | | |
| Abnormal Clin Insignificant | 15 | 12 | | |
| Abnormal Clin Significant | 10 | 4 | | |
| Not Available | 0 | 0 | | |
| Total | 50 | 28 | | |

Notes:

[2] - number of patients at end of trial- completer group

[3] - Number of japanese patients at end of trial with ocular measurements- 2 year completers

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV.

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 | 14.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | myelodysplastic syndrome |
|-----------------------|--------------------------|

Reporting group description:

myelodysplastic syndrome

| | |
|-----------------------|-------|
| Reporting group title | Other |
|-----------------------|-------|

Reporting group description:

very rare diseases (e.g. Diamond Blackfan anemia, myelofibrosis, specific enzyme deficiency).

| | |
|-----------------------|-----------------|
| Reporting group title | aplastic anemia |
|-----------------------|-----------------|

Reporting group description:

aplastic anemia,

| Serious adverse events | myelodysplastic syndrome | Other | aplastic anemia |
|---|--------------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 22 / 42 (52.38%) | 10 / 31 (32.26%) | 14 / 29 (48.28%) |
| number of deaths (all causes) | 1 | 1 | 3 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| ABDOMINAL NEOPLASM | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| ACUTE MYELOID LEUKAEMIA | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| BLADDER NEOPLASM | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| MYELODYSPLASTIC SYNDROME | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MYELOFIBROSIS | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| RECTAL CANCER | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| CHEST DISCOMFORT | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| DISUSE SYNDROME | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| FATIGUE | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| GENERALISED OEDEMA | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| MALAISE | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MULTI-ORGAN FAILURE | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYREXIA | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | 1 / 31 (3.23%) | 2 / 29 (6.90%) |
| occurrences causally related to treatment / all | 3 / 8 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| HYPERSENSITIVITY | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| ADENOIDAL HYPERTROPHY | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| HYPOXIA | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| Psychiatric disorders | | | |
| NEUROSIS | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Investigations | | | |
| BODY HEIGHT BELOW NORMAL | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| C-REACTIVE PROTEIN INCREASED | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| CONTUSION | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LUMBAR VERTEBRAL FRACTURE | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| TOOTH FRACTURE | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| TRAUMATIC HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| TRAUMATIC INTRACRANIAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| ATRIAL FIBRILLATION | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ATRIAL FLUTTER | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 FAILURE | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| PERICARDITIS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| Nervous system disorders | | | |
| CEREBELLAR HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| CEREBRAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CEREBRAL INFARCTION | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| DIZZINESS | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 31 (3.23%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| APLASTIC ANAEMIA | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 3 / 29 (10.34%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DISSEMINATED INTRAVASCULAR COAGULATION | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 2 / 29 (6.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| CATARACT | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| RETINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| Gastrointestinal disorders | | | |
| ASCITES | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |

| | | | |
|---|----------------|----------------|----------------|
| DIARRHOEA | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| ENTEROCOLITIS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROINTESTINAL ULCER | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| PERIODONTAL DISEASE | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| PERIODONTITIS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| RADICULAR CYST | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| VOMITING | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| Hepatobiliary disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| HEPATIC FUNCTION ABNORMAL | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| Skin and subcutaneous tissue disorders | | | |
| HAEMORRHAGE SUBCUTANEOUS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| PANNICULITIS | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| RASH ERYTHEMATOUS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| SKIN ULCER | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| URTICARIA | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| FANCONI SYNDROME ACQUIRED | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |

| | | | |
|---|----------------|----------------|----------------|
| NEPHROLITHIASIS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| Endocrine disorders | | | |
| DELAYED PUBERTY | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| BONE PAIN | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| BONE SWELLING | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MUSCULOSKELETAL CHEST PAIN | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| Infections and infestations | | | |
| BACTERIAL INFECTION | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| BRONCHITIS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| BRONCHOPNEUMONIA | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CELLULITIS | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| ENTEROCOLITIS INFECTIOUS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| FUNGAEMIA | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| FUNGAL OESOPHAGITIS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| GASTRITIS VIRAL | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HERPES ZOSTER | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INFECTION | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INFLUENZA | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MENINGITIS | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ORAL HERPES | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| PARONYCHIA | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERTUSSIS | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| PHARYNGITIS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONIA | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 0 / 31 (0.00%) | 3 / 29 (10.34%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEPSIS | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEPTIC SHOCK | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VIRAL INFECTION | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| ZYGOMYCOSIS | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |
| Metabolism and nutrition disorders | | | |
| DEHYDRATION | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| HYPERCALCAEMIA | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 0 / 29 (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 |
| HYPOGLYCAEMIA | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 0 / 29 (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 |

