Sponsor

Novartis

Generic Drug Name

Deferasirox

Trial Indication(s)

ß-thalassemia with transfusional hemosiderosis

Protocol Number

CICL670AUS04

Protocol Title

An open label trial evaluating cardiac T2* in β-thalassemia patients on deferasirox (ICL670) treatment for 18 months

Clinical Trial Phase

Phase IV

Study Start/End Dates

14-Feb-2006 to 04-Nov-2009

Reason for Termination

Not applicable.

Study Design/Methodology

Thirty patients with abnormal T2*, but normal cardiac function, were enrolled into this open-label, single-arm pilot trial. The screening period lasted up to 4 weeks. Patients were screened for eligibility to determine if they met all inclusion/exclusion criteria. All patients initiated treatment with 30 mg/kg/day deferasirox. Deferasirox was administered orally once per day

for 77 weeks in the core study. Patients whose T2* had improved over the 18 months in the core study but had not yet reached 20ms could continue in a 6-month extension phase. This extension phase allowed patients to continue deferasirox treatment for an additional 6 months following Week 77 (Visit 18) of the core study.

The visit schedule was every 4 weeks for the first 53 weeks (Visit 15). Thereafter, study visits occurred every 8 weeks until the end of the study (Visit 18); however, monthly safety evaluations including serum creatinine and urine protein creatinine ratio continued as recommended by the Exjade® package insert. Eligible patients were treated with study drug beyond the core study and subsequently evaluated on a monthly basis (or as clinically indicated) until Week 101. A window of ±7 days around scheduled visit dates was allowed. All patients had an End of Study visit, including those who discontinued early. The end of the study form on the core protocol was completed for all patients irrespective of participation in the extension study.

Cardiac iron measurement by MRI T2* and evaluation of LIC by MRI R2 or SQUID were performed at screening and Weeks 25, 49, 77, and 101. For those patients who completed a full set of MRI evaluations for calibration with CHLA within 8 weeks prior to study entry, MRI procedures at screening were not repeated. Cardiac function as assessed by ECHO shortening fraction and MRI ejection fraction were also assessed during screening and Weeks 25, 49, 77, and 101. Serum ferritin was assessed at each study visit. Other surrogate markers for iron status (serum iron, transferrin, transferrin saturation) were assessed every 12 weeks until the final study visit (Visit 18) and again at Week 101 for the extension phase patients. Total non transferrin bound iron (NTBI) as well as the NTBI subsets of directly chelatable iron (DCI) and labile plasma iron (LPI) were also evaluated at baseline and Weeks 13, 25, and 49.

Centers

5 centers in 1 country: United States

Publication

http://bloodjournal.hematologylibrary.org/cgi/reprint/116/4/537

http://onlinelibrary.wiley.com/doi/10.1002/ajh.21830/pdf

Objectives:

Primary objective(s)

Core Study

To evaluate changes in cardiac iron as measured by MRI T2* from baseline to 25, 49, and 77 weeks of study in β-thalassemia patients with evidence of cardiac iron overload and normal cardiac function.

Extension Phase

To evaluate changes in cardiac iron as measured by MRI T2* from baseline to 101 weeks of study in β-thalassemia patients with evidence of cardiac iron overload and normal cardiac function.

Secondary objective(s)

Core Study

To evaluate:

• Safety and tolerability of deferasirox 30 - 40 mg/kg/day for up to 77 weeks.
• Changes in liver iron concentration as measured by MRI R2 or SQUID from baseline to 25, 49, and 77 weeks of study.
• Rates of change of cardiac and liver iron from baseline to 25, 49, and 77 weeks of therapy.
• Changes in ventricular ejection fraction as measured by MRI and echocardiography from baseline to 25, 49, and 77 weeks of study.
• Changes in serum ferritin from baseline through 25, 49, and 77 weeks of study.
• Changes in trough NTBI (LPI and DCI), serum iron, transferrin, and transferrin saturation.
• Whether changes in trough NTBI (LPI and DCI) or transferrin saturation correlate with changes in cardiac or liver iron.
• Compliance with use of deferasirox using pill counts at every visit.

Extension Phase

To evaluate:

• Safety and tolerability of deferasirox 30 - 40 mg/kg/day for up to 101 weeks.
• Changes in liver iron concentration as measured by MRI R2 or SQUID from baseline to 101 weeks of study.
• Changes in ventricular ejection fraction as measured by MRI and echocardiography from baseline to 101 weeks of study.
• Changes in serum ferritin from baseline through 101 weeks of study.

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

Deferasirox was taken orally daily, 30 minutes before breakfast, at the same time every morning if possible.

Statistical Methods

Data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, drug exposure, and safety observations and measurements. For the summarization of all continuous variables, univariate statistics displayed included: n, mean, median, standard deviation (SD), standard error of the mean (SEM), 25th and 75th percentiles (P25, P75), and minimum and maximum for all relevant analyses. For the summarization of categorical variables, the statistics displayed included frequencies (n) and percents.

The last available non-missing assessment (including screening assessments) before the start of treatment was considered the 'baseline' assessment. For serum ferritin, baseline values were calculated by averaging screening and Week 1 (pre-dose) levels. Change from baseline summaries for the efficacy variables included the absolute (ie, based on raw data) and percentage changes derived by taking the post-treatment visit value minus the baseline value. The percentage change measurement took the absolute change value and multiplied it by 100.

Within group changes at each study visit versus baseline were tested using a Wilcoxon signed-rank statistic. This statistic tested a null hypothesis that the change from baseline was equal to 0.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male or female β-thalassemia outpatients on chronic transfusion therapy (defined as > 8 transfusions per year)
- Lifetime minimum of 100 previous packed red blood cell transfusions
- Patients currently on chelation therapy will require a one day wash out prior to the first dose of study drug
- Age ≥ 10 years
- Sexually active females of childbearing potential must have a negative serum or urine pregnancy test and use an effective method of contraception, or must have undergone clinically documented total hysterectomy.

Exclusion Criteria:

- Ejection Fraction < 56 % measured using steady-state free precession imaging by MRI
- Contraindication to MRI, including cardiac pacemaker, brain aneurysm clip, implanted neurostimulator, insulin pump, cochlear implant, metal slivers in the eyes, intrauterine device or any other MRI incompatible metal implants or intractable claustrophobia
- Abnormal laboratory values as defined by the protocol

- Clinical or laboratory evidence of active Hepatitis B or Hepatitis C
- History of HIV positive test result (ELISA or Western blot)
- Uncontrolled systemic hypertension
- Second or third degree A-V block
- Life-threatening arrhythmias, including sustained ventricular tachycardia and aborted sudden death, within the last year
- History of cardiac conditions or unstable cardiac disease not controlled by standard medical therapy
- History of clinically relevant ocular toxicity related to iron chelation
- Systemic diseases (cardiovascular, renal, hepatic, etc.) which would prevent study treatment
- Pregnancy or breast feeding (documented negative pregnancy test required for study entry)
- Patients enrolled in an ongoing clinical trial of deferasirox (ICL670) cannot be withdrawn in order to participate in this study
- Treatment with systemic investigational drug within the past 4 weeks or topical investigational drug within the past 7 days
- Other surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of any drug
- History of non-compliance to medical regimens or patients who are considered potentially unreliable and/or not cooperative

Participant Flow Table

	Core Study Patients N=28 n (%)	Extension Phase Patients N=11 n (%)
Patients		
Eligible	28	19
Exposed	27	11
Completed	22	10
Discontinued	6	1
Main cause of discontinuation		
Adverse event(s)	2 (7.1%)*	0 (0.0%)
Abnormal laboratory value(s)	1 (3.6%)	0 (0.0%)
Abnormal test procedure result(s)	1 (3.6%)	0 (0.0%)
Unsatisfactory therapeutic effect	0 (0.0%)	0 (0.0%)
Condition no longer requires treatment	0 (0.0%)	0 (0.0%)
Protocol violation	0 (0.0%)	0 (0.0%)
Subject withdrew consent	2 (7.1%)	1 (3.6%)**
Loss to follow-up	0 (0.0%)	0 (0.0%)
Administrative reasons	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)

* Does not include one patient. This patient was listed as discontinuing study drug due to an AE, but his disposition was early termination due to an abnormal test procedure result.

