Sponsor

Novartis Farmacéutica SA

Generic Drug Name

Deferasirox

Therapeutic Area of Trial

Allogeneic stem cell transplantation

Approved Indication

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.

Protocol Number

CICL670AES04

Title

Open-label, non-randomized, multicenter study that evaluates the efficacy and safety of Deferasirox (Exjade®) in patients with iron overload after allogeneic Hematopoietic Stem Cell Transplantation

Phase of Development

Phase IV

Study Start/End Dates

10 Dec 2008 to 5 May 2011

Study Design/Methodology

A phase IV multicenter, non-controlled clinical trial. This study has been designed to evaluate the efficacy and safety of deferasirox in patients with iron overload after allogeneic HSCT (Hematopoietic Stem Cell Transplant).

Centres

18 in Spain

Outcome measures

Primary outcome measures(s)

To assess the mean change in serum ferritin after 52 weeks of treatment with deferasirox, in patients with iron overload (defined with serum ferritin levels ≥1000 ng/ml and/or receiving ≥20 red blood cell concentrates) after allogeneic HSCT.

Secondary outcome measures(s)

- To assess the safety and tolerability profile of deferasirox in patients with iron overload after allogeneic HSCT.
- To assess the changes in marrow iron using Perls staining, in patients with baseline and final myelogram according to the daily clinical practice.
- To investigate the potential of liver Magnetic resonance (MRI) as non-invasive method for assessing specific iron overload of an organ in a patient sub-group.*
- To assess the incidence of chronic graft versus host disease (GVHD) ("limited" or "extensive", based on Shulman criteria), the incidence of infections (bacterial, viral, fungal), and the incidence of venous-occlusive disease during the study.

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

Oral dispersible tablets available at doses of 125 mg and 500 mg of deferasirox.
The recommended starting daily dose of deferasirox is 10 mg/kg/day p.o.

Statistical Methods

Data were summarized considering the demographic and baseline characteristics, efficacy measurements, and safety observations and measures.

Categorical variables were described by absolute and relative frequencies. Continuous variables will be described using the mean, standard deviation, median, minimum and maximum, including the total number of evaluable values. For the comparison of quantitative variables, parametric tests, Student's "t" or ANOVA, or non-parametric tests, U-Mann-Whitney or Kruskal-Wallis, were used based on compliance with the required assumptions of each test and for comparison of two or more independent groups. For the comparison of two or more paired groups, parametric tests, Student's "t" for paired data or repeated-measure variance analysis, or non-parametric Wilcoxon or Friedman test, were used, based on compliance with the assumptions required for each test. For comparison of categorical variables, the chi-squared test was performed. In all cases, the use of bilateral tests was applied, with a significance level of 0.05.

For the planned analyses, three samples were defined: two samples for the efficacy analysis (intention-to-treat (ITT) sample and sample per protocol (PP)) - and one sample for the safety analysis. Samples were defined as follows:

- ITT sample: patients receiving at least one dose of the study drug and with at least the baseline value and a post-treatment value of the study primary endpoint available.
- PP sample: patients meeting all screening criteria, treated per protocol, completing the study, with all primary efficacy endpoint assessments at the established visits, and with no major protocol violations.

Safety sample: patients included in the study that had been administered at least one dose of the study drug.The primary efficacy variable was evaluated by the difference between final values and baseline values). For the description, the mean, standard deviation, median, minimum and maximum were be used, including the 95% confidence interval. The primary population for this analysis was be the ITT sample, but the analysis of the primary objective was also performed for the PP sample.

The incidence of chronic graft-versus-host disease, the incidence of infections and the incidence of venous-occlusive disease during the study, were calculated for the ITT sample. The incidence rates of chronic graft-versus-host disease were be estimated by the Kaplan-Meier method whereas the incidence of infections and venous-occlusive disease were described as raw rates.

All safety parameters were tested using the Safety Population. All adverse events recorded during the study were summarised by the number and percentage of subjects who had any adverse event (AE).

The determination of sample size was based on the standard deviation of the primary study endpoint obtained in a previous study[1]. Sample size was adjusted assuming 10% dropout rate.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Male or female patients 18 years of age and older
- Patients to undergo allogeneic HSCT between at least 6 months prior to inclusion.
- Patients with screening Absolute Neutrophil Count (ANC) > 1000/mm^3
- Ferritin values ≥ 1000 ng/mL (ferritin values must be measured in two measurements at one-week intervals) and/or patients receiving at least 20 RBC concentrate units or 100mL/kg RBC during their lives.
- Patients giving their informed consent (prior to performing any study procedure).

Exclusion Criteria

- Haemosiderosis not related to transfusion.
- Patients with concomitant active malignancy.
- Active known viral hepatitis or known AIDS-positive.
- Mean levels of alanine aminotransferase (ALT) > 5x ULN
- Treatment with any iron chelating agent after allogeneic HSCT.
- Uncontrolled hypertension.
- Serum creatinine > 2 ULN or creatinine clearance < 50 mL/min.
- Significant proteinuria with a urine ***protein/creatinine*** ratio of >0.5 mg/mg in 2 samples of second voiding at one-week intervals.
- Previous history of clinically significant eye toxicity related to iron chelation.
- Systemic diseases (cardiovascular, renal, liver, etc.) that can prevent the patient from receiving the study treatment.
- Psychiatric diseases or addictions preventing the patients from giving their informed consent or perform the study treatment.
- Treatment with systemic investigational drugs within ≤ four weeks before or topical investigational drug in the seven days before.
- Any surgical or medical condition that can significantly affect absorption, distribution, metabolism or excretion of any drug (e.g.: active intestinal GVHD at the time of inclusion).
- History of non-compliance with medical regimens and patients considered unreliable or non-cooperative.
- History of drug or alcohol abuse within the 12 months prior to the start of the study or evidence of these abuses indicated by laboratory tests performed during the examination.
- Pregnant or nursing women or adults in fertile age not using an effective contraceptive method.*

* Women with child-bearing potential should have a negative pregnancy test in the 48 hours prior to drug administration. Post-menopausal women should have amenorrhea for at least 12 months to consider that they do not have child-bearing potential. Patients from both sexes should agree to use an effective contraceptive method during the study.

Participant Flow

Patients evaluable for safety analysis	
Total - n	30
Patients evaluable for safety analysis - n (%)	30 (100.0)
Patients non-evaluable for safety analysis - n (%)	0 (0.0)
Evaluable patients who completed the study or discontinued prematurely	
Completed - n (%)	**22 (73.3)**
After 52 weeks of treatment - n (%)	14 (46.7)
Serum ferritin ≤ 400 ng/mL in 2 consecutive visits - n (%)	8 (26.7)
Discontinued - n (%)	**8 (26.7)**
Subject withdrew consent - n (%)	1 (26.7)
Lost to follow-up - n (%)	0 (0.0)
Hematologic relapse - n (%)	3 (10.0)
Adverse event drug related (s) - n (%)	1 (3.3)
Unsatisfactory therapeutic effect - n (%)	1 (3.3)
Death - n (%)	2 (6.7)

Baseline Characteristics

Total - n	**30**
Gender, male - n (%)	20 (66.7)
Age, years (n=30) - median (range)	46.7 (20.3-65.3)
Hematological disease - n (%)	30 (100.0)
Acute Myeloid Leukemia (AML) - n (%)	13 (43.3)
Myelodysplastic Syndrome (MDS) - n (%)	3 (10.0)
Non Hodgkin Lymphoma - n (%)	3 (10.0)
AML + MDS - n (%)	2 (6.7)
AML + Non Hodgkin Lymphoma - n (%)	1 (3.3)
AML + Myeloid Sarcoma - n (%)	1 (3.3)
MDS + Non Hodgkin Lymphoma - n (%)	1 (3.3)
Others - n (%)	6 (20.0)
Time from SCT (n=30) - median (range)	12.2 (5.9-38.7)
Transplant characteristics	
Related vs unrelated - n (%)	29 (96.7)
Related - n (%)	14 (46.7)
Unrelated - n (%)	15 (50.0)
Source - n (%)	25 (83.3)
Periferal blood - n (%)	11 (36.7)
Bone marrow - n (%)	9 (30.0)
Cord blood - n (%)	5 (16.7)
Conditioning regimen - n (%)	26 (86.7)
Ablative - n (%)	14 (46.7)
Non-ablative - n (%)	12 (40.0)
Units red blood cell transfusions	
Before SCT (n=16) - median (range)	26.5 (0.0-96.0)
After SCT (n=16) - median (range)	6.0 (0.0-45.0)
Renal function	
Serum creatinine (mg/dL) (n=30) - median (range)	1.0 (0.5-1.8)
Creatinine clearance (mL/min) (n=30) - median (range)	74.6 (40.0-160.0)
Iron metabolism (median, range)	
Serum ferritin (ng/mL) (n=30) - median (range)	1444.0 (788.0-4055.0)
Transferrin (mg/dL) (n=28) - median (range)	197.0 (139.0-286.0)
Transferrin saturation (%) (n=28) - median (range)	54.9 (11.7-103.2)
Liver Iron Concentration (median, range)	
LIC (mg Fe/g dry weight) (n=12) - median (range)	13.4 (5.6-19.0)

Outcome measures

Primary Outcome Result(s)

Median change in Serum Ferritin (SF) levels after 52 weeks treatment with deferasirox or until achieving SF levels ≤ 400 ng/mL in two consecutive occasions, in patients with iron overload after allogeneic HSCT

Median SF at baseline was 1444.0 ng/mL (range 788.0 - 4055.0) and median SF at the end of the study was 755.5 ng/mL (range 96.0 - 6128.8). Based on LOCF analysis, overall median SF significantly decrease from baseline after 52 weeks of deferasirox treatment by -670.5 ng/mL (range -2210.0 - 2530.2.9) (Wilcoxon test, p<0.05).

	n	Mean	SD	Median	Min.	Max.
Baseline SF levels (V1)	30	1677.0	740.9	1444.0	788.0	4055.0
Week 52 SF levels (V18)	30	1115.4	1167.2	755.5	96.0	6128.8
Median change	30	-561.6	906.7	-670.5	-2210.0	2530.2

[1] ITT population
[2] Last-observation-carried-forward (LOCF) approach was used.
[3] Wilcoxon test compared to baseline values; (p< 0.05). There were statistically significant differences from baseline.

	n	Mean	SD	Median	Min.	Max.
Baseline SF levels (V1)	11	1637,9	549,7	1746,0	900,0	2695,0
Week 52 SF levels (V18)	5	836,8	499,4	658,0	195,0	1416,0
Median change	5	-1212,8	599,5	-1117,0	-2045,0	-527,0

[1] PP population
[2] Last-observation-carried-forward (LOCF) approach was used.
[3] Wilcoxon test compared to baseline values; (p< 0.05). There were statistically significant differences from baseline.

	n	Mean	SD	Median	Min.	Max.	p
Baseline SF levels (V1) (ng/mL)	30	1677,0	740,9	1444,0	788,0	4055,0	-
Week 4 SF levels (V6) (ng/mL)	30	1830,2	1874,2	1376,5	664,0	11198,8	0,1087
Month 2 SF levels (V7) (ng/mL)	30	1875,2	2185,7	1396,5	653,2	12766,5	0,1240
Month 3 SF levels (V8) (ng/mL)	30	2463,0	5810,4	1351,5	360,0	33007,0	0,0987
Month 4 SF levels (V9) (ng/mL)	30	1686,3	2055,7	1111,5	317,8	11764,8	0,0113
Month 5 SF levels (V10) (ng/mL)	30	1539,3	1440,3	1144,5	262,0	7743,0	0,0191
Month 6 SF levels (V11) (ng/mL)	30	1525,3	1720,2	1131,0	262,0	9771,5	0,0086
Month 7 SF levels (V12) (ng/mL)	30	1441,8	1460,5	1255,0	96,0	8071,0	0,0069
Month 8 SF levels (V13) (ng/mL)	30	1301,7	1086,8	1161,5	96,0	5543,0	0,0060
Month 9 SF levels (V14) (ng/mL)	30	1281,1	1601,0	918,5	96,0	8961,7	0,0015
Month 10 SF levels (V15) (ng/mL)	30	1190,8	1103,8	924,5	96,0	5832,0	0,0008
Month 11 SF levels (V16) (ng/mL)	30	1242,2	1321,6	986,5	96,0	7325,8	0,0007
Month 12 SF levels (V17) (ng/mL)	30	1166,7	1336,3	820,0	96,0	7325,8	0,0004
Month 13 SF levels (V18) (ng/mL)	30	1115,4	1167,2	755,5	96,0	6128,8	0,0005

[1] ITT population
[2] Last-observation-carried-forward (LOCF) approach was used.
[3] Wilcoxon test compared to baseline values

Secondary Outcome Result(s)

Median change in Liver Iron Concentration (LIC) after 52 weeks treatment with deferasirox or until achieving SF levels ≤ 400 ng/mL in two consecutive occasions, in patients with iron overload after allogeneic SCT

	n	Mean	SD	Median	Min.	Max.
Baseline LIC (V1)	12	13,2	3,7	13,4	5,6	19,0
Month 13 LIC (V18)	8	5,1	4,4	4,6	0,0	12,3
Median change	7	-9,0	3,7	-8,9	-14,8	-3,9

[1] ITT population
[2] Wilcoxon test compared to baseline values; ($p < 0.05$). There were statistically significant differences from baseline.

Safety Results

Adverse Events by System Organ Class

Patients	
Total	30
Patients with AEs	29 (96.7%)

Patients with drug-related AEs (n, %)					
Drug related AEs	**Mild**	**Moderate**	**Severe**	**NA**	**All**
Serum creatinine increase	6 (20.0%)	5 (16.7%)	-	-	11 (36.7%)
AST and ALT elevation	-	2 (6.7%)	2 (6.7%)	-	4 (13.3%)
AST elevation	1 (3.3%)	-	-	-	1 (3.3%)
Diarrhea	2 (6.7%)	-	-	-	2 (6.7%)
Constipation	1 (3.3%)	-	-	-	1 (3.3%)
Nausea	1 (3.3%)	-	-	-	1 (3.3%)
Vomiting	-	1 (3.3%)	-	-	1 (3.3%)
Rash 1	1 (3.3%)	-	-	-	1 (3.3%)
Anorexia	-	1 (3.3%)	-	-	1 (3.3%)
Mucositis	-	-	1 (3.3%)	-	1 (3.3%)
Ear disorder	-	-	-	1 (3.3%)	1 (3.3%)
Eye discomfort	-	1 (3.3%)	-	-	1 (3.3%)

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

				Serious		Intensity			
	n[1]	%[2]	n[3]	0	1	1	2	3	nc
Elevated Blood Creatinine	14	46,7	21			13	8	0	0
Elevated Alanine Aminotransferase	12	40,0	19			7	7	5	0
Elevated Aspartate Aminotransferase	8	26,7	15			7	7	1	0
Nasopharyngitis	6	20,0	13			12	1	0	0
Pyrexia	4	13,3	5		1	2	2	1	0
Diarrhea	4	13,3	6			5	1	0	0
Rash[4]	4	13.3	5			4	1	0	0
Graft versus host disease	3	10,0	4			3	1	0	0
Vomiting	3	10,0	3			2	1	0	0
Nausea	2	6,7	3			3	0	0	0