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

| Non-serious adverse events | myelodysplastic syndrome | Other | aplastic anemia |
|---|--------------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 42 (92.86%) | 25 / 31 (80.65%) | 25 / 29 (86.21%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| MYELODYSPLASTIC SYNDROME | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 4 | 0 | 1 |
| Vascular disorders | | | |
| HYPOTENSION | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 0 | 3 |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 1 / 31 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 1 | 2 |
| CHEST PAIN | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 3 / 29 (10.34%) |
| occurrences (all) | 1 | 0 | 4 |
| FACE OEDEMA | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 0 | 3 |
| FATIGUE | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 31 (9.68%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 3 | 1 |
| MALAISE | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 42 (4.76%) | 2 / 31 (6.45%) | 4 / 29 (13.79%) |
| occurrences (all) | 2 | 2 | 6 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 14 / 42 (33.33%) | 1 / 31 (3.23%) | 7 / 29 (24.14%) |
| occurrences (all) | 19 | 2 | 15 |
| PYREXIA | | | |
| subjects affected / exposed | 11 / 42 (26.19%) | 6 / 31 (19.35%) | 9 / 29 (31.03%) |
| occurrences (all) | 22 | 11 | 16 |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 5 / 31 (16.13%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 5 | 3 |
| DYSPNOEA | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 1 / 31 (3.23%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 2 | 1 |
| EPISTAXIS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 31 (6.45%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 2 | 2 |
| NASAL CONGESTION | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 31 (6.45%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 31 (3.23%) | 3 / 29 (10.34%) |
| occurrences (all) | 1 | 1 | 3 |
| PRODUCTIVE COUGH | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| RHINITIS ALLERGIC | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 31 (6.45%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 3 | 1 |
| Psychiatric disorders | | | |
| DELIRIUM | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| INSOMNIA | | | |

| | | | |
|---|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 6 / 42 (14.29%) 8 | 1 / 31 (3.23%) 1 | 1 / 29 (3.45%) 1 |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 31 (9.68%) | 1 / 29 (3.45%) |
| occurrences (all) | 4 | 3 | 4 |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 31 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 1 | 3 |
| BLOOD ALKALINE PHOSPHATASE INCREASED | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 31 (6.45%) | 3 / 29 (10.34%) |
| occurrences (all) | 1 | 2 | 4 |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 16 / 42 (38.10%) | 2 / 31 (6.45%) | 8 / 29 (27.59%) |
| occurrences (all) | 29 | 4 | 19 |
| C-REACTIVE PROTEIN INCREASED | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 0 / 31 (0.00%) | 5 / 29 (17.24%) |
| occurrences (all) | 7 | 0 | 9 |
| PROTEIN URINE PRESENT | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 5 / 31 (16.13%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 10 | 1 |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 2 / 31 (6.45%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 2 | 2 |
| Injury, poisoning and procedural complications | | | |
| ALLERGIC TRANSFUSION REACTION | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 1 / 31 (3.23%) | 1 / 29 (3.45%) |
| occurrences (all) | 4 | 1 | 1 |
| CONTUSION | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | 0 / 31 (0.00%) | 3 / 29 (10.34%) |
| occurrences (all) | 6 | 0 | 5 |
| FALL | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 31 (0.00%) | 3 / 29 (10.34%) |
| occurrences (all) | 2 | 0 | 3 |

| | | | |
|---|----------------------|---------------------|----------------------|
| SPINAL COMPRESSION FRACTURE subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 2 | 0 / 31 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| TOOTH INJURY subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 31 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| TRANSFUSION REACTION subjects affected / exposed occurrences (all) | 4 / 42 (9.52%) 5 | 1 / 31 (3.23%) 1 | 2 / 29 (6.90%) 3 |
| Cardiac disorders ATRIAL FIBRILLATION subjects affected / exposed occurrences (all) | 4 / 42 (9.52%) 4 | 0 / 31 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| CARDIAC FAILURE subjects affected / exposed occurrences (all) | 4 / 42 (9.52%) 4 | 1 / 31 (3.23%) 1 | 2 / 29 (6.90%) 2 |
| TACHYCARDIA subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | 1 / 31 (3.23%) 1 | 2 / 29 (6.90%) 3 |
| Nervous system disorders DYSGEUSIA subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 0 / 31 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| HEADACHE subjects affected / exposed occurrences (all) | 8 / 42 (19.05%) 9 | 3 / 31 (9.68%) 5 | 4 / 29 (13.79%) 5 |
| SOMNOLENCE subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 1 / 31 (3.23%) 1 | 2 / 29 (6.90%) 2 |
| Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) | 5 / 42 (11.90%) 5 | 1 / 31 (3.23%) 1 | 1 / 29 (3.45%) 1 |
| APLASTIC ANAEMIA subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 31 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| FEBRILE NEUTROPENIA | | | |

