Sponsor

Novartis

Generic Drug Name

Deferasirox

Therapeutic Area of Trial

Renal hemodynamics in patients with β-thalassemia with transfusional iron overload

Approved Indication

Deferasirox is approved for the treatment of transfusional iron overload and has demonstrated acceptable safety and tolerability in adult and pediatric patients in this indication

Protocol Number

CICL670A2123

Title

Phase I study to examine the effect of deferasirox on renal hemodynamics in β-thalassemia patients with transfusional iron overload

Phase of Development

Phase I

Study Start/End Dates

Study initiation date: 13-Sep-2007 (first patient first visit)

Early termination date: 27-Mar-2012

Study completion date: 24-Apr-2012 (last patient last visit)

Enrolment to this study (CICL670A2123) was extremely challenging and slowed by practical issues such as the feasibility of isotope assessments and by the difficulty in enrolling patients with beta-thalassemia who were deferasirox-naïve and willing to participate in this study due to its demanding and invasive nature of assessments. The 10-week interim analysis results suggested that deferasirox produces a mild hemodynamic effect on renal function that is reversible after drug discontinuation. Since then, four patients had completed 2-year treatment and their long-term data was collected and described in the clinical expert statement submitted to European Medicines Agency (EMA) in Sep 2011. Analysis of the renal parameters [glomerular filtration rate (GFR), renal plasma flow (RPF), and filtration fraction (FF)] for the four patients who completed 104 weeks of treatment with deferasirox followed by four weeks wash-out period displayed similar pattern to that observed in the interim analyses (10-week). The findings from this analysis indicated no progressive worsening of renal function parameters over the long term with deferasirox treatment and an agreement was obtained with the European Union health authority to terminate the study due to enrollment difficulties. The enrollment to study was closed early after 11 of 16 planned patients were recruited. Of the 11 patients, only one patient was ongoing at the time of termination and continued to receive deferasirox as planned.

Study Design/Methodology

Phase I, open-label, single arm, and multicenter study in β-thalassemia patients with transfusional iron overload. The study consisted of five periods (screening, initial treatment, first washout, continued treatment, and a second washout). The screening period was up to 2 weeks and the first treatment period lasted 8 weeks. During this period, each patient was treated with a dose of 30 mg/kg/day of deferasirox. Following the 8-week treatment period, patients underwent a 2-week washout period. At the end of the 2-week washout period (Week 10), patients resumed deferasirox 30 mg/kg/day for an additional 94 weeks. Dose adjustments were allowed after Week 10. At the end of Week 104, patients stopped taking the study medication and began a 4-week washout period. The GFR and RPF were measured at baseline, Week 2, 8, 10, 52, 104, and 108 using ethylenediaminetetraacetic acid (^{51}Cr-EDTA) and ^{123}ortho-iodohippurate (^{123}I-OIH).

Centers

Three centers in Italy

Publication

Piga A, Fracchia S, Eliana Lai M et al (2012) Two-year renal hemodynamic effects of deferasirox in patients with transfusion-dependent β-thalassemia. Blood (ASH Annual Meeting Abstracts); 120: 3257.

Outcome measures

Primary outcome measures(s)

- To estimate the effects of deferasirox on changes from baseline in GFR and RPF using chromium labeled ^{51}Cr-EDTA and ^{123}I-OIH respectively, and the corresponding FF in deferasirox naïve patients with β-thalassemia and transfusional iron overload.

Secondary outcome measures(s)

- To explore the relationship between absolute changes from baseline in serum creatinine and absolute changes from baseline in GFR, RPF and FF.
- To explore the relationship between absolute changes from baseline in serum ferritin and absolute changes from baseline in markers of renal function (GFR, RPF, FF, and serum creatinine).

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

Deferasirox was administered as oral dispersible tablets in accordance with a daily dose of 30 mg/kg. Deferasirox was supplied to the Investigators as 125 mg, 250 mg, and 500 mg dispersible tablets.

