## Sponsor

Novartis

## Generic Drug Name

Deferasirox

## Therapeutic Area of Trial

None, pharmacokinetics (PK) study in healthy subjects and in patients with hepatic impairment.

## Approved Indication

Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.

## Study Number

CICL670A2125

## Title

An open label, single-dose, parallel-group study to assess the pharmacokinetics of 20 mg/kg oral deferasirox in patients with impaired hepatic function and healthy subjects with normal hepatic function.

## Phase of Development

Phase I

## Study Start/End Dates

23-Nov-2006 to 24-Aug-2010

## Study Design/Methodology

This was an open-label, single-dose, parallel-group study to assess the PK profile of deferasirox in subjects with varying degrees of hepatic function. In this study, subjects treated with a single dose of 20 mg/kg oral deferasirox had a 21-day screening period, one baseline evaluation, a single dose administration and PK sample collection on Day 1 plus subsequent 4 days for the completion of PK sample collection and an end-of study evaluation (EOS).

## Centres

2 centers in Germany

## Publication

None

## Objectives

Primary objective(s)

- To evaluate the pharmacokinetics of a single dose of 20 mg/kg deferasirox in subjects with impaired hepatic function and in healthy controls.

Secondary objective(s)

- To assess the safety and tolerability of a single dose of 20 mg/kg deferasirox in subjects with impaired hepatic function.
- To assess the protein binding of deferasirox in subjects with impaired hepatic function compared to healthy control subjects.

## Test Product (s), Dose(s), and Mode(s) of Administration

Single dose of 20 mg/kg deferasirox administered orally.

## Reference Product(s), Dose(s), and Mode(s) of Administration

None

## Criteria for Evaluation

Primary variables

Pharmacokinetics: The PK parameters of deferasirox and its iron complex were determined using standard non-compartmental methods as detailed below:

| | |
|---|---|
| AUClast | The AUC from time zero to the last measurable concentration sampling time (mass x time x volume-1) |
| AUCinf | The AUC from time zero to infinity (mass x time x volume-1) |
| Cmax | The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1) |
| Tmax | The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time) |
| T1/2 | The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). |

Secondary variables

Safety and tolerability

Safety was assessed by monitoring adverse events, serious adverse events, laboratory evaluations, vital signs, and electrocardiograms.

Protein binding of deferasirox

The radioactivity in the spiked plasma samples was determined by liquid scintillation counting in a Packard Tricarb liquid scintillation counter in the ultra-filtrate and in the sample introduced into the reservoir before ultra-filtration.

## Statistical Methods

In this study, each PK parameter was analyzed on the log scale by means of an analysis of variance (ANOVA) model which includes group as fixed effect. The contrast was computed between each test group (impaired hepatic function group: Mild, Moderate and Severe) and the control group; as a consequence a 90% two-sided confidence interval (CI) was formed. The difference and its CI were then transformed back to the original scale to give the ratio of the geometric means for the two groups together with the corresponding 90% CIs. The effect of hepatic impairment was estimated separately for each primary PK variables Cmax, AUClast and AUCinf using the ratio and its 90% CI.

The summary of all demographic and baseline variables were tabulated using the FAS as all subjects. Age (years), weight (kg), height (cm), and body mass index (BMI), was summarized with descriptive statistics. Categorical variables like gender, race, and ethnicity were tabulated by frequency distributions.

As a supportive analysis, the relationship between deferasirox PK parameters and hepatic function test values at baseline, including values of prothrombin time, bilirubin levels, albumin levels, and Child's Pugh score was explored in each hepatic impairment group using Pearson's correlation.

Safety parameters were listed and evaluated by summary statistics as appropriate.

## Study Population: Inclusion/Exclusion Criteria and Demographics

### Inclusion criteria: All groups

1. Able to communicate well with the Investigator and comply with the requirements of the study.
2. Able and willing to provide written informed consent prior to study participation.
3. Male and/or female subjects from 18-75 years of age and in good health and no evidence of iron deficiency as determined by past medical history, physical examination, vital signs, 12-lead ECG with rhythm strip, and laboratory tests at screening.
4. All females with negative pregnancy test results at screening and baseline. Females of childbearing potential used double-barrier local contraception with a Pearl index < 1%, i.e. intra-uterine device plus condom, or spermicidal gel plus condom.
   OR:
   Postmenopausal women without regular menstrual bleeding for at least 2 years prior to inclusion. Menopause was confirmed by a plasma follicle-stimulating hormone level of > 40 IU/L.
   OR:
   Females who were surgically sterilized at least 6 months prior to screening.
5. Vital signs (after 3 minutes resting measured in the supine position) must be within the following ranges:
   - Oral body temperature between 35.0-37.5 °C.
   - Systolic blood pressure (SBP), 90-150 mm Hg.
   - Diastolic blood pressure (DBP), 60-90 mm Hg.
   - Pulse rate, 40 – 90 beats per minute.
   - Blood pressure and pulse were taken again in a standing position. After 3 minutes standing, there should be no more than a 20 mm Hg drop in SBP or 10 mm Hg drop in DBP

associated with clinical manifestation of postural hypotension.

6. Subjects weighed at least 50 kg and had a body mass index (BMI) between 19 and 36 $kg/m^2$ to participate in this study.
7. Serum ferritin value ≥70 ng/mL.
8. Serum potassium levels in the range of 3 to 6 mmol/L.

### Additional inclusion criteria for groups 2 and 3 (mild and moderate hepatic impairment)

1. Physical signs consistent with a clinical diagnosis of liver cirrhosis (i.e., liver firmness to palpation, splenic enlargement, spider angioma, palmar erythema, parotid hypertrophy, testicular atrophy, and gynecomastia).
2. Child-Pugh Clinical Assessment Score consistent with degree of hepatic impairment.
3. Platelet count > 50,000 x $10^9$/L at screening and baseline.
4. Serum creatinine within the normal limits.
5. Free of significant medical disorders unrelated to their hepatic disorders.

### Additional inclusion criteria for group 4 (severe hepatic impairment)

1. Physical signs consistent with a clinical diagnosis of liver cirrhosis (i.e., liver firmness to palpation, splenic enlargement, spider angioma, palmar erythema, parotid hypertrophy, testicular atrophy, and gynecomastia).
2. Child-Pugh Clinical Assessment Score consistent with degree of hepatic impairment).
3. Platelet count > 30,000 x $10^9$/L at screening and baseline.
4. Serum creatinine < 2 x ULN.
5. Free of significant medical disorders unrelated to their hepatic disorder.

### Additional inclusion criteria for group 1 (healthy controls)

1. In good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
2. Platelet count > 50,000 x $10^9$/L at screening and baseline.
3. Serum creatinine within the normal limits.

### Exclusion criteria

Subjects meeting any of the following criteria during screening or baseline evaluations were excluded from entry into or continuation in the study:

### All Groups

1. Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulation.
2. Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing.
3. Significant illness within the two weeks prior to dosing.
4. A past medical history of clinically significant ECG abnormalities or a family history of a prolonged QT-interval syndrome.

5. Resting heart rate < 40 bpm.
6. History of autonomic dysfunction.
7. History of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated).
8. History of clinically significant drug allergy; history of atopic allergy (asthma, urticaria, eczematous dermatitis). A known hypersensitivity to the study drug or drugs similar to the study drug.
9. Episodes of gastrointestinal bleeding in the past 3 months before entering the study.
10. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs or which may jeopardize the subject in case of participation in the study. The Investigator was guided by evidence of any of the following:
    - History of major gastrointestinal tract surgery such as gastrectomy, gastroentero-stomy, or bowel resection
    - Polymorphonuclears < 1500/µL at inclusion
    - History of immunocompromise, including known history of human immunodeficiency (HIV) seropositivity.
    - History of drug or alcohol abuse within the 12 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations.
    - Use of tobacco during the study.
    - Past medical history of hypersensitivity to any ingredient of deferasirox tablets (Lactose monohydrate, Crospovidone type A, Cellulose (microcrystalline), Povidone, Sodium lauryl sulphate, Silica (colloidal anhydrous), Magnesium stearate).
    - Past medical history of hereditary galactose intolerance or severe lactase deficiency or of syndrome of glucose galactose malabsorption.

**Additional exclusion criteria for groups 2, 3 or 4 (hepatic impairment)**

1. Clinically significant abnormal findings in physical examination, ECG or laboratory evaluations, not consistent with known clinical disease.
2. Symptoms or history of Stage III of encephalopathy within 6 months of study entry.
3. Clinical evidence of severe ascites.
4. History of surgical portosystemic shunt.
5. Prothrombin time > 22 seconds.
6. Any evidence of progressive liver disease (within the last 2 weeks) as indicated by liver transaminases, alkaline phosphatase, and gamma glutamyltransferase (GGT) or a ≥ 50% worsening of serum bilirubin or prothrombin time.

**Additional exclusion criteria for group 1 (healthy controls)**

1. Clinical evidence of liver disease or liver injury as indicated by abnormal liver function tests such as SGOT, SGPT, GGT, alkaline phosphatase, or serum bilirubin1.5 times above the ULN range.
2. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.

3. Use of any prescription medication within 1 month prior to dosing.
4. Use of over-the-counter medications or vitamins within 14 days prior to dosing.

## Number of Subjects

### Subject disposition by hepatic impairment function group and control group (FAS)

| Disposition Reason | | Level of impairment | | | |
|---|---|---|---|---|---|
| | Control | Mild | Moderate | Severe | All Subjects |
| | (N=7) | (N=6) | (N=6) | (N=1) | (N=20) |
| | n (%) | n (%) | n (%) | n | n (%) |
| Enrolled | 7 (100.0) | 6 (100.0) | 6 (100.0) | 1 | 20 (100.0) |
| Completed | 7 (100.0) | 6 (100.0) | 6 (100.0) | 1 | 20 (100.0) |
| Discontinued | 0 | 0 | 0 | 0 | 0 |
| Reasons for discontinuation | | | | | |
| Adverse event(s) | 0 | 0 | 0 | 0 | 0 |
| Abnormal laboratory value(s) | 0 | 0 | 0 | 0 | 0 |
| Abnormal test procedure result(s) | 0 | 0 | 0 | 0 | 0 |
| Protocol violation | 0 | 0 | 0 | 0 | 0 |
| Subject withdrew consent | 0 | 0 | 0 | 0 | 0 |
| Lost to follow-up | 0 | 0 | 0 | 0 | 0 |
| Administrative problems | 0 | 0 | 0 | 0 | 0 |
| Death | 0 | 0 | 0 | 0 | 0 |

Hepatic function group description:
Control: Normal hepatic function;
Mild impairment: Child-Pugh A: Score 5-6;
Moderate impairment: Child-Pugh B: Score 7-9;
Severe impairment: Child-Pugh C: Score 10-15.

## Demographic and Background Characteristics

The majority of the subjects were male (75%) and Caucasian (95%). The mean age was 50.9 years (range 37 – 68 years) and a mean body weight of 85.62 kg (range 55.4 – 110.7). The demographics of the subjects, including age, weight and BMI, were comparable among the four study groups.

### Demographic summary by treatment group (FAS)

| Demographic Variable | | Level of impairment | | | |
|---|---|---|---|---|---|
| | Control | Mild | Moderate | Severe | All Subjects |
| | (N=7) | (N=6) | (N=6) | (N=1) | (N=20) |
| Age (years) | | | | | |
| N | 7 | 6 | 6 | 1 | 20 |
| Mean | 52.6 | 48.2 | 51.7 | 51.0 | 50.9 |
| SD | 6.16 | 6.85 | 10.17 | | 7.43 |

| | | | | | |
|---|---|---|---|---|---|
| Median | 56.0 | 48.0 | 50.5 | 51.0 | 51.0 |
| Min | 44 | 40 | 37 | 51 | 37 |
| Max | 60 | 57 | 68 | 51 | 68 |
| Sex –n(%) | | | | | |
| Male | 4 (57.1) | 4 (66.7) | 6 (100.0) | 1 | 15 (75.0) |
| Female | 3 (42.9) | 2 (33.3) | 0 | 0 | 5 (25.0) |
| Race–n(%) | | | | | |
| Caucasian | 7 (100.0) | 6 (100.0) | 5 (83.3) | 1 | 19 (95.0) |
| Asian | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| Ethnicity–n(%) | | | | | |
| Other | 7 (100.0) | 6 (100.0) | 6 (100.0) | 1 | 20 (100.0) |
| Weight (kg) | | | | | |
| N | 7 | 6 | 6 | 1 | 20 |
| Mean | 81.39 | 83.07 | 88.93 | 110.70 | 85.62 |
| SD | 10.969 | 16.788 | 17.314 | | 15.372 |
| Median | 83.60 | 87.70 | 96.20 | 110.70 | 87.70 |
| Min | 65.6 | 55.4 | 56.7 | 110.7 | 55.4 |
| Max | 96.3 | 103.0 | 101.2 | 110.7 | 110.7 |
| Height (cm) | | | | | |
| N | 7 | 6 | 6 | 1 | 20 |
| Mean | 174.0 | 174.8 | 178.7 | 183.0 | 176.1 |
| SD | 8.41 | 7.86 | 8.55 | | 8.03 |
| Median | 170.0 | 177.0 | 182.0 | 183.0 | 179.0 |
| Min | 163 | 162 | 168 | 183 | 162 |
| Max | 185 | 183 | 186 | 183 | 186 |
| BMI ($kg/m^2$) | | | | | |
| N | 7 | 6 | 6 | 1 | 20 |
| Mean | 26.79 | 27.17 | 27.82 | 33.10 | 27.53 |
| SD | 2.104 | 5.405 | 5.333 | | 4.298 |
| Median | 26.60 | 27.15 | 28.35 | 33.10 | 27.90 |
| Min | 24.6 | 19.2 | 20.1 | 33.1 | 19.2 |
| Max | 29.3 | 34.7 | 35.1 | 33.1 | 35.1 |
| Hepatic function group description:<br>Control: Normal hepatic function;<br>Mild impairment: Child-Pugh A: Score 5 - 6;<br>Moderate impairment Child-Pugh B: Score 7 - 9;<br>Severe impairment Child-Pugh C : Score 10 - 15; | | | | | |

BMI (Kg/m$^2$): Weight (Kg)/((Height (cm)/100)^2).

## Primary Objective Result(s)

In the healthy control group, deferasirox Cmax was observed at a median time of 3 hours, with Cmax averaging 65.7 µmol/L following a single oral dose of 20 mg/kg deferasirox. The mean AUCinf of deferasirox was 932 µmol·h/L and the mean half-life was 15 hours.

As compared to the healthy control group, deferasirox AUCinf was increased on average by 16% in the mild impairment group and 76% in the moderate impairment group while Cmax was increased by 22% in the mild and moderate impairment groups. AUCinf in the one severe hepatic impaired subject was 2.8-fold greater than in the healthy control group whereas Cmax in this subject was slightly lower than in the healthy control subjects. The mean half-life of deferasirox was found to be comparable in all groups ranging from 12.5 to 15.1 hours except the one subject with severe hepatic impairment (21.6 hours). Inter-individual variability in AUCinf was moderate across study groups: 48% in healthy control, 41% in mild impairment group, and 26% in the moderate impairment.

### Geometric mean ratio and 90% confidence intervals for deferasirox primary PK parameters in subjects with hepatic impairment to those in control group after deferasirox 20 mg/kg single oral dose (PK set)

| | | | | | Treatment Comparison | | |
|---|---|---|---|---|---|---|---|
| | | | | | | 90% CI | |
| **PK Parameter (unit)** | **Treatment** | **n*** | **Adjusted Geo-mean** | **Comparison** | **Geo-mean Ratio** | **Lower** | **Upper** |
| AUCinf (h.µmol/L) | Control | 6 | 932.12 | | | | |
| | Mild | 6 | 1084.40 | Mild: Control | 1.16 | 0.792 | 1.708 |
| | Moderate | 6 | 1644.90 | Moderate: Control | 1.76 | 1.202 | 2.591 |
| AUClast (h.µmol/L) | Control | 6 | 907.01 | | | | |
| | Mild | 6 | 1040.82 | Mild: Control | 1.15 | 0.773 | 1.703 |
| | Moderate | 6 | 1615.55 | Moderate: Control | 1.78 | 1.200 | 2.643 |
| Cmax (µmol/L) | Control | 6 | 65.67 | | | | |
| | Mild | 6 | 79.80 | Mild: Control | 1.22 | 0.935 | 1.579 |
| | Moderate | 6 | 80.14 | Moderate: Control | 1.22 | 0.939 | 1.586 |

Hepatic function group description:

Control: Normal hepatic function;

Mild impairment: Child-Pugh A: Score 5 - 6;

Moderate impairment Child-Pugh B: Score 7 - 9;

Severe impairment Child-Pugh C : Score 10 - 15;

Following log-transformation, the PK parameters AUClast, AUCinf, and Cmax were analyzed using a mixed effects model including terms for group as a fixed factor. Point estimates and the corresponding 90% confidence intervals were calculated for the differences between least squares means of control group and mild, control and moderate, control and severe. These were anti-logged to obtain the point estimates and the 90% confidence intervals for the ratios of the geometric means on the untransformed scale.

n* = number of subjects with non-missing values

## Summary of PK parameters of deferasirox by hepatic impaired and control group after a deferasirox 20 mg/kg single oral dose (PK set)

| PK Parameter (unit) | | Level of impairment | | |
|---|---|---|---|---|
| | Control | Mild | Moderate | Severe |
| | (N=6) | (N=6) | (N=6) | (N=1) |
| AUCinf (h.µmol/L) | 932.119 (48.49) | 1084.400 (41.16) | 1644.901 (25.68) | 2584.290 |
| AUClast (h.µmol/L) | 907.014 (49.93) | 1040.822 (42.91) | 1615.550 (25.84) | 2444.610 |
| Cmax (µmol/L) | 65.665 (36.04) | 79.798 (9.03) | 80.143 (27.10) | 48.300 |
| Tmax (h) | 3.000 (1.50 - 3.00) | 3.000 (1.00 - 4.00) | 3.500 (2.00 - 4.02) | 4.000 |
| T1/2 (h) | 15.154 (38.73) | 13.945 (37.85) | 12.464 (17.57) | 21.560 |

Values are median (range) for Tmax, and geometric mean (CV%) for all the other parameters.
Hepatic function group description:
Control: Normal hepatic function;
Mild impairment: Child-Pugh A: Score 5 - 6;
Moderate impairment Child-Pugh B: Score 7 - 9;
Severe impairment Child-Pugh C: Score 10 – 15.