| | | | |
|-----------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 1 | 2 |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 4 | 0 | 2 |
| Eye disorders | | | |
| CATARACT | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 4 | 0 | 2 |
| CONJUNCTIVAL HAEMORRHAGE | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 4 | 0 | 1 |
| EYE PAIN | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 0 | 3 |
| RETINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 31 (9.68%) | 3 / 29 (10.34%) |
| occurrences (all) | 2 | 3 | 5 |
| Gastrointestinal disorders | | | |
| ABDOMINAL DISCOMFORT | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 3 / 29 (10.34%) |
| occurrences (all) | 0 | 3 | 6 |
| ABDOMINAL DISTENSION | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 0 | 1 |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 7 / 42 (16.67%) | 2 / 31 (6.45%) | 4 / 29 (13.79%) |
| occurrences (all) | 8 | 2 | 4 |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 1 / 31 (3.23%) | 3 / 29 (10.34%) |
| occurrences (all) | 4 | 1 | 3 |
| APHTHOUS STOMATITIS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 31 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 2 | 2 |
| CONSTIPATION | | | |

| | | | |
|--|------------------|-----------------|-----------------|
| subjects affected / exposed | 13 / 42 (30.95%) | 3 / 31 (9.68%) | 5 / 29 (17.24%) |
| occurrences (all) | 15 | 3 | 6 |
| DENTAL CARIES | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 0 | 2 |
| DIARRHOEA | | | |
| subjects affected / exposed | 10 / 42 (23.81%) | 5 / 31 (16.13%) | 7 / 29 (24.14%) |
| occurrences (all) | 13 | 7 | 8 |
| GASTRITIS | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 0 | 2 |
| HAEMORRHOIDS | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 3 / 29 (10.34%) |
| occurrences (all) | 3 | 0 | 3 |
| NAUSEA | | | |
| subjects affected / exposed | 9 / 42 (21.43%) | 2 / 31 (6.45%) | 6 / 29 (20.69%) |
| occurrences (all) | 10 | 2 | 7 |
| STOMATITIS | | | |
| subjects affected / exposed | 8 / 42 (19.05%) | 0 / 31 (0.00%) | 7 / 29 (24.14%) |
| occurrences (all) | 8 | 0 | 10 |
| VOMITING | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 4 / 29 (13.79%) |
| occurrences (all) | 5 | 0 | 4 |
| Hepatobiliary disorders | | | |
| HEPATIC FUNCTION ABNORMAL | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 0 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| DERMATITIS ALLERGIC | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 31 (6.45%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| DRY SKIN | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 4 / 31 (12.90%) | 3 / 29 (10.34%) |
| occurrences (all) | 1 | 4 | 3 |
| MADAROSIS | | | |

| | | | |
|---|------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 31 (6.45%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| PETECHIAE | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 1 / 31 (3.23%) | 0 / 29 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| PRURITUS | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 1 / 31 (3.23%) | 4 / 29 (13.79%) |
| occurrences (all) | 2 | 2 | 4 |
| RASH | | | |
| subjects affected / exposed | 11 / 42 (26.19%) | 1 / 31 (3.23%) | 3 / 29 (10.34%) |
| occurrences (all) | 17 | 1 | 3 |
| SKIN ULCER | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 2 / 31 (6.45%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Renal and urinary disorders | | | |
| PROTEINURIA | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 1 / 31 (3.23%) | 1 / 29 (3.45%) |
| occurrences (all) | 4 | 1 | 1 |
| RENAL FAILURE | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 2 / 31 (6.45%) | 3 / 29 (10.34%) |
| occurrences (all) | 6 | 2 | 7 |
| RENAL IMPAIRMENT | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 2 / 31 (6.45%) | 6 / 29 (20.69%) |
| occurrences (all) | 7 | 4 | 7 |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 0 | 1 |
| BACK PAIN | | | |
| subjects affected / exposed | 7 / 42 (16.67%) | 1 / 31 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 7 | 1 | 3 |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 1 / 31 (3.23%) | 3 / 29 (10.34%) |
| occurrences (all) | 3 | 1 | 3 |
| MUSCULOSKELETAL PAIN | | | |