Statistical Methods

Renal hemodynamics and safety: Safety set was used for all renal hemodynamics and safety analysis. Safety set included all the patients who were enrolled and received at least one dose of study medication and who have at least one post baseline measurement. The primary endpoint was absolute change from baseline in GFR, RPF, and FF. There was no formal statistical hypothesis being tested. Descriptive statistics (mean, median, standard deviation, median, coefficient of variation, minimum, and maximum) were provided for GFR, RPF, and FF by visit

(baseline, Week 2, 8, 10, 52, 104, and 108). Absolute change from baseline in GFR, RPF, and FF was summarized by visit (Week 2, 8, 10, 52, 104, and 108).

The secondary endpoints of the study were addressed by performing exploratory analyses using a linear or a non-linear mixed effects model, such as Emax models. In these models, the independent variables were changes in serum creatinine or serum ferritin, respectively, as a fixed factor and patient as a random factor. The dependent variable was GFR, RPF or FF (or serum creatinine when the independent variables included serum ferritin) change from baseline.

All AEs recorded during the study were listed. The incidence (number and percentage) of treatment-emergent adverse events (TEAEs) (new or worsening from baseline) was summarized by system organ class (SOC), severity (mild, moderate and severe), preferred term, and relation to the study medication (not suspected and suspected). Laboratory data collected from both central and local laboratories were combined. All values were converted into SI units and severity grade calculated using CTCAE (version 3.0). Vital sign data was summarized by presenting summary statistics of raw data and change from baseline (shift table) for weight by visit. Individual listings were provided for the ECG parameters by visit with out-of-range and notable values flagged.

Pharmacokinetics (PK): The PK set was used for all PK analysis which included all patients present in the safety set and who have at least one evaluable PK sample. The trough levels of deferasirox were summarized (mean, median, SD, CV, minimum, and maximum) by visit using PK set. Plasma concentrations were plotted over time by patient. Mean plasma deferasirox trough levels were plotted by visit.

PK and renal function: A linear model was fitted to log-transformed renal hemodynamic parameters (GFR, RPF, and FF) including the log-transformed trough concentration at week (Week 8 and Week 2 for Model-1 and Week 2 only for Model-2) and the corresponding log-transformed baseline renal hemodynamic parameters (GFR, RPF, and FF) as covariates in the model. This analysis included long term and short term patients.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

Patients who met the following criteria were eligible:

- Male or female patient's ≥ 18 years of age without prior history of deferasirox treatment.
- Patients with β-thalassemia receiving regular transfusions every 2 to 5 weeks leading to iron intake equal or greater than 0.25 mg/kg/day.
- Transfusion history of ≥ 20 units of packed red blood cells (pRBC).
- Serum ferritin values ≥ 500 µg/L or liver iron concentration (LIC) ≥ 2 mg/kg of dry weight as measured by superconducting quantum interference device (SQUID) at screening or baseline. If SQUID was the regional standard of care, then the assessment was to be done at screening only if serum ferritin value ≤ 500 µg/L; if serum ferritin values ≥ 500 µg/L then SQUID was to be completed at baseline.

Exclusion criteria:

Patients who met any of the following criteria were ineligible:

- Creatinine above the ULN range at screening.

