Sponsor Novartis Pharma GmbH
Generic Drug Name Deferasirox (ICL670)
Therapeutic Area of Trial Transfusion-dependent iron overload
Approved Indication Exjade (deferasirox) is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis)
Study Number CICL670ADE03
Title A one-year, open-label, single arm, multi-center trial evaluating the efficacy and safety of oral ICL670 in patients diagnosed with Low and INT-1 risk Myelodysplastic Syndrome (MDS) and transfusion-dependent iron overload
Phase of Development Phase IV
Study Start/End Dates 30May 2007 to 06 Sep 2010
Study Design/Methodology The study employs a single arm, multi-center, open-label trial design. The study provides efficacy and safety data collected during 52 weeks treatment with ICL670 in patients presenting with low or INT-1 risk MDS and transfusion induced iron overload. The target patient pool consists of patients with a serum ferritin level of > 1000 ng/ml at start of study and with history of multiple transfusions (>20 transfusions or 100 mL/kg of packed red blood cells).

Centres

19 centers in Germany

Objectives

Primary objective

The primary objective of this study is to evaluate if fixed starting doses of ICL670, dependent on transfusion history, and subsequent dose titration can provide clinically acceptable chelation among low and INT-1 risk MDS patients.

Secondary objective(s)

- safety and tolerability
- change in LIC and the relationship between LIC and serum ferritin
- whether treatment with ICL670 reduces the blood transfusion requirement by inducing a hematologic response
- mean daily number of diarrhea episodes
- mean duration of diarrhea episodes and incidence of either moderate or severe diarrhea episodes

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

- drug formulation: dispersible tablets

• strength – 125 mg, 250 mg, 500 mg

• mode of administration: oral use (suspension can be prepared in water, orange or apple juice)

The starting dose is determined by the frequency of blood transfusions .The recommended initial daily dose of ICL670 is 20 mg/kg/day body weight for patients receiving < 4 units of packed red blood cells/month (or 7 – 14 mL/kg/month). An initial daily dose of 30 mg/kg/day may be considered for patients receiving more frequent blood transfusions.

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

There was no reference therapy in this study.

Criteria for Evaluation

Primary variables

The primary efficacy variable was the absolute change of serum ferritin vs. baseline after 52 weeks of treatment.

Secondary variables

- absolute and relative change in LIC as measured by MRI R2
- transfusion requirements during study
- hematologic response

Safety and tolerability

Monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), the regular monitoring of hematology, blood chemistry, and regular measurement of vital signs and the performance of physical examinations.

Pharmacology

N/A

Other

N/A

Statistical Methods

Primary efficacy: The primary efficacy analysis is based on the differences in serum ferritin from baseline vs. 52 weeks of treatment. The following hypothesis system will be tested purely exploratory:
H0: The difference in serum ferritin between baseline and week 52 is equal to zero.
vs.
H1: The difference in serum ferritin between baseline and week 52 is unequal to zero.
The hypothesis will be tested using a paired t-test with a 0,05 two-sided significance level.
The primary population for the statistical testing is the ITT population. Additionally, the statistical testing will be performed for the PP population. For robustness, Wilcoxon's signedrank test will be computed additionally for the ITT and PP populations. Summary statistics will be provided by visit. Changes from baseline will be summarized descriptively by visit together with the corresponding 95% confidence interval. Mean course of

serum ferritin and mean changes from baseline will be displayed graphically. Summary statistics will be calculated additionally for the PP population. If no serum ferritin value is available after 52 weeks, the last available post-baseline observation will be carried forward (last observation carried forward, LOCF). Baseline is defined to be the last available serum ferritin value before or at the start of treatment.