[1] 1) Number of patients with adverse events
[2] 2) Percentage of patients with adverse events with respect to the total (n=30)
[3] 3) Number of adverse events
[4] 4) including 1 case of erytthematous rash

All AEs

				Serious		Intensity			
System organ class and AEs	**n[1]**	**%[2]**	**n[3]**	**0**	**1**	**1**	**2**	**3**	**nc**
Complementary explorations	**20**	**66,7**	**57**						
Elevated Alanine Aminotransferase	12	40,0	19			7	7	5	0
Elevated Aspartate Aminotransferase	8	26,7	15			7	7	1	0
Elevated Blood Creatinine	14	46,7	21			13	8	0	0
Elevated Alkaline Phosphatase	1	3,3	1			0	1	0	0
High hematocrit	1	3,3	1			0	1	0	0
Infections and infestations	**12**	**40,0**	**21**						
Herpes zoster	1	3,3	1		1	0	0	1	0
Ear infection	2	6,7	2			1	1	0	0
Respiratory tract infection	2	6,7	2		1	1	0	1	0
Upper respiratory tract infection	1	3,3	1			1	0	0	0
Urinary tract infection	1	3,3	1			0	1	0	0
Cytomegalovirus infection	1	3,3	1			1	0	0	0
Nasopharyngitis	6	20,0	13			12	1	0	0
Traumatic injuries, poisonings and complications of therapeutic procedures	**2**	**6,7**	**2**						
Joint sprain	1	3,3	1			0	1	0	0
Subdural hematoma	1	3,3	1		1	0	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**3,3**	**1**						
Acute Myeloid Leukemia	1	3,3	1		1	1	0	0	0
Alterations of skin and subcutaneous tissue	**8**	**26,7**	**11**						
Dermatitis	1	3,3	1			1	0	0	0
Seborrheic dermatitis	2	6,7	2			1	1	0	0
Eczema	1	3,3	1			0	1	0	0
Rash	3	10,0	4			3	1	0	0
Erythematous rash	1	3,3	1			1	0	0	0
Hyperhidrosis	1	3,3	1			1	0	0	0
Skin injury	1	3,3	1			0	1	0	0
Blood and lymphatic system disorders	**6**	**20,0**	**7**						
Leukocytosis	1	3,3	1		1	0	1	0	0
Leukopenia	1	3,3	1			0	1	0	0
Febrile neutropenia	1	3,3	1		1	0	0	1	0
Polycytemia	1	3,3	1			0	1	0	0
Blood disorder	2	6,7	2		2	0	0	2	0
Thrombocytopenia	1	3,3	1			0	1	0	0
Reproductive system and breast	**1**	**3,3**	**1**						