- A family history of a prolonged QT-interval syndrome or any electrocardiogram (ECG) abnormalities at screening.
- Estimated creatinine clearance <60 mL/min at screening (using Cockcroft-Gault formula shown below, where creatinine clearance is "*x*" (in mL/min), age was measured in years, weight in kg, creatinine in µmol/L, and the constant is 1.23 for men and 1.04 for women).
- Urine protein/creatinine ratio of >0.5 mg/mg at screening.
- Alanine aminotransferase (ALT) greater than 5 x ULN at screening.
- History of nephrotic syndrome.
- History of relevant ocular or auditory toxicity related to iron chelation.
- History of human immunodeficiency virus (HIV) positivity.
- History of hypertension, diabetes, hypoproteinemia, obesity.
- Patients with a surgical or medical condition that could have significantly alter the absorption, distribution, metabolism or excretion of deferasirox or study agents used to measure GFR and RPF at screening.
- Allergy or contraindication to the administration of deferasirox, ^{51}Cr-EDTA or ^{123}I-OIH.
- Any disease that could have prevented the patient from undergoing study treatment and study procedures (including providing informed consent).
- History of drug or alcohol abuse within the 12 months prior to enrollment.
- Patients treated with systemic investigational drug within 4 weeks prior or with topical investigational drug within 7 days prior to the screening visit.
- Patients with underlying cardiac disease requiring continuous iron chelation therapy.
- Treatment with drugs that could have affected renal parameters (i.e., angiotensin converting enzyme (ACE) inhibitors, cyclosporine, etc).
- Pregnant or breast feeding patients.
- Sexually active pre-menopausal female patients without adequate contraception. Female patients had to use double-barrier contraception, oral contraceptive plus barrier contraceptive, or could have undergone clinically documented total hysterectomy and/or oophorectomy, tubal ligation or be postmenopausal defined by amenorrhea for at least 12 months.
- Inability to comply with all study related procedures, medications and evaluations.

Participant Flow

Patient disposition

Disposition Reason	All patients N=11 n (%)
Enrolled	11 (100.0)
Patients completed 10 weeks of study duration	10 (90.9)
Patients completed 108 weeks of study duration	5 (45.5)
Patients discontinued prior to 10 weeks of study duration	1 (9.1)
Primary reason for premature discontinuation	
Adverse event(s)	0
Abnormal laboratory value(s)	0
Abnormal test procedure result(s)	0
Patient withdrew consent	1 (9.1)
Lost to follow-up	0
Administrative problems	0
Death	0
Protocol deviation	0

Baseline Characteristics

Patient demographics

Demographic variable	All patients N=11
Age (years)	
Mean (SD)	35.2 (6.79)
Median	33.0
Min-Max	24 to 48
Sex, n (%)	
Male	7 (63.6)
Female	4 (36.4)
Race, n (%)	
Caucasian	11 (100.0)
Ethnicity, n (%)	
Hispanic/Latino	3 (27.3)
Other	8 (72.7)
Weight	
Mean	61.15 (11.58)
Median	59.00
Min-Max	47 to 83.5
Height	
Mean	162.1 (5.30)
Median	162.0
Min-Max	155 to 175
BMI	
Mean	23.25 (4.04)
Median	22.48

Min-Max	17.4 to 30.5

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

Outcome measures

Primary Outcome Result(s)

Summary of renal hemodynamic and renal parameters (Safety set)

Visit	Statistics	Serum creatinine umol/L	Est. CrCL mL/min	GFR mL/min	RPF mL/min	FF	BUN mmol/L	Urea mmol/L	Cystatin C mmol/L
Baseline (N=11)	n	11	11	11	11	11	3	8	1
	Mean	61.96	121.71	111.5	603.55	0.19	6.07	5.12	0.86
	SD	14.147	16.808	17.473	94.345	0.026	1.287	2.276	NA
	Median	65.42	130.54	104	613.37	0.18	6.43	5.33	0.86
	Min	44.2	96.7	95.3	435.1	0.2	4.6	2.2	0.9
	Max	81.3	143.6	147.1	799.3	0.2	7.1	9.5	0.9
Wk 2 Day 14 (N=11)	n	11	11	10	10	10	3	7	1
	Mean	64.53	115.44	109.07	557.36	0.2	6.19	5.47	0.82
	SD	13.26	17.237	19.605	127.429	0.034	1.486	2.482	NA
	Median	63.65	109.02	101.05	536.42	0.19	5.71	5.66	0.82
	Min	42.4	96.7	82.1	448	0.2	5	2.2	0.8
	Max	84.9	148.6	139.7	882.8	0.3	7.9	9	0.8
%Chg. from BL Wk 2 Day 14	n	11	11	10	10	10	3	7	1
	Mean	5.43	-4.44	-2.97	-10.71	10.83	3.62	7.89	-4.65
	SD	14.379	12.175	10.534	10.557	22.19	23.314	17.075	
	Median	0	-1.8	-5.41	-11.31	5.72	10	7.69	-4.65
	Min	-11.1	-31.6	-13.9	-27.5	-11.1	-22.2	-13.3	-4.7
	Max	40	12.5	21.7	10.4	66.7	23.1	25.9	-4.7
Wk 8 Day 56 (N=11)	n	10	10	10	10	10	2	8	1
	Mean	76.29	100.59	96.75	529.4	0.18	7.68	5.95	0.89
	SD	16.322	12.187	19.61	102.423	0.033	1.767	2.212	NA
	Median	75.14	98.71	96.55	502.55	0.17	7.68	6.58	0.89
	Min	52.2	85.9	70.5	431.2	0.2	6.4	2.2	0.9
	Max	110.5	121.7	140.4	748.6	0.2	8.9	8	0.9
%Chg. from BL Wk 8 Day 56	n	10	10	10	10	10	2	8	1
	Mean	21.37	-16.2	-14.08	-14.95	2	12.5	19.43	3.49
	SD	20.131	13.452	10.061	8.974	15.66	17.678	24.471	NA
	Median	12.5	-11.38	-14.52	-14.4	2.17	12.5	21.77	3.49
	Min	0	-40.2	-26	-29.1	-20	0	-21.1	3.5
	Max	60	0	0.2	-5.3	27.8	25	50	3.5
Wk 10 Day 70 (N=11)	n	11	11	10	10	10	2	7	1
	Mean	62.44	119.41	112.95	577.23	0.2	6.61	4.73	0.89
	SD	13.297	16.543	23.539	107.964	0.023	0.757	1.526	NA
	Median	61.88	117.60	101.35	561.32	0.19	6.60	5.16	0.89
	Min	41.6	96.7	93.8	416.3	0.2	6.1	2.5	0.9
	Max	82.2	153.4	163.8	750.1	0.2	7.1	6.3	0.9
%Chg. from BL Wk 10 Day 70	n	11	11	10	10	10	2	7	1

	Mean	1.92	-0.98	-0.12	-6.94	8.25	-2.78	7.03	3.49
	SD	14.659	12.907	6.617	13.047	10.717	3.928	10.909	NA
	Median	0.00	0.00	-2.64	-7.20	5.90	-2.78	8.82	3.49
	Min	-13.5	-31.6	-5.4	-24.7	-5.9	-5.6	-13.9	3.5
	Max	40.0	16.1	16.9	19.5	27.8	0.00	18.8	3.5

Est CrCL=Estimated creatinine clearance; GFR=Glomerular filtration rate; RPF=Renal plasma flow, FF=Filtration fraction, Wk=Week; Chg=Change; BL=Baseline; NA=Not applicable
Baseline is the last available non-missing value before the first dose of the study medication.
At each time point, a patient must have both baseline and post-baseline values to be included.

Summary of special renal function parameters long term patients (Safety set)

