Sponsor

Novartis Pharmaceuticals Corporation (Novartis)

Generic Drug Name

Deferasirox

Trial Indications

Severe cardiac iron overload due to chronic blood transfusion

Protocol Number

CICL670A2214

Protocol Title

Phase II, open-label, single-arm, multicenter study to evaluate the efficacy and safety of deferasirox in combination with deferoxamine followed by deferasirox monotherapy in patients with severe cardiac iron overload due to chronic blood transfusion (HYPERION)

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase IV

Study Start/End Dates

19-Jan-2011/18-Nov-2013

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a prospective, Phase II, open-label, single-arm, multi-center study to evaluate the efficacy and safety of the deferasirox (DFX)-deferoxamine (DFO) combination followed by DFX monotherapy in transfusion-dependent patients with β-thalassemia major (TM), diamond-blackfan anemia (DBA) or congenital sideroblastic anemia with severe cardiac iron overload (T2* values of 5 to <10 ms measured by magnetic resonance imaging (MRI), with no symptoms of cardiac dysfunction (New York Heart Association Functional Classification (NYHA) I) and a MRI-measured Left Ventricular Ejection Fraction (LVEF) ≥ 56%.

Following a washout period, all patients were started on DFX-DFO combination treatment. Patients were allowed to be switched from the DFX-DFO combination to DFX monotherapy at any time point after Month 6, if they met both of the following criteria: cardiac T2* ≥ 10 ms and a relative increase in T2* by ≥ 10% from baseline. Cardiac T2* assessments were performed at Months 6, 12, 18 and 24 as per protocol. Patients who switched to DFX monotherapy could return to DFX-DFO combination if their cardiac T2* value fell below 10 ms with at least 10% relative decrease compared to the previous cardiac T2* value.

Centers

International, multicenter trial: 18 centers in 8 countries worldwide: Canada (1), Egypt (2), Greece (3), Italy (3), Taiwan (1), Thailand (3), Turkey (4), United Kingdom (1)

Publication

None

Objectives:

The primary objective was to evaluate the effect of DFX-DFO combination therapy followed by DFX monotherapy on myocardial iron content as depicted by change in cardiac T2* at Month 12.

The key secondary objective was to determine the proportion (%) of patients achieving T2*≥ 10 ms (but at least 10% relative increase from baseline) at Months 6, 12, 18, and 24.

Other secondary objectives were:

- To evaluate change in cardiac T2* at Month 6, 18 and 24
- To evaluate change in MRI-measured parameters of the left and right heart (left and right ventricle ejection fraction, left and right ventricular volumes and masses) at Month 6, 12, 18 and 24
- To evaluate time to achieve cardiac T2* ≥ 10 ms (but at least 10% relative increase from baseline)
- To evaluate the safety of DFX-DFO combination therapy followed by DFX monotherapy
- To evaluate trends and any associations between cardiac T2*, cardiac parameters, liver iron concentration (LIC), and serum ferritin (SF) levels during the study

Test Products, Doses, and Modes of Administration

Clinical supplies of DFX (ICL670, Exjade®) consisted of dispersible tablets in strengths of 125 mg, 250 mg and 500 mg packaged in bulk bottles. Clinical supplies of DFO (Desferal®) vials consisted of a powder formulation in vials of 500 mg and 2000 mg. DFO was given via parenteral infusion. Both study drugs were commercially available and local purchasing of the supplies was possible.

Statistical Methods

Primary efficacy endpoint: The change in cardiac iron content was assessed descriptively by calculating the geometric mean (GM) for the ratio cardiac T2* at Month 12 divided by cardiac T2* at Baseline.

Key secondary endpoint: The achievement of cardiac T2* ≥ 10 ms (but at least 10% relative increase from baseline) at Month 6, 12, 18, and 24 were presented as proportions with a 95% confidence interval.

Other efficacy endpoints included the change from baseline in cardiac T2* and in cardiac function parameters at Months 6, 12, 18 and 24, time to achieve T2* ≥ 10 ms (but at least 10% relative increase from baseline), liver iron content, serum ferritin. In addition, total body iron excretion (TBIE), and iron balance were also summarized.