Secondary efficacy:
Secondary variables will be analyzed in a purely exploratory manner.
Liver iron concentration (LIC) determined by R2-MRI and change from baseline will be summarized descriptively for the ITT population. The 95% confidence interval (CI) for change from baseline will be computed additionally. Changes from baseline will be tested exploratory as described for the primary variable. Pearson's correlation coefficient will be calculated to estimate the relationship between changes in LIC and serum ferritin concentration. Analyses will be performed with the ITT population.
The number of transfusions required during the treatment period and the average number of transfusions required (e.g. transfusions per month of treatment) will be summarized descriptively for the ITT population. Changes from baseline in the average number of transfusions required per month will be calculated and summarized descriptively together with their 95% CI. Changes in transfusion requirements will be classified and absolute and relative frequencies will be given.
Hematologic response will be reported by the investigator using IWG guidelines provided in section 6.1 (Cheson 2006, 2000). Hematologic response will be analyzed separately for the cell lines (erythroid, platelet and neutrophil response). A logistic regression model with covariates age, number of prior transfusions, number of days exposed to ICL670, and change from baseline in serum ferritin) will be calculated for each hematologic response. The odds ratios together with their confidence interval will be reported. Analyses of hematologic response will be performed with the hematologic improvement population.

Safety: The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs, special tests) will be considered as appropriate. Adverse events will be listed by patient. Adverse events will be summarized by presenting, the number and percentage of patients having any adverse event, having an adverse event in each body system and preferred term and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate. Laboratory data will be summarized by presenting shift tables using normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by the flagging of notable values in data listings. Data from other tests (e.g. electrocardiogram or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data may be used only to highlight any interesting comparisons that may warrant further consideration.

No interim analysis was planned in the protocol nor performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patient population:
Low and INT-1 risk MDS patients presenting with transfusional hemosiderosis, either naïve to chelation therapy or previously treated with DFO and/or deferiprone.

Inclusion criteria:

MDS patients presenting with low or intermediate-1 IPSS risk and transfusional iron overload as shown by a serum ferritin level of > 1000 ng/ml; aged 18 years or older; with life expectancy > 12 months and history of at least 20 units of red blood cell transfusions or 100mL/kg of prepacked red blood cells (PRBCs); patients could be either naïve to iron chelation or have had prior treatment with deferoxamine (DFO) or deferiprone (L1); effective birth control for female patients of childbearing potential and written informed consent provided.

Exclusion criteria:

Non-transfusion related hemosiderosis; treatment with ICL670 before study start; concomitant malignant disease; mean levels of alanine aminotransferase (ALT) > 5x ULN; uncontrolled systemic hypertension; serum creatinine > 1.5x the upper limit of normal (ULN); history of nephrotic syndrome; previous history of clinically relevant ocular toxicity related to iron chelation; systemic diseases (cardiovascular, renal, hepatic, etc.) which would prevent the patient from undergoing study treatment; psychiatric or addictive disorders which prevent from giving informed consent or undergoing study treatment; treated with systemic investigational drugs within the past 4 weeks or topical investigational drug within the past 7 days; any 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 and patients who were considered potentially unreliable and/or not cooperative; 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 run-in period; active uncontrolled infectious disease; pregnancy or breast feeding; QT > 470 msec on screening ECG and history of Torsade de Pointes

Number of Subjects

	ICL670
Number (%) of patients	
Enrolled	63 (100.0%)
Exposed to treatment with study medication	54 (85.7%)
Completed study	26 (41.3%)
Discontinued study prematurely	28 (44.4%)
Reason for discontinuation - n (%) for patients exposed to treatment with study medication (N=54)	
Adverse event(s)	15 (27.8%)
Abnormal laboratory value(s)	4 (7.4%)
Abnormal test procedure result(s)	0 (0.0%)
Unsatisfactory therapeutic effect	1 (1.9%)
Protocol violation (only if patient's safety is affected)	0 (0.0%)
Subject withdrew consent	3 (5.6/%)
Lost to follow-up	0 (0.0%)
Administrative problems	1 (1.9%)
Death	3 (5.6%)
Other (Disease improvement under study)	1 (1.9%)