| | | | |
|-----------------------------|------------------|-----------------|------------------|
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 31 (9.68%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 3 | 1 |
| MYALGIA | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 2 / 31 (6.45%) | 1 / 29 (3.45%) |
| occurrences (all) | 4 | 2 | 1 |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 3 / 31 (9.68%) | 2 / 29 (6.90%) |
| occurrences (all) | 5 | 4 | 2 |
| Infections and infestations | | | |
| BRONCHITIS | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 4 / 31 (12.90%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 6 | 0 |
| CYSTITIS | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 0 / 31 (0.00%) | 3 / 29 (10.34%) |
| occurrences (all) | 9 | 0 | 4 |
| EAR INFECTION | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 31 (6.45%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| FURUNCLE | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 3 |
| HERPES SIMPLEX | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| HERPES ZOSTER | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| INFLUENZA | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 31 (6.45%) | 3 / 29 (10.34%) |
| occurrences (all) | 1 | 2 | 3 |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 14 / 42 (33.33%) | 6 / 31 (19.35%) | 10 / 29 (34.48%) |
| occurrences (all) | 36 | 18 | 21 |
| ORAL CANDIDIASIS | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |

| | | | |
|------------------------------------|-----------------|-----------------|-----------------|
| OTITIS MEDIA | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 31 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 3 | 2 |
| OTITIS MEDIA CHRONIC | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 31 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| PHARYNGITIS | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 2 / 31 (6.45%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 5 | 1 |
| TONSILLITIS | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 31 (9.68%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 9 | 0 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 9 / 31 (29.03%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 29 | 3 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 31 (9.68%) | 0 / 29 (0.00%) |
| occurrences (all) | 6 | 5 | 0 |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 7 / 42 (16.67%) | 1 / 31 (3.23%) | 4 / 29 (13.79%) |
| occurrences (all) | 9 | 1 | 7 |
| DEHYDRATION | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 0 / 31 (0.00%) | 3 / 29 (10.34%) |
| occurrences (all) | 6 | 0 | 4 |
| DIABETES MELLITUS | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 1 / 31 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 4 | 1 | 2 |
| HYPOGLYCAEMIA | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 1 / 31 (3.23%) | 4 / 29 (13.79%) |
| occurrences (all) | 6 | 1 | 5 |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 31 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 19 October 2006 | <ul style="list-style-type: none">• Added a recommendation to refer patients whose serum creatinine remained elevated despite dose reduction and interruption, and in whom there was also a persistent abnormality of another marker of renal function (e.g. proteinuria, Fanconi's syndrome), to a renal specialist for further specialized investigations• Updated the language for a potential dose adjustment, which was updated as a standard for all Exjade clinical protocols• Amended the exclusion criterion for patients with a baseline serum creatinine level that was above the ULN• Removed the language regarding the availability of commercial Exjade that triggered a withdrawal of the patient from the study• Changed the collection of data with an eCRF to collection on a paper CRF. |
| 02 May 2007 | <ul style="list-style-type: none">• Modified the study design and scope to investigate the safety and efficacy of deferasirox in patients with transfusion-dependent anemias other than β-thalassemia or sickle cell disease, especially in Japanese patients; this included the removal of the baseline LIC classification (i.e. < 7 mg Fe/g dw vs. ≥ 7 mg Fe/g dw)• Revised the primary endpoint: absolute change in LIC from baseline to end of Year 1• Revised the endpoint, change in serum ferritin from baseline to end of study, to a secondary efficacy assessment• Excluded patients with either β-thalassemia or sickle cell disease• Increased the serum ferritin inclusion criterion to more than 1000 ng/mL• Reduced the sample size estimate to 114 enrolled patients, which included 50 Japanese patients enrolled in Japan, using nQuery Advisor Version 5.0• Extended the ophthalmologic assessments for an additional year (i.e. Year 2) in at least 60 patients• Updated the informed consent form |
| 29 August 2007 | <ul style="list-style-type: none">• Revised the protocol to include reference to the yearly audiometric tests: this was part of the revised informed consent form issued with Amendment 2• Modified the collection of ECG assessments at baseline only and can be repeated in the event of a cardiac adverse event• Clarified the assessments for the routine urinalysis and microscopic analysis only in case of a positive dipstick |
| 29 April 2008 | <ul style="list-style-type: none">• Revised the protocol introduction to include new safety information on deferasirox that has emerged since the original protocol was issued• Increased clarity on the definition of the Per-protocol population• Modified the criteria for the analyses on serum ferritin changes during the study• Introduced greater protocol adherence by avoidance of protocol deviations• Updated the informed consent form |
| 05 August 2008 | <ul style="list-style-type: none">• Extended the duration of the study to include Year 2 to collect long-term data for safety and efficacy• Continued assessments for hematology, biochemistry, and urinalysis on a monthly basis• Repeated physical examination every 6 months• Performed measurements of LIC, audiometry, and prothrombin time after one year of treatment again• Assessed growth velocity and sexual development in pediatric patients• Clarified when Year 2 started in relation to the end of Year 1 dosing• Defined that baseline values during the core phase were used as a reference for a potential dose adjustment |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported