Sponsor

Novartis Hungary Ltd.

Generic Drug Name

Deferasirox

Therapeutic Area of Trial

Myelodyplastic syndrome, Beta-thalassaemia

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.

Study Number

CICL670AHU02

Title

Evaluating the efficacy of deferasirox in transfusion dependent chronic anaemias (Myelodysplastic Syndrome, Beta-thalassaemia patients) with chronic iron overload

Phase of Development

Phase IV

Study Start/End Dates

Study period:
First patient enrolled: 02/12/2008;
Last patient completed: 08/07/2010.

Study Design/Methodology

This is a multicentre, open-label, one-armed, non-randomized, 12 months long trial. The purpose of the present study is to investigate the response to the deferasirox treatment in Myelodysplastic Syndrome or Beta-thalassemia major patients, who have chronic iron overload as a consequence of blood transfusions by the changes in serum ferritin level during the study from the baseline up to the 48$_{th}$ week of the treatment.

Centres

2 centers (Hungary 2)

Objectives

Primary objective(s)

Primary objective: to evaluate the clinical response to treatment with deferasirox (Exjade®) from baseline to the 48th week by following serum ferritin change in patients with transfusion dependent chronic anaemias (Myelodysplastic Syndrome, Beta-thalassaemia maior patients) with chronic iron overload.

Secondary objective(s)

- To assess drug usage compliance, evaluate patient's compliance by monthly counting the returned study medication
- To assess the safety data during 48 week long treatment with deferasirox (Exjade®)

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

Exjade® (deferazirox) 500 mg is a dispersing tablet in PVC/PE/PVDC/aluminium bubble package
Exjade® was administered once a day and was taken, at least 30 minutes before meal, if possible at the same time every day.
Tablets were solved with stirring in a glass (100-200 ml) of water, or orange, or apple juice till achieving suspension. After swallowing the suspension drug remained in the glass should be solved again in some water or fruit juice. The tablets cannot be chewed or swallowed in full.
The recommended daily dose is 20 mg/bodyweight-kilogram.

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

None

Criteria for Evaluation

Primary variables

The primary objective was to evaluate the clinical response to treatment with deferasirox (Exjade®) from baseline to weeks 48 by following serum ferritin change in patients.
Primary analysis was to be carried out on the ITT population. For strengthening the results, the analysis was to be repeated on the per-protocol population.
In the primary analysis the change in ferritin level from baseline and its 90% confidence interval was planned to be estimated and the mean change was planned to be compared to 0 with a one-side t-test on 95% level of significance.
Furthermore, a repeated measures ANOVA for the ferritin levels measured in different timepoints was to be applied including the baseline ferritin level as a covariate. This model would have been also showed whether the baseline ferritin level in the indication range had any significant influence on the efficacy of deferazirox.
The effect of the possible dose modifications was planned to be analyzed by a one-way ANOVA (patients will be devided into 3 groups: 1. unchanged dose; 2. decreased dose; 3. increased dose).
Because of the small number of patients and the large number of missing values in the primary efficacy variable only a listing of the ferritin levels was presented in the statistical analysis.

Secondary variables

The secondar efficacy analysis was planned to be carried out on the Safety Population.
The patient compliance was planned to be analyzed by descriptive statistics presenting the mean and standard deviation of the number of remaining tablets. Since there were a large number of missing values in compliance data only a listing of the prescribed doses and the number of remaining tablets was given with the calculated % of used tablets (where it could be calculated).The changes from baseline in safety laboratory parameters (se creatinine, creatinine clearence) were planned to be given with their means and 95% confidence intervals at each timepoint. Only listings were given and the mean, SD, minimum and maximum was calculated for se creatinine.
Urine parameters (gravity, protein, creatinine, glucose, acetone, UBG, deposit) was planned to analyze with descriptive statistics but only listings were given.
Adverse events were presented by frequency tables (by severity, outcome and relationship) and an individual listing was also given. Serious adverse events were planned to be given in separate tables but they were only presented within the adverse events tables because of the small number of events.