Demographic and Background Characteristics

	ICL670 N = 50
Gender - n (%)	
Male	28 (56.0%)
Female	22 (44.0%)
Race - n (%)	
Caucasian	50 (100.0%)
Body weight at Visit 1 - n (%)	
< 50 kg	1 (2.0%)
≥ 50 kg and < 100 kg	49 (98.0%)
≥ 100 kg	0 (0.0%)
Age (years)	
Mean	67.9
Standard deviation (SD)	9.0
Median	69.0
Range	40.0-83.0

Primary Objective Result(s)

Serum ferritin during the study, by visit (Intent-to-treat population)

Serum Ferritin [µg/l]	ICL670 N = 50							
	N	Mean	SD	Min	Med	Max	LL	UL
Change (V16-baseline) incl. LOCF	50	-668.7	1799.0	-8379.0	-488.5	5827.0	-1180.0	-157.4
Visit 1 (Day -14 to -1)	46	2975.4	3074.9	1136.0	2415.0	21545.0	2062.3	3888.5
Visit 3 (Day 1)	45	2584.1	1314.9	872.0	2447.0	7202.1	2189.1	2979.2
Visit 4 (Week 5)	47	2940.9	3510.1	761.0	2014.0	24674.0	1910.3	3971.5
Visit 5 (Week 9)	42	2919.5	3577.7	674.0	2106.5	23831.0	1804.6	4034.4
Visit 6 (Week 13)	44	2658.3	3432.4	592.0	1855.5	23102.0	1614.7	3701.8
Visit 7 (Week 17)	41	2484.9	3303.8	643.0	1579.0	21615.0	1442.1	3527.7
Visit 8 (Week 21)	42	2344.8	2598.3	640.0	1686.7	16905.0	1535.1	3154.5
Visit 9 (Week 25)	39	2198.5	2296.8	506.0	1519.0	14142.0	1454.0	2943.0
Visit 10 (Week 29)	39	2313.2	2859.9	528.0	1579.0	17817.0	1386.1	3240.2
Visit 11 (Week 33)	31	1888.4	1940.9	286.0	1241.0	11190.0	1176.5	2600.4
Visit 12 (Week 37)	35	2048.1	2241.9	307.3	1377.0	13166.0	1278.0	2818.3
Visit 13 (Week 41)	32	1901.6	1386.3	336.6	1643.5	6400.0	1401.8	2401.4
Visit 14 (Week 45)	28	1985.7	1404.1	364.0	1717.5	6914.0	1441.2	2530.2
Visit 15 (Week 49)	29	2018.5	1446.0	402.0	1717.0	6994.0	1468.4	2568.5
Visit 16 (Week 53) incl. LOCF	50	2239.5	2273.3	294.0	1684.5	13166.0	1593.5	2885.6
Change (V4-baseline)	47	42.7	1182.9	-3382.0	21.0	4027.0	-304.6	390.0
Change (V5-baseline)	42	-178.6	862.3	-1848.0	-65.0	2286.0	-447.3	90.1
Change (V6-baseline)	44	-187.7	1249.8	-3262.0	-226.0	5209.0	-567.7	192.3
Change (V7-baseline)	41	-559.0	822.4	-3002.0	-464.0	686.0	-818.5	-299.4
Change (V8-baseline)	42	-664.7	1150.6	-4640.0	-366.5	1300.0	-1023.3	-306.2
Change (V9-baseline)	39	-876.4	1381.1	-7403.0	-515.0	539.0	-1324.1	-428.7
Change (V10-baseline)	39	-744.2	1015.0	-3728.0	-451.0	1030.0	-1073.2	-415.2
Change (V11-baseline)	31	-1018.8	1958.3	-10355.0	-555.0	783.0	-1737.2	-300.5
Change (V12-baseline)	35	-885.7	1564.3	-8379.0	-469.0	677.0	-1423.1	-348.3
Change (V13-baseline)	32	-681.7	937.1	-2802.0	-590.0	1200.0	-1019.6	-343.9
Change (V14-baseline)	28	-745.9	1035.3	-2894.0	-717.5	1375.0	-1147.4	-344.5
Change (V15-baseline)	29	-678.7	1127.6	-2978.2	-656.0	1593.0	-1107.6	-249.8
Change (V16-baseline) excl. LOCF	47	-533.4	1453.3	-3092.0	-512.0	5827.0	-960.1	-106.6