Visit	Statistics	Serum creatinine umol/L	Est. CrCL mL/min	GFR mL/min	RPF mL/min	FF	BUN mmol/L	Urea mmol/L	Cystatin C mmol/L
Baseline (N=5)	n	5	5	5	5	5	2	3	1
	Mean	61.53	115.02	108.52	595.44	0.18	6.78	7.05	0.86
	SD	15.126	21.328	18.107	43.065	0.029	0.505	2.121	NA
	Median	65.42	101.66	101.9	605.64	0.18	6.78	5.99	0.86
	Min	44.2	96.7	95.3	552.1	0.2	6.4	5.7	0.9
	Max	79.6	143.6	140.1	653	0.2	7.1	9.5	0.9
Wk 2 Day 14 (N=5)	n	5	5	5	5	5	2	3	1
	Mean	62.59	111.14	104.86	502.19	0.21	6.43	7.16	0.82
	SD	12.351	21.435	19.663	41.155	0.032	2.019	1.754	NA
	Median	63.65	104.3	100.9	510.04	0.19	6.43	6.99	0.82
	Min	42.4	96.7	82.1	448	0.2	5	5.5	0.8
	Max	74.3	148.6	129.2	548.5	0.3	7.9	9	0.8
%Chg. from BL Wk 2 Day 14	n	5	5	5	5	5	2	3	1
	Mean	3.9	-1.94	-2.94	-15.34	15.51	-6.11	3.31	-4.65
	SD	20.609	17.245	14.772	8.808	28.755	22.785	17.577	
	Median	-2.7	2.6	-7.78	-15.78	5.56	-6.11	-5.26	-4.65
	Min	-11.1	-31.6	-13.9	-27.5	-0.6	-22.2	-8.3	-4.7
	Max	40	12.5	21.7	-4	66.7	10	23.5	-4.7
Wk 8 Day 56 (N=5)	n	5	5	5	5	5	2	3	1
	Mean	70.72	97.33	99.28	489.71	0.2	7.68	6.88	0.89
	SD	11.577	14.803	26.297	64.673	0.038	1.767	0.673	NA
	Median	70.72	93.12	97.2	459.95	0.21	7.68	6.99	0.89
	Min	52.2	85.9	70.5	431.2	0.2	6.4	6.2	0.9
	Max	81.3	121.7	140.4	578.7	0.2	8.9	7.5	0.9
%Chg. from BL Wk 8 Day 56	n	5	5	5	5	5	2	3	1
	Mean	18.15	-13.72	-9.49	-17.84	9.92	12.5	1.75	3.49
	SD	23.695	15.235	10.854	7.913	12.804	17.678	22.309	NA
	Median	9.26	-8.39	-4.61	-17.8	6.67	12.5	2.78	3.49
	Min	2.2	-40.2	-26	-27	-5.9	0	-21.1	3.5
	Max	60	-1.1	0.2	-5.7	27.8	25	23.5	3.5
Wk 10 Day 70 (N=5)	n	5	5	5	5	5	2	2	1
	Mean	60.47	114.91	112.04	543.05	0.2	6.61	5.66	0.89

