Sponsor

Novartis Pharma GmbH

Generic Drug Name

Deferasirox

Therapeutic Area of Trial

Patient post Hematopoietic Stem cell transplantation

Approved Indication

Approval text from the EMA for European Countries

EXJADE is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

EXJADE is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years,

in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,

in patients with other anaemias aged 2 years and older.

EXJADE is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

Protocol Number

CICL670ADE02

Title

A one-year, open-label, single arm, multi-center trial evaluating the efficacy and safety of oral ICL670 (20 mg/kg/day) in patients three to twelve months after allogeneic hematopoietic cell transplantation in whom iron overload is present.

Study Phase

IV

Study Start/End Dates

24 Apr 2008 to 29 Jun 2012

Study Design/Methodology

This was a single arm, multi-center, open-label clinical trial to study the efficacy and safety during 52 weeks of treatment with ICL670 in patients with evidence of iron overload three to twelve months after HCT. The study was divided in two periods: a screening period and a 52-week evaluation and treatment period in which the daily dose of ICL670 was escalated from 10 mg/kg/day at to 20 mg/kg body weight during the first 4 weeks of the study. The 20 mg/kg/day ICL670 dose was maintained during the residual 48 week treatment period or until a serum ferritin level < 500 ng/ml was reached (whichever was first) unless the combined evaluation of safety markers and surrogate efficacy markers suggest a dose adjustment.

Centers

6 centers in Germany

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

- **Instructions for prescribing and taking the study drug**

The daily dose of deferasirox (ICL670) will be escalated in every patient during the initial study phase starting with 10 mg/kg body weight/day at day one of study treatment and reaching the final daily dosis of 20 mg/kg body weight after 4 weeks. In more detail, patients will receive 10 mg/kg/day during days 1 (visit 2) -14 after study start, 15 mg/kg/day from day 15 (visit 3) until the end of week 4 and 20 mg/kg/day from week 5 (Visit 4) on.

The individual daily doses of ICL670 and the exact amount of tablets (125, 250 or 500 mg [ICL670/tablet]) contributing to each dose will be calculated by the investigator based on the patient's body weight. Each daily dose will be prepared according to ICL670 dosing tables from 125 mg, 250 mg or 500 mg ICL670 tablets, as detailed in Post-text supplement 1, which provides dosing for a multiple tablet strength strategy.

Three tablet sizes (125 mg, 250 mg and 500 mg [ICL670/tablet]) are available and at the disposition of the patient. The patient will be instructed on how to prepare his/her personal daily dose from these three dosages available.

Each time when study medication is dispensed to the patient the investigator will provide detailed instructions on how to prepare and administer drugs properly according to the following schedule:

- It is strongly suggested that the ICL670 study medication should be taken daily 30 minutes before the intake of lunch at the same time every day. Please note: On visits 2, 8 and EOS supervised administration of study medication will be performed 30 minutes prior to lunch (see Sections 7.5.4 and 7.9).
- For daily doses less than 1 g, the tablets should be dispersed in a small glass of water or orange juice (at least 100 ml).
- For daily dose from 1 g to 3 g, the tablets should be dispersed in a large glass of water or orange juice (at least 200 ml).
- For daily dose higher than 3 g, the tablets should be dispersed in a large glass of water or orange juice (at least 300 ml).

In all cases, gentle stirring has to be applied and continued until the tablets are fully disintegrated), which usually takes approximately 1 to 3 minutes. Immediately after full disintegration of the tablets the content of the glass has to be swallowed. Any residue in the glass and/or on the stirrer should be dispersed in additional water and swallowed.

Statistical Methods

Demographic and background information were summarized descriptively for the SAF-, ITT-, and PP-populations. Categorical variables were presented as frequency distributions (N, %). Continuous variables were presented as number of observations (N), mean, standard deviation (SD), median, minimum, and maximum.

Efficacy

For the primary efficacy variable the following hypothesis system was tested:

H0: The mean difference in serum ferritin between baseline and week 52 was equal to zero.