All AEs recorded during the study were coded using medical dictionary for regulatory activities (MedDRA) (version 16.1) and summarized. Adverse events were not assessed according to the common terminology criteria for AEs (CTCAE) in this study. The incidence of AEs after start of study drug was summarized by system organ class, preferred term, severity, type of AE, and relationship to the study drug.

The analysis of all efficacy endpoints was based on the Full Analysis Set (FAS) and only evaluable patients were summarized. Supportive analyses were based on the Per-Protocol Set for selected key efficacy endpoints. Safety analyses were based on the Safety Set. Demographic data and other baseline data were summarized descriptively for the FAS, PPS, and the Safety Set. All efficacy and safety analysis are based on the available data up to the Month 24 visit for each patient.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Age ≥ 10 years
- Patients with β-thalassemia major or Diamond-Blackfan anemia (DBA) or congenital sideroblastic anemia on chronic transfusion therapy
- Myocardial T2* value that was ≥ 5 and <10 ms
- Left ventricular ejection fraction (LVEF) ≥ 56% as determined by MRI
- Lifetime history of at least 50 units of red blood cell transfusions, and must have been receiving at least ≥ 8 units/year of red blood cell transfusions

Key Exclusion Criteria:

- Patients with clinical symptoms of cardiac dysfunction (shortness of breath at rest or exertion, orthopnea, exercise intolerance, lower extremity edema, arrhythmias)
- Patients unable to undergo study assessments including MRI

- Patients with serum creatinine greater than Upper limit of normal (ULN) range or with significant proteinuria as indicated by a urinary protein/creatinine ratio (UPCR) ≥ 1.0 mg/mg in a non-first void urine sample at baseline.

Other protocol-defined inclusion/exclusion criteria applied.

Participant Flow Table

Disposition Reason	All patients N=60 n (%)
Completion of 24 months	
Yes	34 (56.7)
No	26 (43.3)
Completion of 12 months	
Yes	39 (65.0)
No	21 (35.0)
Reason for premature discontinuation[a]	
Subject withdrew consent	6 (10.0)
Lost to follow-up	6 (10.0)
Adverse Event(s)	5 (8.3)
Abnormal test procedure result(s)	5 (8.3)
Administrative problems	2 (3.3)
Death	1 (1.7)
Protocol deviation	1 (1.7)

[a] The reasons for discontinuation are sorted in descending order of frequency as per the all patients column.

Baseline Characteristics

Variable	Statistics	All patients N=60
Age (years)	N	60
	Mean (SD)	22.8 (7.33)
	Median	22.0
	Range (min, max)	10.0, 41.0
Age group (years) – n (%)	10 to <18	14 (23.3)
	≥ 18	46 (76.7)
Sex – n (%)	Male	28 (46.7)
	Female	32 (53.3)
Race – n (%)	Caucasian	50 (83.3)
	Black	1 (1.7)
	Asian	9 (15.0)
History of disease – n (%)	β-thalassemia major	59 (98.3)

Variable	Statistics	All patients N=60
	Diamond-blackfan anemia	1 (1.7%)
Hepatitis status – n (%)	Hepatitis B	1 (1.7%)
	Hepatitis B and C	1 (1.7%)
	Hepatitis C	16 (26.7)
	No Hepatitis	42 (70.0)
T2* (ms) – n (%)	5 - <6	10 (16.7)
	6 - <10	50 (83.3)
LVEF by Westwood (%)– n (%)	< LLN by Westwood[a]	9 (15.0)
	≥ LLN by Westwood	51 (85.0)
LVEF (%)– n (%)	≥ 56%	60 (100.0)
LIC (mg Fe/g dw) – n (%)	7 - <15	6 (10.0)
	≥ 15	54 (90.0)
LIC (mg Fe/g dw) – n (%)	<30	19 (31.7)
	≥ 30	41 (68.3)
Serum ferritin (µg/L) – n (%)	1000 - <2500	7 (11.7)
	2500 - <5000	16 (26.7)
	≥ 5000	37 (61.7)