	SD	12.29	22.932	29.767	118.619	0.022	0.757	0.706	NA
	Median	61.88	111.18	96.4	506.71	0.19	6.6	5.66	0.89
	Min	41.6	96.7	93.8	416.3	0.2	6.1	5.2	0.9
	Max	71.6	153.4	163.8	733.2	0.2	7.1	6.2	0.9
%Chg. from BL Wk 10 Day 70	n	5	5	5	5	5	2	2	1
	Mean	0.71	1.6	2.1	-8.96	12.15	-2.78	-2.53	3.49
	SD	22.628	19.511	9.104	17.66	12.467	3.928	16.06	NA
	Median	-10.00	10.02	-1.57	-10.34	11.77	-2.78	-2.53	3.49
	Min	-13.5	-31.6	-5.4	-24.7	-4.4	-5.6	-13.9	3.5
	Max	40	16.1	16.9	19.5	27.8	0	8.8	3.5
Wk 52 Day 364 (N=5)	n	5	5	5	5	5	2	3	1
	Mean	70.37	98.96	89.41	439.81	0.20	6.07	6.83	1.02
	SD	12.26	11.81	16.65	34.80	0.03	0.50	0.50	NA
	Median	70.72	96.67	90.00	435.50	0.22	6.07	6.83	1.02
	Min	53.9	89.8	69.9	400.5	0.2	5.7	6.3	1.0
	Max	88.4	119.4	112.6	478.6	0.2	6.4	7.3	1.0
%Chg. from BL Wk 52 Day 364	n	5	5	5	5	5	2	3	1
	Mean	17.63	-12.13	-17.67	-26.15	10.22	-10.56	0.95	18.61
	SD	24.262	14.688	7.262	2.002	11.288	0.786	20.600	NA
	Median	11.11	-8.82	-19.63	-26.72	6.67	-10.56	11.77	18.61
	Min	0.0	-37.5	-26.7	-28.1	0.00	-11.1	-22.8	18.6
	Max	60.0	0.0	-8.9	-23.1	22.2	-10.0	13.9	18.6
Wk 104 Day 728 (N=5)	n	5	5	5	5	5	2	3	5
	Mean	65.42	107.37	90.16	479.5	0.19	8.21	6.94	1.05
	SD	15.106	13.765	17.848	87.643	0.022	2.019	1.083	0.128
	Median	63.65	105.37	84.9	432.16	0.2	8.21	6.99	1
	Min	51.3	92.1	75.6	401.2	0.2	6.8	5.8	1
	Max	88.4	124.3	121.3	615	0.2	9.6	8	1.3
%Chg. from BL Wk 104 Day 728	n	5	5	5	5	5	2	3	1
	Mean	7.16	-5.73	-17.18	-19.59	4.28	20.28	4.03	16.28
	SD	9.07	8.219	3.591	12.324	11.448	20.82	34.257	NA
	Median	7.41	-5.93	-16.68	-21.72	6.67	20.28	-2.78	16.28
	Min	-2.7	-17.6	-21.1	-33.8	-13	5.6	-26.3	16.3
	Max	20	3.7	-13.4	0.3	16.7	35	41.2	16.3
EOS – Wk 108 (N=5)	n	5	5	5	5	5	2	2	5
	Mean	62.94	109.94	103.54	553.54	0.19	7.32	6.24	0.96
	SD	10.707	8.765	17.091	91.767	0.027	1.262	0.118	0.118
	Median	61.88	110.48	94.5	527.58	0.2	7.32	6.24	0.93
	Min	51.3	101.5	91.2	434.1	0.2	6.4	6.2	0.9
	Max	80.4	123.5	132.6	667.7	0.2	8.2	6.3	1.2
%Chg. from BL EOS	n	5	5	5	5	5	2	2	1
	Mean	5.31	-2.05	-4.54	-7.31	5.23	7.5	7.27	9.3

	SD	20.981	17.172	3.277	11.485	13.086	10.607	6.355	NA
	Median	1.11	1.81	-5.35	-5.02	5.88	7.5	7.27	9.3
	Min	-12.5	-29.3	-7.9	-21.5	-13	0	2.8	9.3
	Max	40	14.3	-1	8.9	22.2	15	11.8	9.3

Est CrCL=Estimated creatinine clearance; GFR=Glomerular filtration rate; RPF=Renal plasma flow; FF=Filtration fraction, Wk=Week; Chg=Change; BL=Baseline; EOS=End of study; NA=Not applicable.
Baseline is the last available non-missing value before the first dose of the study medication.
At each time point, a patient must have both baseline and post-baseline values to be included.
Table includes only long term patients.

Secondary Outcome Result(s)

Serum creatinine versus GRF, RPF, and FF

Absolute changes from baseline in serum creatinine and creatinine clearance were plotted against absolute changes in GFR, RPF, and FF. Despite no clear trend in the relationship between changes could be established from the scatterplots due to limited number of patients, overall results still suggested that the decrease in GFR and RPF were accompanied by small increase in serum creatinine and a decrease in creatinine clearance.

Serum ferritin versus GFR, RPF, FF, and serum creatinine

Absolute changes from baseline in serum ferritin were plotted against absolute changes in GFR, RPF, and FF. Due to the limited number of patients, no clear trend in the relationship between changes could be established from the scatterplots.