## Summary of PK parameters of iron complex of deferasirox by hepatic impaired and control group after a deferasirox 20 mg/kg single oral dose (PK set)

| PK Parameter (unit) | | Level of impairment | | |
|---|---|---|---|---|
| | Control | Mild | Moderate | Severe |
| | (N=6) | (N=6) | (N=6) | (N=1) |
| AUCinf (h.µmol/L) | ND | ND | 57.831 (61.11) | ND |
| AUClast (h.µmol/L) | 2.560 (170.91) | 12.070 (78.01) | 22.458 (85.94) | 14.410 |
| Cmax (µmol/L) | 0.528 (21.81) | 1.267 (26.14) | 1.439 (48.78) | 0.570 |
| Tmax (h) | 4.000(3.00-36.00) | 3.000(1.00-8.02) | 3.000(1.00-8.00) | 12.000 |
| T1/2 (h) | ND | 8.887 (51.92) | 13.012 (27.79) | ND |

Values are median (range) for Tmax and geometric mean (CV%) for all the other parameters.
ND: not determined
Hepatic function group description:
Control: Normal hepatic function;
Mild impairment: Child-Pugh A: Score 5 - 6;
Moderate impairment Child-Pugh B: Score 7 - 9;
Severe impairment Child-Pugh C: Score 10 – 15.

## Relationship between deferasirox PK and hepatic function

Deferasirox Cmax and hepatic function did not reveal any apparent relationship. Deferasirox AUCinf showed high correlations with all the hepatic function test values explored; high negative correlation with albumin levels ($r = -0.720$, $p = 0.001$), and high positive correlations with bilirubin levels ($r = 0.637$, $p = 0.003$), prothrombin time ($r = 0.764$, $p = 0.002$), and Child-Pugh

score (r = 0.761, p = 0.003).

## Relationship between deferasirox pharmacokinetics and hepatic function test values (PK set)

| | Hepatic Function | | | |
|---|---|---|---|---|
| **PK parameter** | **Albumin** | **Bilirubin** | **Prothrombin time** | **Child Pugh score** |
| AUCinf (h.µmol/L) | -0.7201( 0.001) | 0.6374( 0.003) | 0.7644( 0.002) | 0.7610( 0.003) |
| AUClast (h.µmol/L) | -0.7160( 0.001) | 0.6101( 0.006) | 0.7423( 0.004) | 0.7446( 0.004) |
| Cmax (µmol/L) | -0.0991( 0.687) | -0.2620( 0.279) | -0.0099( 0.974) | -0.2936( 0.330) |
| Values are correlation coefficient (pvalue).<br>Calculation for Prothrombin time and Child Pugh score are based on N=13;<br>Calculation for other parameters are based on N=19. | | | | |

## Secondary Objective Results

### Plasma protein binding of deferasirox

Overall, the extent of deferasirox binding to plasma proteins was extremely high in all the groups (≥99.5%). The free fraction of deferasirox was greater in the impairment groups averaging 0.389%, 0.453%, and 0.301% in the mild, moderate, and severe groups, respectively, as compared to the healthy control group (0.156%).

### Summary of deferasirox unbound fraction by hepatic impaired and control group after a deferasirox 20 mg/kg single oral dose (PK set)

| Group | Deferasirox Unbound Fraction (%) |
|---|---|
| Control (N=6) | 0.1585 (0.073 - 0.431) |
| Mild impairment (N=6) | 0.3890 (0.169 - 0.655) |
| Moderate (N=6) | 0.4530 (0.300 - 0.716) |
| Severe (N=1) | 0.3010 (0.301 - 0.301) |

Values are median (range) for protein binding.
Hepatic function group description:
Control: Normal hepatic function;
Mild impairment: Child-Pugh A: Score 5 - 6;
Moderate impairment Child-Pugh B: Score 7 - 9;
Severe impairment Child-Pugh C: Score 10 – 15.