** Denominator is the number of patients enrolled in the core study.

Baseline Characteristics

Demographic summary by treatment group (ITT Population)

		All Patients N=28
Age (years)	Mean	22.6
	SD	8.67
	Median	21.0
	Min, Max	10, 44
Age group – n (%)	10 – 16 years	5 (17.9%)
	17 – 40 years	21 (75.0%)
	> 40 years	2 (7.1%)
Sex – n (%)	Male	8 (28.6%)
	Female	20 (71.4%)
Race – n (%)	Caucasian	9 (32.1%)
	Black	0 (0.0%)
	Oriental	7 (25.0%)
	Other	12 (42.9%)
Weight (kg)	Mean	53.7
	SD	14.13
	Median	52.7
	Min, Max	29, 91
Weight group (kg)	<30	1 (3.6%)
	30 – <50	10 (35.7%)
	50 - <75	15 (53.6%)
	≥ 75	2 (7.1%)

Summary of Efficacy

Primary Outcome Result(s)

MRI T2* and change from baseline (absolute and percent) in MRI T2* during study (Completer Population)

Visit		MRI T2* (msec)	Absolute change from baseline (msec)	% change from baseline
Baseline	N	22		
	Mean	9.92		
	SD	3.922		
	Median	9.25		
	Min, Max	4.6, 16.1		
Week 25	N	21	21	21
	Mean	11.73	1.77	15.13
	SD	6.091	3.203	25.801
	Median	10.20	1.30	12.68
	Min, Max	4.6, 27.5	-2.3, 11.4	-25.7, 79.4
	p-value[1]		0.015	0.011
Week 49	N	22	22	22
	Mean	11.93	2.01	17.30
	SD	6.489	3.792	31.548
	Median	10.45	0.85	8.76
	Min, Max	4.0, 26.3	-3.1, 10.3	-27.9, 75.3
	p-value[1]		0.043	0.036
Week 77	N	22	22	22
	Mean	12.10	2.18	19.35
	SD	6.461	3.927	34.489
	Median	10.55	2.20	23.68
	Min, Max	3.7, 25.9	-6.5, 11.5	-41.7, 79.9
	p-value[1]		0.015	0.020

MRI T2* and change from baseline (absolute and percent) in MRI T2* during study (Extension Population)

Visit		MRI T2* (msec)	Absolute change from baseline (msec)	% change from baseline
Baseline	N	11		
	Mean	8.27		
	SD	2.085		
	Median	8.10		
	Min, Max	5.2, 11.5		
Week 25	N	10	10	10
	Mean	9.50	1.29	16.14
	SD	3.362	2.630	26.942
	Median	8.90	1.20	14.67
	Min, Max	5.4, 17.4	-2.3, 7.7	-20.7, 79.4
	p-value[1]		0.131	0.084
Week 49	N	11	11	11
	Mean	9.37	1.10	13.52
	SD	3.235	2.556	26.525
	Median	8.70	1.10	11.46
	Min, Max	4.9, 17.0	-3.1, 7.3	-27.9, 75.3
	p-value[1]		0.153	0.123
Week 77	N	11	11	11
	Mean	9.94	1.66	19.67
	SD	3.404	2.544	28.761
	Median	10.50	1.60	17.98
	Min, Max	4.5, 15.5	-3.0, 5.8	-27.0, 59.8
	p-value[1]		0.067	0.067
Week 101	N	10	10	10
	Mean	11.30	3.31	41.08
	SD	3.808	2.840	33.306
	Median	11.70	3.30	45.28
	Min, Max	5.7, 18.1	-0.6, 8.5	-8.5, 88.5
	p-value[1]		0.006	0.0039