Safety and tolerability

Safety parameters were based on the severity and causality of adverse events experienced by subjects who underwent drug administration.
For laboratory variables descriptive statistic was performed, comprising the n, mean, SD, minimum,maximum.

Vital signs were reported with the n, mean, SD, minimum, maximum particularly involving physical examination, baseline vital signs e.g.ECG, blood pressure, pulse data , baseline laboratory values additionally ECOG status, ophtalmology and audiometry data, and medical history

Statistical Methods

As there were only 5 patients in the study and data were missing in many visits, efficacy results could only be listed and plotted in 2 cases.

Efficacy analysis

The primary efficacy parameter was the change in serum ferritin values. Since serum ferritin values were missing in several visits for several patients, results of primary efficacy parameter were only listed and plotted in 2 cases.

Safety analysis

Descriptive statistics (n, mean, SD, minimum, maximum) and list of parameter values are presented for each l parameters. For creatinin clearence only listing is presented since several data are non numerical.

Adverse events were categorised by body system and preferred terminology according to MedDRA.

Study Population: Inclusion/Exclusion Criteria and Demographics

In- or outpatient with Myelodysplastic Syndrome with risk of low or intermedier-1 according to the International Prognostic Scoring System (IPSS) or Beta-thalassemia major patients aged between 18-80, who have chronic iron overload as a consequence of frequent and at least 30 units of packed red cells blood transfusion and deferoxamin therapy is contraindicated or inadequate.

Inclusion criteria

1. Age: 18-85 years.
2. Man and women.
3. In- or outpatients with Myelodysplastic Syndrome with risk of low or intermedier-1 according to the International Prognostic Scoring System (IPSS) confirmed by bone marrow evaluation within 3 months or beta-thalassemia major patients, who have chronic iron overload as a consequence of frequent blood transfusion.
4. Chronic iron overload caused by at least 30 and maximum 100 units of packed red blood cells in patients with Myelodysplastic Syndrome or Beta-thalassemia major.
5. Serum ferritin > 1800 µg/L.
6. Deferoxamin (Desferal®) therapy is contraindacated or inadequate or unable to use in the recommended dose due to intolerability or other reason.
7. Signed informed consent.
8. ECOG Performance Status score between 0-2.

Exclusion criteria

1. Beta-thalassemia minor.
2. Myelodysplastic Syndrome (MDS) with poor prognostic kariotype according to the IPSS /complex (>=3 abnormalities), or chromosome 7 anomalies/.
3. Hemosiderosis caused by other than chronic transfusional iron overload.

4. Patients with impaired renal function, creatinin clearance < 60ml/min (according to the Cockcroft-Gault formula).
5. Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 (mg/mg) in urine samples taken either visit 1 or 2.
6. History of nephrotic syndrome.
7. Clinically relevant QT prolongation or drug taking which may prolong the QT interval.
8. Patient with malabsorption or impaired drug distribution or metabolism for example caused by inflammatory bowel disease, gastrectomy, pancreatitis in the patient history or impaired pancreatic function.
9. History of non-compliance to medical regimen.
10. History of alcohol or drug abuse within 12 month before enrolment.
11. History of ocular disease caused by chelating agent.
12. Patient with positive test to HIV.
13. Pregnancy .
14. Lactation.
15. Patient of childbearing potential unwilling to use contraceptive precautions. (double method).
16. Known hypersensitivity to Exjade or any ingredients.
17. Impaired hepatic function / SGOT, SGPT >5x above ULN)
18. Patient severely ill due to underlying disease progression or other severe concomitant disease.
19. Life expectancy less than 1 year.
20. Patients who participated in other clinical trial 30 days prior enrolment.
21. ECOG Performance Status score >2.

Number of Subjects

	Novartis product	Comparator
Planned N	30	
Randomised n		
Intent-to-treat population (ITT) n (%)	5 (100%)	
Completed n (%)	3 (60%)	
Withdrawn n (%)	1 (20%)	
Withdrawn due to adverse events n (%)	0 (0%)	
Withdrawn due to lack of efficacy n (%)	0 (0%)	
Withdrawn for other reasons n (%)	1 (20%)	

Demographic and Background Characteristics

Demographical data (date of birth, age, sex) have to be documented on the first/screening visit.