LLN=Lower limit of normal

[a] Westwood criteria: Criteria Low, Normal, and High for males: <59, ≥ 59 - ≤ 83,and >83; for females: <63, ≥ 63 - ≤ 87, and >87

Summary of Efficacy

Primary Outcome Results

Cardiac T2* (ms) at Baseline and Month 6, 12 LOCF, 18, and 24 (FAS)

Cardiac T2* (ms)	All patients N=60
Baseline	
n	60
Mean (SD)	7.34 (1.442)
Geometric mean	7.19
95% CI of geometric mean	(6.83, 7.58)
Lower quartile	6.10
Median	7.25
Upper quartile	8.45
Range (minimum – maximum)	5.0, 9.9
Month 6	
n	48

Cardiac T2* (ms)	All patients N=60
Mean (SD)	7.44 (2.082)
Geometric mean	7.16
95% CI of geometric mean	(6.60, 7.76)
Lower quartile	5.75
Median	6.95
Upper quartile	9
Range (minimum, maximum)	4.4, 12.0
Month 6 Change from Baseline	
n	48
Geometric mean ratio Month 6/Baseline[a]	1.02
95% CI of GM ratios	(0.98, 1.07)
Lower quartile	-0.4
Median	0.2
Upper quartile	0.9
Range (minimum, maximum)	-3.6, 2.6
Month 12 LOCF	
n	52
Mean (SD)	7.97 (2.180)
Geometric mean	7.68
95% CI of geometric mean	(7.10, 8.30)
Lower quartile	6.25
Median	8.1
Upper quartile	9.5
Range (minimum, maximum)	4.4, 13.0
Month 12 LOCF Change from Baseline	
n	52
Geometric mean ratio Month 12 LOCF/Baseline[a]	1.09
95% CI of GM ratios	(1.04, 1.15)
Lower quartile	-0.25
Median	0.65
Upper quartile	1.75
Range (minimum, maximum)	-3.1, 4.5
Month 18	
n	33
Mean (SD)	8.90 (2.496)
Geometric mean	8.54
95% CI of geometric mean	(7.69, 9.49)
Lower quartile	6.8
Median	9.1

Cardiac T2* (ms)	All patients N=60
Upper quartile	10.6
Range (minimum, maximum)	4.4, 13.5
Month 18 Change from Baseline	
n	33
Geometric mean ratio Month 18/Baseline[a]	1.17
95% CI of GM ratios	(1.08, 1.28)
Lower quartile	-0.3
Median	1.3
Upper quartile	3
Range (minimum, maximum)	-2.4, 6.0
Month 24	
n	36
Mean (SD)	10.01 (3.264)
Geometric mean	9.50
95% CI of geometric mean	(8.48, 10.64)
Lower quartile	7.70
Median	9.85
Upper quartile	11.95
Range (minimum – maximum)	(4.8, 19.3)
Month 24 Change from Baseline	
n	36
Geometric mean ratio Month 24/Baseline[a]	1.30
95% CI of Geometric Mean ratios	(1.17, 1.44)
Lower quartile	0.55
Median	2.40
Upper quartile	3.60
Range (minimum – maximum)	(-2.4, 10.0)

CI: Confidence interval; LOCF=Last observation carried forward

Month 6, 12 LOCF, 18, and 24 value is the last available T2* value in Day (1, 210], (1, 390], and (390, 570], (570, 750], respectively.

[a] Only patients with post-baseline values available in the respective time window are taken into consideration for calculating the geometric mean ratio.