Secondary Outcome Result(s)

LIC by MRI R2 or SQUID and change from baseline (absolute and percent) in LIC* during study (Completer Population)

Visit		LIC by MRI R2 or SQUID (mg Fe/g dw liver)	Absolute change from baseline (mg Fe/g dw liver)	% change from baseline
Baseline	N	22		
	Mean	19.85		
	SD	3.309		
	Median	16.35		
	Min, Max	3.6, 62.3		
Week 25	N	21	21	21
	Mean	17.23	-2.89	-22.72
	SD	15.393	4.169	25.081
	Median	11.90	-1.50	-16.25
	Min, Max	2.0, 50.1	-12.2, 6.5	-67.7, 21.9
	p-value[1]		0.0005	0.0001
Week 49	N	22	22	22
	Mean	17.00	-2.85	-25.27
	SD	17.548	4.883	29.341
	Median	8.50	-1.65	-26.44
	Min, Max	1.3, 64.1	-13.9, 5.9	-80.8, 19.9
	p-value[1]		0.013	0.0005
Week 77	N	22	22	22
	Mean	16.62	-3.23	-34.04
	SD	20.114	7.708	38.082
	Median	6.95	-4.60	-41.14
	Min, Max	1.0, 82.0	-14.8, 19.7	-86.0, 36.4
	p-value[1]		0.018	0.0003

LIC by MRI R2 or SQUID and change from baseline (absolute and percent) in LIC during study (Extension Population)

Visit		LIC by MRI R2 or SQUID (mg Fe/g dw liver)	Absolute change from baseline (mg Fe/g dw liver)	% change from baseline
Baseline	N	11		
	Mean	21.73		
	SD	16.346		
	Median	17.60		
	Min, Max	5.5, 62.3		
Week 25	N	10	10	10
	Mean	17.90	-4.59	-26.89
	SD	15.254	4.199	23.439
	Median	12.95	-3.85	-20.39
	Min, Max	2.4, 50.1	-12.2, 0.4	-60.8, 1.2
	p-value[1]		0.006	0.0039
Week 49	N	11	11	11
	Mean	17.45	-4.28	-27.42
	SD	18.306	4.318	24.103
	Median	9.50	-3.10	-25.45
	Min, Max	4.1, 64.1	-12.1, 1.8	-68.8, 2.9
	p-value[1]		0.007	0.0029
Week 77	N	11	11	11
	Mean	17.30	-4.43	-37.62
	SD	23.309	8.685	30.844
	Median	7.90	-5.10	-43.40
	Min, Max	2.7, 82.0	-13.1, 19.7	-74.4, 31.6
	p-value[1]		0.054	0.007
Week 101	N	10	10	10
	Mean	13.91	-6.42	-48.59
	SD	19.440	4.715	30.365
	Median	4.75	-6.50	-59.59
	Min, Max	1.8, 63.6	-13.8, 1.3	-78.4, 2.1
	p-value[1]		0.0039	0.0039

Left ventricular ejection fraction and change from baseline (absolute and percent) in left ventricular ejection fraction during study (Completer Population)

Visit		Left ventricular ejection fraction (%)	Absolute change from baseline (%)	% change from baseline
Baseline	N	21		
	Mean	64.01		
	SD	6.751		
	Median	63.30		
	Min, Max	51.1, 77.7		
Week 25	N	21	21	21
	Mean	62.17	-1.84	-2.23
	SD	6.352	7.306	11.010
	Median	60.50	-2.10	-3.44
	Min, Max	50.0, 78.0	-15.5, 8.4	-19.9, 16.4
	p-value[1]		0.408	0.490
Week 49	N	22	21	21
	Mean	61.61	-2.68	-3.42
	SD	13.726	14.546	24.321
	Median	65.25	-0.10	-0.17
	Min, Max	5.8, 74.4	-55.2, 19.6	-90.5, 38.4
	p-value[1]		0.662	0.750
Week 77	N	22	21	21
	Mean	63.84	0.11	0.87
	SD	6.112	7.299	11.344
	Median	64.45	0.00	0.00
	Min, Max	48.3, 73.0	-15.2, 9.7	-20.3, 17.4
	p-value[1]		0.956	0.729