Safety Results

Adverse Events by System Organ Class

All AEs regardless of study drug relationship by primary system organ class (Safety set)

Primary system organ class	All patients N=11 n (%)
Any system organ class	**11 (100.0)**
Cardiac disorders	1 (9.1)
Gastrointestinal disorders	7 (63.6)
General disorders and administration site conditions	5 (45.5)
Immune system disorders	1 (9.1)
Infections and infestations	4 (36.4)
Investigations	1 (9.1)
Metabolism and nutrition disorders	1 (9.1)
Musculoskeletal and connective tissue disorders	4 (36.4)
Nervous system disorders	3 (27.3)
Respiratory, thoracic and mediastinal disorders	4 (36.4)
Skin and subcutaneous tissue disorders	2 (18.2)

Primary system organ classes are presented alphabetically
A patient with multiple occurrences of an AE is counted only once in that AE category.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Most frequently Reported AEs Overall by Preferred Term n (%)

All AEs regardless of study drug relationship by preferred term (Safety set)

Preferred term	All patients N=11 n (%)
Abdominal pain upper	3 (27.3)
Diarrhea	3 (27.3)
Pyrexia	3 (27.3)
Rhinitis	3 (27.3)
Cough	3 (27.3)
Oropharyngeal pain	3 (27.3)
Abdominal pain	2 (18.2)
Back pain	2 (18.2)
Headache	2 (18.2)
Rash	2 (18.2)
Tachycardia	1 (9.1)
Hemorrhoids	1 (9.1)
Nausea	1 (9.1)
Vomiting	1 (9.1)
Asthenia	1 (9.1)
Oedema peripheral	1 (9.1)

Seasonal allergy	1 (9.1)
Influenza	1 (9.1)
Pharyngitis	1 (9.1)
Tooth abscess	1 (9.1)
Platelet count decreased	1 (9.1)
Zinc deficiency	1 (9.1)
Musculoskeletal pain	1 (9.1)
Myalgia	1 (9.1)
Osteoporosis	1 (9.1)
Tendonitis	1 (9.1)
Radicular pain	1 (9.1)
Pruritus	1 (9.1)

Preferred terms are sorted by descending order of frequencies, as reported in the 'all patients' column.

Serious Adverse Events and Deaths

There were no serious adverse events and deaths in this study.

Other Relevant Findings

Summary of deferasirox trough concentration (PK set)

Visit	Time Point	Statistics	Concentration (µmol/L)
Baseline	Pre dose	n	11
		Mean (SD)	0 (0)
		CV% mean	NA
		Geo-mean	NA
		CV% geo-mean	NA
		Median	0
		Min-Max	0
Wk 1 Day 7	Pre dose	n	11
		Mean (SD)	37.25 (29.181)
		CV% mean	78.33
		Geo-mean	28.62
		CV% geo-mean	88.46
		Median	21.9
		Min-Max	9.3 to 101
Wk 2 Day 14	Pre dose	n	8
		Mean (SD)	32.13 (15.081)
		CV% mean	46.92
		Geo-mean	29.46
		CV% geo-mean	46.01
		Median	30.1
		Min-Max	15.9 to 63.6
Wk 3 Day 21	Pre dose	n	10
		Mean (SD)	29.64 (23.429)
		CV% mean	79.04
		Geo-mean	23.81
		CV% geo-mean	74.52
		Median	19.2
		Min-Max	8.5 to 85.3
Wk 4 Day 28	Pre dose	n	10
		Mean (SD)	33.75 (27.934)
		CV% mean	82.75
		Geo-mean	24.24
		CV% geo-mean	113.27
		Median	18.9
		Min-Max	4.1 to 95.2
Wk 8 Day 56	Pre dose	n	9
		Mean (SD)	31.88 (24.612)
		CV% mean	77.20

		Geo-mean	25.73
		CV% geo-mean	76.35
		Median	22
		Min-Max	9.0 to 91
Wk 10 Day 70	Pre dose	n	10
		Mean (SD)	0 (0)
		CV% mean	NA
		Geo-mean	NA
		CV% geo-mean	NA
		Median	0
		Min-Max	0
Wk 52 Day 364	Pre dose	n	5
		Mean (SD)	39.4 (32.460)
		CV% mean	82.38
		Geo-mean	44.42
		CV% geo-mean	54.26
		Median	40.4
		Min-Max	0 to 89.3
Wk 104 Day 728	Pre dose	n	4
		Mean (SD)	41.75 (31.577)
		CV% mean	75.63
		Geo-mean	53.32
		CV% geo-mean	38.83
		Median	49.9
		Min-Max	0 to 67.1
Wk 108 Day 756	Pre dose	n	4
		Mean (SD)	4.55 (9.1)
		CV% mean	200
		Geo-mean	18.2
		CV% geo-mean	NA
		Median	0
		Min-Max	0 to 18.2