## Safety Results

### Adverse Events by System Organ Class

### Adverse events, regardless of study drug relationship, by primary system organ class, preferred term and hepatic impaired and control group (Safety set)

| Primary system organ class<br>Preferred term | | Level of impairment | | | |
|---|---|---|---|---|---|
| | Control | Mild | Moderate | Severe | All Subjects |
| | (N=7) | (N=6) | (N=6) | (N=1) | (N=20) |
| | n (%) | n (%) | n (%) | n | n (%) |
| Any primary system organ class (Total number of subjects that experienced at least one AE) | 4 (57.1) | 1 (16.7) | 3 (50.0) | 1 | 9 (45.0) |
| **Nervous system disorders** | 4 (57.1) | 0 | 0 | 0 | 4 (20.0) |
| Headache | 4 (57.1) | 0 | 0 | 0 | 4 (20.0) |
| **Investigations** | 0 | 1 (16.7) | 1 (16.7) | 0 | 2 (10.0) |
| Hemoglobin decreased | 0 | 1 (16.7) | 0 | 0 | 1 (5.0) |
| Lipase increased | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |

| | | | | | |
|---|---|---|---|---|---|
| **Metabolism and nutrition disorders** | 0 | 0 | 2 (33.3) | 0 | 2 (10.0) |
| Hyperuricaemia | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| Hypoalbuminaemia | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| **Blood and lymphatic system disorders** | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| Erythropenia | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| **General disorders and administration site conditions** | 0 | 0 | 0 | 1 | 1 (5.0) |
| Edema peripheral | 0 | 0 | 0 | 1 | 1 (5.0) |
| **Hepatobiliary disorders** | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| Hyperbilirubinaemia | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| **Infections and infestations** | 1 (14.3) | 0 | 0 | 0 | 1 (5.0) |
| Genital herpes | 1 (14.3) | 0 | 0 | 0 | 1 (5.0) |

Hepatic function group description:

Control: Normal hepatic function;

Mild impairment: Child-Pugh A: Score 5 - 6;

Moderate impairment Child-Pugh B: Score 7 - 9;

Severe impairment Child-Pugh C: Score 10 – 15.

A subject with multiple AEs within a system organ class was counted only once in the total row and all subject column.

A subject with multiple AEs in different primary system organ classes or within primary system organ class was counted only once in the system organ class total row.

## Most Frequently Reported AEs Overall by Preferred Term n (%)

The most frequent AEs by system organ class were mainly nervous system disorders; as per preferred term, headache was the most commonly reported. No noticeable trends in the frequency of these AEs were discernible among the hepatic impairment groups.

| Preferred term | | Level of impairment | | | |
|---|---|---|---|---|---|
| | Control | Mild | Moderate | Severe | All Subjects |
| | (N=7) | (N=6) | (N=6) | (N=1) | (N=20) |
| | n (%) | n (%) | n (%) | n | n (%) |
| Headache | 4 (57.1) | 0 | 0 | 0 | 4 (20.0) |
| Hemoglobin decreased | 0 | 1 (16.7) | 0 | 0 | 1 (5.0) |
| Lipase increased | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| Hyperuricaemia | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| Hypoalbuminaemia | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| Erythropenia | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| Oedema peripheral | 0 | 0 | 0 | 1 | 1 (5.0) |
| Hyperbilirubinaemia | 0 | 0 | 1 (16.7) | 0 | 1 (5.0) |
| Genital herpes | 1 (14.3) | 0 | 0 | 0 | 1 (5.0) |

Hepatic function group description:

Control: Normal hepatic function;

Mild impairment: Child-Pugh A: Score 5 - 6;

Moderate impairment Child-Pugh B: Score 7 - 9;

Severe impairment Child-Pugh C: Score 10 – 15.

A subject with multiple AEs within a system organ class was counted only once in the total row and all subject column.

## Serious Adverse Events and Deaths

None of the subjects died or experienced an SAE or an AE that led to discontinuation from the study.

## Other Relevant Findings

None

| |
|---|
| **Date of Clinical Trial Report**<br>02-Dec-2010 |
| **Date Inclusion on Novartis Clinical Trial Results Database**<br>15 Jul 2011 |
| **Date of Latest Update** |