disorders									
Pelvic pain	1	3,3	1			1	0	0	0
Nutritional and metabolic disorders	**2**	**6,7**	**2**						
Decreased appetite	1	3,3	1			0	1	0	0
Hypertriglicerydemia	1	3,3	1			1	0	0	0
Ear and labyrinth disorders	**2**	**6,7**	**2**						
Ear congestion	1	3,3	1			1	0	0	0
Ear disorder	1	3,3	1						1
Inmune System disorders	**3**	**10,0**	**4**						
Graft versus host disease	3	10,0	4			3	1	0	0
Nervous system disorders	**3**	**10,0**	**4**						
Cephalea	1	3,3	1			1	0	0	0
Epilepsy	1	3,3	2			1	1	0	0
Speech disorder	1	3,3	1			0	1	0	0
Gastrointestinal disorders	**7**	**23,3**	**16**						
Diarrhea	4	13,3	6			5	1	0	0
Constipation	2	6,7	2			1	1	0	0
Abdominal discomfort	1	3,3	1			1	0	0	0
Mouth discomfort	1	3,3	1			0	1	0	0
Nausea	2	6,7	3			3	0	0	0
Vomiting	3	10,0	3			2	1	0	0
General disorders and administration site conditions	**10**	**33,3**	**13**						
Asthenia	1	3,3	1			0	1	0	0
Torax pain	1	3,3	1			1	0	0	0
Edema	2	6,7	2			1	1	0	0
Peripheral edema	1	3,3	2			0	2	0	0
Mucosa inflammation	2	6,7	2			1	0	1	0
Pyrexia	4	13,3	5		1	2	2	1	0
Hepatobiliary disorders	**2**	**6,7**	**2**						
Cholestasis	1	3,3	1			1	0	0	0
Hyperbilirubinemia	1	3,3	1			0	1	0	0
Musculoskeletal and connective tissue disorders	**3**	**10,0**	**4**						
Arthralgia	1	3,3	1			1	0	0	0
Back pain	1	3,3	1			0	1	0	0
Muscle spasms	1	3,3	1			1	0	0	0
Myalgia	1	3,3	1			1	0	0	0
Eye disorders	**4**	**13,3**	**7**						
Eyelid eczema	1	3,3	1			1	0	0	0
Glaucoma	1	3,3	1			1	0	0	0
Hyperemia of the conjunctiva	1	3,3	1			1	0	0	0
Increased tearing	1	3,3	1			1	0	0	0
Eye discomfort	1	3,3	2			1	1	0	0
Dry eye	1	3,3	1			1	0	0	0
Renal and urinary disorders	**1**	**3,3**	**1**						
Renal failure	1	3,3	1			1	0	0	0
Respiratory thoracic and mediastinal disorders	**2**	**6,7**	**2**						
Rhinorrhea	2	6,7	2			1	1	0	0
Total patients with adverse events	**29**	**96,7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Total adverse events	**-**	**-**	**157**	**0**	**9**	**88**	**54**	**14**	**1**

[1] 1) Number of patients with adverse events
[2] 2) Percentage of patients with adverse events with respect to the total (n=30)
[3] 3) Number of adverse events

Serious Adverse Events and Deaths

Number of patients studied	30
Patients with AEs – n (%)	29 (96.7%)

Deaths – n (%)	2 (6.7)
Patients with SAEs –n (%)[1]	8 (26.7)
Patients who discontinued due to SAEs –n (%)	3 (10)

[1] 1) 9 SAEs were reported in 8 patients. None of them were considered to be drug-related.

System organ class	Preferred term	Reported term	Serious	Intensity
Infections and infestations	Herpes zoster	Herpes zoster	Yes	Severe
Blood and lymphatic disorders	Blood disorder	Hematologic relapse	Yes	Severe
Infections and infestations	Respiratory tract infection	Respiratory infection	Yes	Severe
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute Myeloid Leukemia	AML progression	Yes	Mild
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos	Subdural hematoma	Acute subdural hematoma	Yes	Severe
Blood and lymphatic disorders	Febrile neutropenia	Febrile neutropenia	Yes	Severe
General disorders and administration site conditions	Pyrexia	Febrile syndrome	Yes	Severe
Blood and lymphatic disorders	Blood disorder	Hematologic relapse	Yes	Severe
Blood and lymphatic disorders	Leukocytosis	Leukocytosis	Yes	Moderate

Other Relevant Findings

Patients with increase in serum creatinine > 33% above baseline on two consecutive visits and serum creatinine above ULN, with and without concomitant cyclosporine use.

	Two consecutive values > 33% and >ULN[1,2]
No cyclosporine (n=16) - n (%)	5 (31.3)
Conconmitant cyclosporine (n=14) - n (%)	7 (50.0)
Total – n (%)	**12 (40.0)**

[1] There were no statistically significant differences (Chi square test; $p > 0.05$).
[2] Four patients had baseline serum creatinine above ULN

Date of Clinical Trial Report 30 April 2012
Date Inclusion on Novartis Clinical Trial Results Database 16 May 2012
Date of Latest Update