LOCF: Last observation carried forward

H_0 "The difference in serum ferritin between baseline and week 53 is equal to zero":

Two-sided p-Value of the paired t-test: P = 0.0114

Two-sided p-Value of the Wilcoxon signed rank test: P = 0.0002

N: Number of patients, Min: Minimum, Max: Maximum

LL: Lower limit of the two-sided 95% confidence interval for the mean

UL: Upper limit of the two-sided 95% confidence interval for the mean

Secondary Objective Result(s)

Hematologic response (Hematologic improvement population)

	Evaluable patients	Patients with response n	[%]	LL	UL
Hematologic response					
Erythroid response	33	2	(6.1%)	(0.7%)	(20.2%)
Platelet response	10	3	(30.0%)	(6.7%)	(65.2%)
Neutrophil response	6	1	16.7%)	(0.4%)	(64.1%)

LL: Lower limit of the exact two-sided 95% confidence interval for the relative number of patients with response

UL: Upper limit of the exact two-sided 95% confidence interval for relative number of patients with response

mean number of RBC transfusion per month during study period: 3,3

Safety Results

Adverse Events by System Organ Class

	Novartis product N (%)
Patients studied	
Randomized patients	63
Patients with drug-related AE	40 (63.5)
Drug-related AEs by primary system organ class	
Blood and lymphatic disorders	1 (2.5)
Ear and labyrinth disorders	3 (5.6)
Gastrointestinal disorders	30 (75.0)
General disorders	1 (2.5)
Hepatobiliary disorders	1 (2.5)
Immune system disorders	1 (2.5)
Investigations	19 (47.5)
Metabolism and nutrition disorders	2 (5.0)
Nervous system disorders	1 (2.5)
Renal and urinary disorders	6 (15.0)
Skin and subcutanous tissue disorders	10 (25.0)

Number (%) of patients with most frequent AEs (10% or more) (Safety population)

	ICL670
Total number (%) of patients	54 (100.0%)
Number (%) of patients with AE(s)	53 (98.1%)
AE preferred term	**n (%)**
Diarrhoea	32 (59.3%)
Nausea	23 (42.6%)
Blood creatinine increased	17 (31.5%)
Abdominal pain upper	15 (27.8%)
Nasopharyngitis	13 (24.1%)
Dyspnoea	11 (20.4%)
Urinary tract infection	11 (20.4%)
Fatigue	10 (18.5%)
Back pain	9 (16.7%)
Dyspepsia	9 (16.7%)
Vertigo	8 (14.8%)
Headache	7 (13.0%)
Proteinuria	7 (13.0%)
Pruritus	7 (13.0%)
Rash	7 (13.0%)
Abdominal pain	6 (11.1%)
Anaemia	6 (11.1%)
Epistaxis	6 (11.1%)
Oedema peripheral	6 (11.1%)

Serious Adverse Events and Deaths

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them (Safety population)

	ICI 670
Total number (%) of patients	54 (100.0%)
Number (%) of patients with AE(s)	53 (98.1%)
Number (%) of patients with	**n (%)**
Death	3 (5.6%)
SAE(s)	26 (48.1%)
AE(s) leading to discontinuation of study drug	20 (37.0%)
SAE(s) leading to discontinuation of study drug	7 (13.0%)
AE(s) with suspected drug relation	40 (74.1%)
SAE(s) with suspected drug relation	1 (1.9%)
AE(s) leading to dose adjustment or study drug interruption	33 (61.1%)
AEs requiring concomitant medication/non-drug therapy	49 (90.7%)

3 ONJs were observed (1x mild, 2x severe) and 1 patient showed delayed wound healing.

Other Relevant Findings

None

Date of Clinical Trial Report

15 Jul 2011

Date Inclusion on Novartis Clinical Trial Results Database

9 Dec 2011

Date of Latest Update