Secondary Outcome Results

Proportion of patients with cardiac T2* equal to or greater than 10 ms and at least 10% relative increase from Baseline (FAS)

	All patients N=60
Month 6	
n	6
Proportion[a]	12.50
95% CI of proportion	(5.86, 24.70)
Month 12 LOCF	
n	10
Proportion[a]	19.23
95% CI of proportion	(10.80, 31.90)
Month 18	
n	11
Proportion[a]	33.33
95% CI of proportion	(19.75, 50.39)
Month 24	
n	17
Proportion[a]	47.22
95% CI of proportion	(31.99, 62.99)

LOCF=Last observation carried forward
Month n value (n=12, and 24) is the last available value in Day (1, 390] and (570, 750], respectively.
[a] Only evaluable patients at each visit were used as the denominator for the calculation of proportion

Evaluation of change in cardiac T2* at Months 6, 18, and 24

See table presented for primary outcome results.

Evaluation of change in MRI-measured parameters of the left and right heart (left and right ventricle ejection fraction, left and right ventricular volumes and masses) at Month 6, 12, 18 and 24

The mean absolute change (SD) from Baseline in LVEF (%) for the FAS was 0.1 (4.62) at Month 6, -0.2 (4.84) at Month 12, 0.6 (7.04) at Month 18, and 0.9 (5.98) at Month 24. The distribution of LVEF (%) is remaining constant over time and no trend in change of LVEF (%) is visible from Baseline to Month 24.

The mean absolute change from Baseline (SD) in RVEF (%) for the FAS was −1.2 (5.35) at Month 6, −1.6 (4.40) at Month 12, -2.1 (6.10) at Month 18, and -1.4 (4.25) at Month 24 No clinically relevant changes of RVEF (%) values over time have been observed.

The mean absolute change from Baseline (SD) in LVESVI (mL) for the FAS was 0.4 (8.15) at Month 6, 1.2 (6.96) at Month 12, 1.2 (9.69) at Month 18, and 2.1 (9.17) at Month 24.

The mean absolute change from Baseline (SD) in LVEDVI (mL) for the FAS was 1.4 (15.71) at Month 6, 1.7 (15.15) at Month 12, 3.8 (12.81) at Month 18, and 8.3 (14.55) at Month 24.

The mean absolute change from Baseline (SD) in RVESVI (mL) for the FAS was 1.8 (9.79) at Month 6, 2.5 (7.95) at Month 12, 4.5 (8.84) at Month 18, and 5.4 (8.54) at Month 24.

The mean absolute change from Baseline (SD) in RVEDVI (mL) for the FAS was 2.3 (17.04) at Month 6, 1.6 (17.24) at Month 12, 6.6 (14.30) at Month 18, and 11.6 (18.31) at Month 24.

Boxplots for the absolute change from Baseline for LVESVI (mL), LVEDVEI (mL), RVESVI (mL), and RVEDVI (mL) did not reveal any clinically relevant changes over time for any of these parameters.

The mean absolute change from Baseline (SD) in LVMI (g) for the FAS was 3.0 (15.61) at Month 6, -4.4 (14.07) at Month 12, -6.5 (10.56) at Month 18, and -4.9 (10.44) at Month 24.

The mean absolute change from Baseline (SD) in RVMI (g) for the FAS was 5.4 (6.95) at Month 6, 5.2 (6.08) at Month 12, 5.2 (6.43) at Month 18, and 5.8 (6.44) at Month 24.

There were no clinically relevant changes of LVMI (g) or RVMI (g) at Month 6, 12, 18, or 24.

Evaluation of time to achieve cardiac T2* ≥ 10 ms (but at least 10% relative increase from baseline) (FAS)

	All patients N=60
No. of events	21 (40.4%)
No. of censored	31 (59.6%)
At death date	0
At the latest date of last visit date and discontinuation date for patients who discontinued for 'Unsatisfactory therapeutic effect'[a]	5 (9.6%)
At last T2* assessment date	26 (50.0%)
Reverse Kaplan-Meier estimates[a] [95% CI] (days) at:	
25th percentile probability	441.0 [219.0, 539.0][c]
75th percentile probability	NE[b] [727.0, NE]
Median time to achieve T2*≥ 10 ms and at least 10% relative increase from Baseline [95% CI]	722.0 [520.0, NE]

[a] Unsatisfactory therapeutic effect': T2*<5ms
[b] Reverse Kaplan-Meier estimate = 1 – Kaplan-Meier estimate.
[c] NE: not estimable.
Note: Only patients with Baseline T2* and at least one post-baseline T2* value were used for analysis.