	Novartis product	Comparator
N (ITT)	5	
Females : males	3, 2	
Mean age, years (SD)	57	
Mean weight, kg (SD)	83,6	
Race	White n=5, (100%)	

White n (%) Black n (%) Asian n (%) Other n (%)		
Characteristics relevant to study population (eg, mean FEV1 % predicted [SD])		

Primary Objective Result(s)

Primary end point:

• Assesment of the efficacy of the Exjade® treatment in patient with transfusional iron overload in MDS patients and Beta-thalassaemia maior patients based on changes in serum ferritin level during the study from the baseline up to the 48th weeks of the treatment. (estimated one sample t-test 90% CI)

NOVARTIS HUNGARY LTD
FINAL REPORT: **CICL670AHU02**

TABLE 9.19.5-1. Serum ferritin values by visit and patient

Vizit	Patient 11	Patient 21	Patient 22	Patient 23	Patient 24
1	>2000	>2000	>2000	1866	>2000
3	NT.	>2000	>2000	>2000	ND
7	>2000		1659	ND	
8	NT		2000	>2000	>2000
9	NT.		>2000	>2000	ND
10			1927	>2000	ND
11			ND	>2000	ND
12			1595	>2000	1302
13			1261	>2000	ND
14			1232	>2000	ND
15		NA	1183	>2000	ND
16				1570	
17				1487	
18				953	ND

Secondary Objective Result(s)

Secondary end points:

- Drug intake compliance: evaluate patient's compliance by monthly counting the returned study medication assessing the mean value and the standard deviation.

Compliance was measured between Visit3 and Visit18.

For Patient11 and Patient21 no compliance data were available.

For Patient22 compliance could be calculated for 10 different visits and ranged between 67 and 100%. For 6 visits data were missing.

For Patient23 compliance could be calculated for 11 different visits and ranged between 70 and 100%. For 5 visits data were missing.

For Patient24 compliance could be calculated for 4 different visits and it was 100%. For thr other visits data were missing.

- Changes in laboratory parameters compared to baseline.

There was no clinically significant, treatment related changes in laboratory values.

Safety Results

There was no clinically significant, treatment related changes in laboratory values.

Creatinine clearance:

As most of the values of creatinine clearence was given as >60 no changes could be detected during the study.

Se creatinin:

Se creatinin values were in the normal range for three patients. For Patient 23 values were slightly lower than the lower limit of the normal range, but all abnormal values were within +/-10% from the normal range. For Patient24 se creatinin values showed a slight increase. The values fluctuated during the study between 60 and 140 Umol/l (normal range: 53-100Umol/l).

BUN

BUN values were within the normal range during the visit, except 2 cases: Patient11 at Visit7 and Patient24 at Visit9 had slightly increased BUN values but these values were within +/-10% of the limits of the normal range.

WBC

Patient21 had normal WBC values during the study, Patient23 and Patient24 had 1 value below the normal range but the later values were in normal range again. Patient11 and Patient22 had all their WBC values below the normal range. Patient11 did not show any tendency but Patient 22 had decreasing WBC values during the study.

Hemoglobin

Hemoglobin values were below the lower limit of the normal range for each subject but the values did not show any relevant changes during the study except for Patient22 who showed a slight decrease and Patient24 where a slight increase could be detected.

Hematocrit

Hematocrit values were below the lower limit of the normal range for each subject but the values did not show any relevant changes during the study except for Patient22 who showed a slight decrease and Patient24 where a slight increase could be detected.

Thrombocytes

Patient21 and Patient24 had very low thrombocytes values but both patients showed slight increase during the studies. Patient22 and Patient23 had most values in the normal range with some slightly abnormal exceptions. Patient11 had decreasing thrombocytes during the study.

RBC

Each patient had RBC values below the normal range. Patient11 and Patient21 showed slight increase during the study.

MCV

Patient11 had all his values below the normal range but the values did not change during the study. Patient22 had all his values above the normal range and showed a slight decrease during the study while Patient24 also had all his values above the normal range but did not showed any relevant changes.