H1: The mean difference in serum ferritin between baseline and week 52 was not equal to zero.

The hypotheses were tested using a paired t-test with a 0.05 two-sided significance level and the primary population for the statistical testing was the ITT-population.

Summary statistics for serum ferritin and change from baseline were provided by visit with their corresponding 95% confidence interval (CI). Mean course of serum ferritin was displayed graphically.

Missing values were handled according to the point in time of their occurrence: (a) when a serum ferritin value at a later point in time was available the last observation before the missing value was imputed; and (b) if no serum ferritin value is available after 52 weeks, the last available post-baseline observation will be carried forward until week 52.

The incidence of adverse events (AEs) was summarized through frequency tables by MedDRA system organ class (SOC) and preferred term (PT), severity, and suspected relationship to study drug.

All laboratory values and vital signs were summarized using descriptive statistics (n, mean, SD, minimum, median, maximum) by visit and as changes from baseline.

Results of ECG and echocardiogram measurements (normal, clinically insignificant abnormality, clinically significant abnormality) were presented by shift tables analyzing the frequency of changes in results between baseline, week 25 and EOS.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients were eligible for inclusion if they met all of the following criteria:

- Transfusional iron overload three to twelve months after HCT (mean serum ferritin level > 1000 ng/ml) with no evidence of active inflammation (C-reactive protein [CAP] < 10 mg/l) at the time of measurement.
- Engrafted with ANC > 1000 /mm³.
- History of at least 20 units of red blood cell (RBC) transfusions or 100 mL/kg of pre-packed red blood cells (PRBCs).
- Patients of either gender and age ≥ 18 years.
- Female patients who had reached menarche and who were sexually active had to use double-barrier contraception, oral contraceptive plus barrier contraception , or had to have undergone clinically documented total hysterectomy and/or ovariectomy, or tubal ligation or be postmenopausal defined by amenorrhea for at least 12 months. Only contraception with a pearl-Index below 1% should be considered.
- Written informed consent by the patient.

Patients were to be excluded from participation if they met any of the following criteria:

- Non-transfusion related haemosiderosis.
- Active malignancy.
- Active GvHD at the time of enrolment.
- Known active viral hepatitis or known human immunodeficiency virus positiveness.
- Uncontrolled systemic hypertension.
- 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.
- Torsades de Pointes risk (patients with congenital long QT syndrome, heart insufficiency New York Hearth Association II-IV etc.).
- Psychiatric or addictive disorders which prevent them from giving their informed consent or undergoing study treatment.
- Mean levels of alanine aminotransferase (ALT) > 5x upper limit of normality (ULN).
- Serum creatinine > 1.5 ULN and/or serum creatinine clearance < 60 ml/min.
- QT > 470 msec on screening electrocardiogram (ECG).
- Treatment with any iron chelator after HCT.

- History of clinically relevant auditory toxicity in combination with chelation therapy.
- Simultaneous consumption of aluminium-containing antacid preparations.
- Treatment with systemic investigational drugs within the past 4 weeks or topical investigational drug within the past 7 days as well as the simultaneous participation in other clinical trials.
- Galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Any other surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of any drug (see protocol CICL670ADE02 Section 5.1, Appendix 1.1).
- Pregnant or breast feeding patients.
- History of non-compliance to medical regimens and patients who are 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 screening period.

Participant Flow

Number (%) of patients	
Enrolled	82 (100.0)
Screening failures	6 (7.3)
SAF-population	76 (92.7)
ITT-population	76 (92.7)
PP-population	65 (79.3)
Completed	46 (56.1)
Non-Completers	30 (36.6)
Main reason for discontinuation	n (%)
Death	2 (2.6)
Adverse event(s)	23 (30.3)
Subject withdrew consent	4 (5.3)
Administrative reasons	1 (1.3)