Left ventricular ejection fraction and change from baseline (absolute and percent) in left ventricular ejection fraction during study (Extension Population)

Visit		Left ventricular ejection fraction (%)	Absolute change from baseline (%)	% change from baseline
Baseline	N	11		
	Mean	64.22		
	SD	3.512		
	Median	63.30		
	Min, Max	60.1, 71.0		
Week 25	N	11	11	10
	Mean	64.59	0.37	0.61
	SD	7.479	6.721	10.575
	Median	65.60	0.30	0.48
	Min, Max	50.0, 78.0	-12.1, 8.1	-19.5, 12.8
	p-value[1]		0.747	0.638
Week 49	N	11	11	11
	Mean	63.53	-0.69	-0.97
	SD	7.157	7.002	11.091
	Median	66.00	0.90	1.38
	Min, Max	47.0, 74.0	-15.1, 7.8	-24.3, 13.0
	p-value[1]		0.983	1.000
Week 77	N	11	11	11
	Mean	66.18	1.96	3.40
	SD	4.708	6.510	9.904
	Median	66.00	2.90	4.75
	Min, Max	59.0, 73.0	-10.7, 9.7	-15.2, 15.3
	p-value[1]		0.365	0.320
Week 101	N	10	10	10
	Mean	67.10	3.56	5.73
	SD	3.643	3.983	6.460
	Median	68.20	2.95	4.61
	Min, Max	60.0, 70.9	-2.7, 8.8	-4.3, 14.6
	p-value[1]		0.027	0.027

Serum ferritin and change from baseline (absolute and percent) in serum ferritin during study (Completer Population)

Visit		Serum ferritin (µg/L)	Absolute change from baseline (µg/L)	% change from baseline
Baseline	N	22		
	Mean	4343.75		
	SD	3486.525		
	Median	3807.50		
	Min, Max	394.5, 16249.0		
Week 25	N	22	22	22
	Mean	4280.77	-62.98	-16.11
	SD	5261.563	2294.635	35.967
	Median	3384.00	-692.00	-24.40
	Min, Max	201.0, 23712.0	-3270.0, 7463.0	-59.3, 68.7
	p-value[1]		0.117	0.043
Week 49	N	21	21	21
	Mean	3759.29	-593.36	-21.64
	SD	3966.107	1534.040	35.770
	Median	2180.00	-616.00	-26.99
	Min, Max	225.0, 15633.0	-4401.0, 2729.0	-75.2, 54.8
	p-value[1]		0.026	0.006
Week 77	N	21	21	21
	Mean	3179.81	-882.74	-31.31
	SD	3439.357	1368.202	36.846
	Median	2444.00	-893.00	-32.23
	Min, Max	213.0, 14649.0	-3398.5, 2177.5	-85.1, 42.1
	p-value[1]		0.0040	0.0008

Serum ferritin and change from baseline (absolute and percent) in serum ferritin during study (Extension Population)