Evaluation of trends and any associations between cardiac T2*, cardiac parameters, liver iron concentration (LIC), and serum ferritin (SF) levels during the study

A moderate negative correlation was seen for T2* and LIC at Month 12 (r=−0.6047) and Month 24 (r=−0.5192). A moderate positive correlation was seen for R2* and LIC at Month 12 (r=0.6492) and Month 24 (r=0.4803). A moderate positive correlation was seen for serum ferritin and LIC at Baseline (r=0.5904), Month 12 (r=0.6109) and Month 24 (r=0.6201). A moderate negative correlation was seen for T2* and serum ferritin at Month 24 (-0.4781). Other correlations were weak (r <0.4) or not visible.

A moderate positive correlation was observed for serum ferritin and LIC at Month 24 (r=0.6104). Other correlations were weak (<0.4) or not visible.

Change in serum ferritin and liver iron concentration from Baseline to Month 24

The mean Baseline (SD) in SF for the FAS was 5686 (2528) µg/L. Mean absolute change from Baseline in SF was −1597 (1360) µg/L at Month 6, −2229 (1625) µg/L at Month 12, -2429 (2016) at Month 18, and -2325 (2154) at Month 24. There was a mean (SD) relative decrease of SF already at Month 1 of −13.2 (19.68), which became more pronounced over time. Around Month 12 the decrease leveled off; mean relative change from Baseline was -41.6 (31.02) at this time-point. The maximum mean relative change from Baseline was recorded at Month 21 with -48.1 (36.51). At Month 24 the corresponding decrease was - 43.4 (37.11). There is a gradual decrease of both mean and medium SF (µg/L) in the first year of treatment. The decrease achieved at Month 12 persists in the second year of treatment.

The mean (SD) baseline in LIC (mg Fe/g dw) for the FAS was 33.43 (14.547). Mean absolute change (SD) from Baseline in LIC (mg Fe/g dw) was −9.20 (8.696) at Month 6, −14.35 (12.060) at Month 12, -17.50 (12.528) at Month 18, and -17.30 (15.031) at Month 24. There was a mean relative decrease (SD) from Baseline of LIC (mg Fe/g dw) of −30.5% (26.35) at Month 6, of −46.4% (30.91) at Month 12, of -55.5% (34.31) at Month 18, and of −52.3% (47.43) at Month 24. Liver iron content over time shows a gradual decrease of the median and the mean in the first year of treatment. The decrease achieved at Month 12 persists in the second year of treatment.

Summary of Safety

Safety Results

Adverse events by system organ class (Safety set)

System organ class	All patients N=60 n (%)
Total	54 (90.0)
Infections and infestations	39 (65.0)
Musculoskeletal and connective tissue disorders	25 (41.7)
Gastrointestinal disorders	24 (40.0)
General disorders and administration site conditions	24 (40.0)

System organ class	All patients N=60 n (%)
Investigations	19 (31.7)
Nervous system disorders	14 (23.3)
Respiratory, thoracic and mediastinal disorders	13 (21.7)
Metabolism and nutrition disorders	12 (20.0)
Renal and urinary disorders	12 (20.0)
Injury, poisoning and procedural complications	11 (18.3)
Cardiac disorders	10 (16.7)
Skin and subcutaneous tissue disorders	9 (15.0)
Eye disorders	7 (11.7)
Ear and labyrinth disorders	6 (10.0)
Reproductive system and breast disorders	4 (6.7)

System organ classes are sorted in descending frequency. A patient with multiple occurrences of an AE is counted only once in the AE category. Events provided for on treatment period, Day 1 to (last study drug day + 28 days).
Note: A cut-off of >5% of patients in any SOC is applied.