Serum glucose

Patient11 and Patient21 had slightly increased serum glucose values but their values did not change during the study. Patient23 and Patient24 had also values above the normal range and these values slightly increased during the study.

Serum Natruim
All values were within the normal range except for Patient23 at Visit10 but this value was within the +/-10% of the lower limit of the normal range.
Serum Potassium
All Se Potassium values were within the normal range.
Serum Magnesium
Most of the values were within the normal range. Patient11, Patient22 and Patient23 had some values slightly lower/upper than the limits of the normal range.
Serum Phosphor
Most of the values were within the normal range. Patient23 and Patient24 had some values slighly lower/upper than the limits of the normal range.
SGOT
Most of the values were within the normal range. Patient11 and Patient23 had some values above the upper limit of the normal range but both subjects showed decrease during the study.
SGPT
4 of the 5 subjects had SGPT values above the normal range and all these subjects showed decrease in SGPT during the study. Patient24 had SGPT values within the normal range except for 1 visit.
SGGT
Patient11 had SGGT values above the normal range but these values showed strong decrease during the study. The other 4 subjects did not have any relevant abnormalities in SGGT.
Se AP
There were no abnormal Se AP values during the study except for Patient11 at Visit2 but this value was also in the +/-10% of the upper limit of the normal range.
Se Bilirubin
Patient11 and Patient22 had Se bilirubin values above the normal range but the values did not show any relevant changes during the study.
Urinalysis (Urine sediment, Urine protein,
There were no significant abnormalities.

Adverse Events by System Organ Class

10 adverse events arose during the study.
2 adverse events are possibly drug related (both were observed in the same patient)

	Novartis product N (%)
Patients studied	
Randomized patients	5(100%)
Patients drug-related AE	1(20%)
Drug-related AEs by primary system organ class	
Respiratory, thoracic and mediastinal disorders	()
Nervous system disorders	0 (0.0)
Gastrointestinal disorders	0 ()
General disorders	0)
Cardiac disorders	0 ()
Vascular disorders	0 ()
Skin and subcutaneous tissue disorders	1(20%)
Musculoskeletal and connective tissue disorders	1 (20%)
Ear and labyrinth disorders	
Reproductive system and breast disorders	0 (0.0)
Renal and urinary disorders	0 (0.0)
Infections and infestations	0 (0.0)
Psychiatric disorders	0 (0.0)
Immune system disorders	0 (0.0)

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

2 serious adverse events, not related to study treatments, were reported during the trial. (2SAE's, 1pt pneumonia, 1st outcome: ceased, 2nd outcome: death).
No patient withdrew for adverse events.
From the 8 non serious adverse events, 2 were possibly related to the treatment (both were observed in the same patient). Their GRADE were 1 and 2, and both AEs ceased without residuum.
No clinically relevant changes in vital signs were observed.
Several patients had abnormal and physiologically impossible potassium levels (≥ 6.0 mmol/L) which was probably due to technical problems during sample handling. Overall, there was no evidence of decrease in potassium levels with administration of study treatments.
Several patients had high blood glucose levels. The reason was that the study protocol did not require that patients were fasting at clinic visits. Overall, there was no evidence of consistent increase of blood glucose with any of the study treatments
No consistent, clinically significant changes in other laboratory parameters were observed.
Overall, it can be concluded that all treatments were safe and well tolerated.

Serious Adverse Events and Deaths

Serious adverse event	N	%
Yes	2	20.0%
No	8	80.0%
Total	**10**	**100.0%**

Severity	N	%
GRADE1	3	33.3%
GRADE2	4	44.4%
GRADE4	2	22.2%
Total	**9**	**100.0%**
Number of missing values:1		

Relation	N	%
Not related	7	70.0%
Probably not related	1	10.0%
Possibly related	2	20.0%
Total	**10**	**100.0%**

Outcome	N	%
Ceased	7	77.8%
Unchanged	1	11.1%
Death	1	11.1%
Total	**9**	**100.0%**
Number of missing values:1		

Other Relevant Findings

Date of Clinical Trial Report **20 Sep 2011**
Date Inclusion on Novartis Clinical Trial Results Database **27 Sep 2011**
Date of Latest Update