Visit		Serum ferritin (µg/L)	Absolute change from baseline (µg/L)	% change from baseline
Baseline	N	11		
	Mean	3848.95		
	SD	2353.243		
	Median	3784.50		
	Min, Max	1514.0, 10249.0		
Week 25	N	11	11	11
	Mean	4085.73	236.77	-3.27
	SD	3815.214	1793.411	37.557
	Median	2924.00	-464.00	-17.47
	Min, Max	806.0, 14632.0	-1547.0, 4383.0	-55.3, 68.7
	p-value[1]		0.765	0.700
Week 49	N	10	10	10
	Mean	3972.80	154.65	-5.02
	SD	3551.672	1437.037	38.100
	Median	3147.00	-168.50	-5.31
	Min, Max	803.0, 12978.0	-1664.0, 2729.0	-50.5, 54.8
	p-value[1]		1.000	1.625
Week 77	N	10	10	10
	Mean	2156.60	-1052.35	-35.27
	SD	1285.769	982.941	26.839
	Median	2315.50	-913.50	-37.15
	Min, Max	658.0, 4361.0	-3311.0, 576.5	-79.6, 15.2
	p-value[1]		0.006	0.0039
Week 101	N	10	10	10
	Mean	3339.40	-425.05	-26.10
	SD	4320.809	2245.139	44.900
	Median	1711.00	-922.25	-38.68
	Min, Max	631.0, 14769.0	-3526.0, 4520.0	-84.8, 59.1
	p-value[1]		0.375	0.160

Summary of Safety

Safety Results

Incidence of treatment-emergent SAEs occurring in 5% or more patients (Safety Population)

Primary system organ class Preferred term	All Patients N=27 n (%)
Patients with any SAE	8 (29.6%)
General disorders and administrative site conditions	
Pyrexia	5 (18.5%)
Gastrointestinal disorders	
Abdominal pain	4 (14.8%)
Vomiting	3 (11.1%)
Metabolism and nutritional disorders	
Dehydration	2 (7.4%)
Vascular disorders	
Hypotension	2 (7.4%)

SAEs are listed by descending frequency of preferred terms.

Incidence of moderate or severe treatment-emergent AEs by preferred term occurring in 5% or more of patients (Safety Population)

	All Patients N=27	
	Total n (%)	Moderate/ Severe n (%)
Patients with at least one AE	27 (100.0%)	24 (88.9%)
Preferred term		
Abdominal pain	10 (37.0%)	8 (29.6%)
Pyrexia	12 (44.4%)	7 (25.9%)
Nasopharyngitis	11 (40.7%)	6 (22.2%)
Headache	9 (33.3%)	5 (18.5%)
Nausea	16 (59.3%)	5 (18.5%)
Rash	7 (25.9%)	5 (18.5%)
Vitamin D deficiency	5 (18.5%)	5 (18.5%)
Vomiting	8 (29.6%)	5 (18.5%)
Cough	10 (37.0%)	4 (14.8%)
Blood creatinine increased	3 (11.1%)	3 (11.1%)
Dehydration	3 (11.1%)	3 (11.1%)
Hyperglycaemia	3 (11.1%)	3 (11.1%)
Hypotension	4 (14.8%)	3 (11.1%)
Vitamin B complex deficiency	3 (11.1%)	3 (11.1%)
Alanine aminortransferase increased	2 (7.4%)	2 (7.4%)
Aspartate aminotransferase increased	2 (7.4%)	2 (7.4%)
Carnitine deficiency	2 (7.4%)	2 (7.4%)
Ejection fraction decreased	2 (7.4%)	2 (7.4%)
Fatigue	9 (33.3%)	2 (7.4%)
Sinusitis	3 (11.1%)	2 (7.4%)
Urinary tract infection	3 (11.1%)	2 (7.4%)
Urticaria	3 (11.1%)	2 (7.4%)
Zinc deficiency	2 (7.4%)	2 (7.4%)

AEs are listed by descending frequency of patients reporting moderate/severe events.

A patient with multiple severity ratings for an AE while on a study treatment was only counted in the most severe category reported.

Number of patients who died or experienced other serious or clinically significant adverse events (Safety Population)

	All Patients N=27 N (%)
Serious or significant AE	17 (63.0%)
Death	0 (0.0%)
Non-fatal SAE	8 (29.6%)
Discontinued due to SAE	1 (3.7%)
Discontinued due to non-serious AE*	3 (11.1%)
AE leading to dose adjustment or temporary interruption	13 (48.1%)

* One patient discontinued due to an AE and multiple SAEs.

Date of Clinical Trial Report

24-Aug-2010