Adverse events by preferred term (Safety set)

Preferred term	All patients N=60 n (%)
Any preferred term	**54 (90.0)**
Pyrexia	15 (25.0)
Back pain	12 (20.0)
Upper respiratory tract infection	10 (16.7)
Headache	9 (15.0)
Nasopharyngitis	9 (15.0)
Abdominal pain	8 (13.3)
Arthralgia	8 (13.3)
Diarrhoea	8 (13.3)
Influenza	8 (13.3)
Nausea	8 (13.3)
Toothache	7 (11.7)
Oropharyngeal pain	6 (10.0)
Proteinuria	6 (10.0)
Urine protein/creatinine ratio increased	6 (10.0)
Asthenia	5 (8.3)
Blood creatinine increased	5 (8.3)

Preferred term	All patients N=60 n (%)
Cough	5 (8.3)
Tooth abscess	5 (8.3)
Abdominal pain upper	4 (6.7)
Electrocardiogram T wave inversion	4 (6.7)
Gastroenteritis	4 (6.7)
Hypocalcaemia	4 (6.7)
Pain in extremity	4 (6.7)
Tonsillitis	4 (6.7)
Vomiting	4 (6.7)

Preferred terms are sorted in descending frequency. A patient with multiple occurrences of an AE is counted only once in the AE category. Events provided for on treatment period, Day 1 to (last study drug day + 28 days).
Note: A cut-off of >5% of patients in any Preferred term is applied.

Serious adverse events by preferred term (Safety Set)

Preferred Term	All patients N=60 n (%)
Any preferred term	**17 (28.3)**
Abdominal pain	2 (3.3)
Abscess neck	1 (1.7)
Altered state of consciousness	1 (1.7)
Anaemia	1 (1.7)
Asthenia	1 (1.7)
Biliary colic	1 (1.7)
Bronchitis	1 (1.7)
Calcium deficiency	1 (1.7)
Chest injury	1 (1.7)
Cholecystitis	1 (1.7)
Costochondritis	1 (1.7)
Dermoid cyst	1 (1.7)
Drug reaction with eosinophilia and systemic symptoms	1 (1.7)
Fallopian tube cyst	1 (1.7)
Febrile infection	1 (1.7)
Hyperglycaemia	1 (1.7)
Hypocalcaemia	1 (1.7)
Hypoglycaemia	1 (1.7)

Preferred Term	All patients N=60 n (%)
Any preferred term	**17 (28.3)**
Hypophosphataemia	1 (1.7)
Infection	1 (1.7)
Irritable bowel syndrome	1 (1.7)
Ischaemic stroke	1 (1.7)
Myalgia	1 (1.7)
Ovarian cyst	1 (1.7)
Ovarian germ cell teratoma benign	1 (1.7)
Pancreatitis acute	1 (1.7)
Pharyngitis	1 (1.7)
Pyrexia	1 (1.7)
Reflux gastritis	1 (1.7)
Spinal column injury	1 (1.7)
Type 1 diabetes mellitus	1 (1.7)
VIIth nerve paralysis	1 (1.7)
Vomiting	1 (1.7)

Overall summary of adverse events (Safety Set) – Deaths, SAEs or AEs leading to discontinuation

	All patients N=60 n (%)
Patients with any AE(s)	54 (90.0)
SAE or AE leading to discontinuation.	18 (30.0)
Death	1 (1.7)[a]
SAE(s)	17 (28.3)
Discontinued due to AE(s)	5 (8.3)
AEs leading to dose adjustment or interruption	29 (48.3)
AEs of special interest	15 (25.0)

Other Relevant Findings

None

Conclusion:

In summary, in both the heart and liver, there was a clinically meaningful decrease in iron burden over time, as measured by the change in the GM of cardiac T2* and change in mean

LIC. This clinically relevant improvement in iron severe overload status was unequivocally apparent for both heart and liver, although changes were faster in the liver than the heart echoing data from the literature regarding the dynamics of longitudinal iron loading and unloading in both vital organs.

The DFX-DFO combination was generally well tolerated with a favorable benefit to risk profile.

Date of Clinical Trial Report

03-Apr-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

04-Nov-2014

Date of Latest Update

Reason for Update