Baseline Characteristics

		N = 76
Age (years)	Mean	51.8
	SD	14.0
	Median	56.0
	Range	19.0-70.0
Gender – n(%)	Male	47 (61.8)
	Female	29 (38.2)
Race – n(%)	Caucasian	75 (98.7)
	Other	1 (1.3)
Weight (kg)	Mean	69.5
	SD	12.7
	Median	68.0
	Range	43.0-104.0
Height (cm)	Mean	172.9
	SD	9.6
	Median	172.0
	Range	150.0-194.0

Outcome Measures

Primary Outcome Result(s)

Absolute change from baseline in serum ferritin (ITT-population)

Week	**n**	**Baseline value** Mean (SD) (µg/L)	**Mean change** Mean (SD) (µg/L)	**95% CI**	**p-value** (paired t-test)
Baseline	75	2642.1 (1513.5)			
Week 3	71		-125.0 (492.6)	[-241.6 ,-8.4]	
Week 5	73		-202.1 (614.4)	[-345.5 ,-58.8]	
Week 7	70		-321.5 (699.8)	[-488.4 ,-154.7]	
Week 9	68		-276.7 (905.3)	[-495.8 ,-57.5]	
Week 11	67		-133.3 (1389.2)	[-472.2 ,205.5]	
Week 13	66		-58.7 (2068.2)	[-567.2 ,449.7]	
Week 17	63		-598.0 (894.5)	[-823.3 ,-372.8]	
Week 21	60		-696.7 (956.7)	[-943.8 ,-449.5]	
Week 25	58		-653.3 (1153.6)	[-956.6 ,-350.0]	
Week 29	48		-746.8 (808.0)	[-981.4 ,-512.2]	
Week 33	47		-970.9 (960.9)	[-1253.0,-688.8]	
Week 37	46		-1087.4 (983.2)	[-1379.4,-795.4]	
Week 41	45		-1151.5 (1025.6)	[-1459.7,-843.4]	
Week 45	45		-1080.3 (933.7)	[-1360.9,-799.8]	
Week 49	44		-1115.2 (978.9)	[-1412.8,-817.5]	
Week 53/EOS	68		-1012.2 (1256.5)	[-1316.3,-708.1]	
LOFC	75		-913.9 (1312.5)	[-1215.8,-611.9]	<0.0001

n is the number of patients with observations at both baseline and endpoint

Safety Results

Number (%) of patients with AEs overall and by system organ class

	ICL670 mg
No. (%) of patients studied	76 (100.0)
No. (%) of patients with AE(s)	76 (100.0)
System organ class affected	n (%)
Gastrointestinal disorders	56 (73.7)
Infections and infestations	54 (71.1)
Investigations	52 (68.4)
General disorders and administration site disorders	41 (53.9)
Respiratory, thoracic and mediastinal disorders	33 (43.4)
Immune system disorders	32 (42.1)
Musculoskeletal and connective tissue d.	31 (40.8)
Skin and subcutaneous tissue disord.	31 (40.8)
Nervous system disorders	29 (38.2)
Eye disorders	27 (35.5)
Metabolism and nutrition disorders	20 (26.3)
Renal and urinary disorders	16 (21.1)
Ear and labyrinth disorders	13 (17.1)
Neoplasms benign, malignant and unspecified	13 (17.1)
Blood and lymphatic system disorders	11 (14.5)
Cardiac disorders	11 (14.5)
Psychiatric disorders	10 (13.2)
Vascular disorders	10 (13.2)
Reproductive system and breast disorders	7 (9.2)
Endocrine disorders	4 (5.3)
Injury, poisoning and procedural complications	4 (5.3)
Hepatobiliary disorders	3 (3.9)
Surgical and medical procedures	2 (2.6)

Number (%) of patients with most frequent AEs

	ICL670 mg
No. (%) of patients studied	76 (100.0)
No. (%) of patients with AE(s)	76 (100.0)
AE preferred term	n (%)
Blood creatinine increased	41 (53.9)
Nausea	32 (42.1)
Vomiting	30 (39.5)