Wk=Week; NA = Not applicable
Consider only pre dose concentrations at each visit to calculate summary statistics.
Coefficient of variation (CV%) = SD/mean*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Summary of statistical analysis of GFR, RPF, and FF with trough concentration - Model 1 (Safety set)

			Parameter ratio for 2 fold PK exposure increase	
Parameter (unit)	**Effect**	**Coefficient**	**Estimate**	**90% Confidence interval**
GFR (mL/min)	Log (baseline(GFR))	1.08		
	Trough concentration (Week 8)	-0.09	0.92	(0.85, 0.99)
	Trough concentration (Week 2)	0.11	1.12	(1.00, 1.25)
RPF (mL/min)	Log (baseline(RPF))	0.50		
	Trough concentration (Week 8)	0.01	1.01	(0.87, 1.18)

	Trough concentration (Week 2)	-0.17	0.84	(0.65, 1.10)
FF	log(baseline(FF))	0.85		
	Trough concentration (Week 8)	-0.08	0.92	(0.87, 0.97)
	Trough concentration (Week 2)	0.21	1.23	(1.14, 1.32)

All patients data included in the analysis.
Renal hemodynamic parameter (at Week 8) = baseline renal hemodynamic parameter + trough concentration (at Week 8) + trough concentration (at Week 2).

Summary of statistical analysis of GFR, RPF, and FF with trough concentration – Model 2 (Safety set)

			Parameter ratio for 2 fold PK exposure increase	
Parameter (unit)	**Effect**	**Coefficient**	**Estimate**	**90% Confidence interval**
GFR (mL/min)	Log (baseline(GFR))	0.43		
	Trough concentration (Week 2)	-0.12	0.89	(0.75, 1.04)
RPF (mL/min)	Log (baseline(RPF))	0.19		
	Trough concentration (Week 2)	0.00	1.00	(0.85, 1.18)
FF	Log (baseline(FF))	0.17		
	Trough concentration (Week 2)	-0.13	0.88	(0.68, 1.13)

All patients data included in the analysis
Renal hemodynamic parameter (at Week 2) = baseline renal hemodynamic parameter + trough concentration (at Week 2).

Summary of liver function parameters (Safety set)

Visit	**Statistics**	**SGOT (AST) U/L**	**SGPT (ALT) U/L**
Baseline (N=11)	n	11	11
	Mean (SD)	28.82 (11.591)	41.73 (32.116)
	Median	26.00	29.00
	Min-Max	16.00 to 52.00	13.00 to 125.00
%Change from BL Week 8 Day 56	n	10	10
	Mean (SD)	5.27 (21.175)	-8.09 (30.857)
	Median	0.00	-12.25
	Min-Max	-25.00 to 50.00	-55.56 to 43.48
%Change from BL Week 10 Day 70	n	11	11
	Mean (SD)	1.30 (24.733)	14.58 (67.202)
	Median	-5.41	-12.00
	Min-Max	-23.08 to 58.33	-50.00 to 169.23
%Change from BL Week 104 Day 728	n	5	5
	Mean (SD)	8.47 (48.458)	-11.51 (41.757)
	Median	-12.50	-19.64
	Min-Max	-33.33 to 87.50	-54.55 to 50.00
%Change from BL Week 108 Day 756	n	5	5
	Mean (SD)	13.92 (47.144)	22.71 (82.451)
	Median	-5.00	-17.24
	Min-Max	-24.14 to 93.75	-32.00 to 162.50

Date of Clinical Trial Report 23-Oct-2012
Date Inclusion on Novartis Clinical Trial Results Database 22-Jan-2013
Date of Latest Update