	ICL670 mg
Diarrhoea	25 (32.9)
Cough	24 (31.6)
Nasopharyngitis	23 (30.3)
Pyrexia	17 (22.4)
Rash	17 (22.4)
Oedema peripheral	16 (21.1)
GvHD	14 (18.4)
Chronic GvHD	12 (15.8)
Fatigue	11 (14.5)
Headache	10 (13.2)
Conjunctivitis	10 (13.2)
Muscle spasms	9 (11.8)
Herpes zoster	9 (11.8)
Pneumonia	8 (10.5)
Rhinitis	8 (10.5)
Urinary tract infection	9 (11.8)
C-reactive protein increased	8 (10.5)
Hepatic enzyme increased	8 (10.5)
Oropharingeal pain	8 (10.5)
Back pain	8 (10.5)
Preferred terms are listed by frequency	

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

	ICL670 mg
No. (%) of patients studied	76 (100.0%)
No. (%) of patients with AE(s)	76 (100.0%)
Number (%) of patients with serious or other significant events	n (%)
Death	2 (2.6)
SAE(s)	30 (39.5)
Discontinued due to SAE(s)	3 (3.9)

Other Relevant Findings

Number (%) of patients with newly occurring or worsening hematology abnormalities (relevant findings only)

		ICL670 mg
No. of patients studied		76 (100.0)
Notable abnormality		n (%)
Hb	Low	6 (7.9)
	High	--
Hematocrit	Low	5 (5.3)
	High	1 (1.3)
RBC	Low	1 (1.3)
	High	--
WBC	Low	8 (10.5)
	High	7 (9.2)
Patelet count	Low	11 (14.5)
	High	2 (2.6)
Neutrophil granulocytes	Low	14 (18.4)
	High	5 (6.6)
Neutrophil bands	Low	1 (1.3)*
	High	4 (5.3)
Segmented neutrophils	Low	8 (10.5)
	High	2 (2.6)
Lymphocytes	Low	11 (14.5)
	High	11 (14.5)**
Eosinophils	Low	5 (6.7)***
	High	7 (9.2)
Basophils	Low	--
	High	7 (9.2)
Monocytes	Low	2 (2.6)
	High	17 (22.4)
Others	Low	--
	High	5 (6.6)

*shift above →below
**2 patients with shift below→ above
***2 patients with shift above →below

Number (%) of patients with newly occurring or worsening serum chemistry values at LOFC based on normal ranges

		ICL670 mg
No. of patients studied		76 (100.0)
Notable abnormality		n (%)
AST	Low	--
	High	8 (10.5)
GGT	Low	--
	High	10 (13.2)
ALT	Low	1 (1.3)
	High	6 (9.2)
AP	Low	
	High	14 (18.4)
Serum creatinine	Low	--
	High	27 (35.5)
Sodium	Low	3 (3.9)
	High	3 (3.9)
Potassium	Low	2 (2.6)
	High	4 (5.3)
Chloride	Low	--
	High	2 (2.6)
Calcium	Low	5 (6.6)
	High	1 (1.3)
Magnesium	Low	9 (11.8)
	High	--
Phosphate	Low	6 (7.9)
	High	3 (3.9)
Total protein	Low	12 (15.8)
	High	--
Serum albumin	Low	5 (6.6)
	High	--
Total bilirubin	Low	1 (1.3)
	High	--
Glucose	Low	4 (5.3)
	High	8 (10.5)
LDH	Low	1 (1.3)
	High	14 (18.4)
Cholesterol	Low	--
	High	9 (11.8)
Triglycerides	Low	--
	High	6 (7.9)
Uric acid	Low	4 (5.3)*

		ICL670 mg
	High	9 (11.8)
C-reactive protein	Low	--
	High	20 (26.3)
Urea	Low	1 (1.3)
	High	14 (18.4)
Cholesterol	High	
Triglycerides	High	
*2 patients with shift above → below		

Date of Clinical Trial Report

January 30, 2012

Date Inclusion on Novartis Clinical Trial Results Database

January 30, 2013

Date of Latest Update

July 27, 2013