Synopsis

(according to ICH Topic E3 Structur and Content of Clinical Study reports – Annex I)

Name of Sponsor: Friedrich-Alexander-Universität Erlangen-Nürnberg
Prof. Dr. med. Jürgen Schüttler, Dekan

Name of Finished Product: Exjade®

Name of Active Ingredient: Deferasirox

Title of Study: Early treatment with deferasirox (Exjade®) in low risk MDS - a prospective multicentre single-arm single-stage Phase II study - (Exjade-Early-Trial)

Investigators:
LKP (AMG): Prof. Dr. med. Stefan Krause

Study centre(s):

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(3) Universität Regensburg,
Medizinische Fakultät am Universitätsklinikum Regensburg,
Abteilung für Hämatologie und internistische Onkologie
Prof. Dr. M. Edinger
Franz-Josef-Strauß Allee 11
93042 Regensburg

Publication (reference):

Studied period (years)	**Phase:** II
first patient in: 29.10.2010	
last patient out: stop of recruitment August 2012	

Objectives:
To investigate, if early initiation of iron chelation using deferasirox is safe and will improve cytopenias in MDS patients. If some patients improve, first hints will be collected, which parameters predict such a success.

Methodology: single-arm, single-stage, multicentre, open-label Phase II trial

Number of patients (planned and analyzed):
- planned sample size: 45 patients
- analyzed sample size: 2 patients

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Diagnosis and main criteria for inclusion:

Indication: MDS of subtype RA, RARS, RCMD, RCMD-RS (i.e. lower risk)

Inclusion criteria:

- IPSS score ≤ intermediate-1
- transfusion dependent or Hb < 10,5 g/dl
- History of less than 20 units of red blood cell transfusions or 100mL/kg of prepacked red blood cells (PRBCs), except for tranfusions for acute bleeding
- Serum ferritin > 300 µg/l and < 1500 µg/l. This level should have been verified at least at two occasions within 3 months. Samples must be obtained in the absence of concomitant severe infection
- no indication for EPO (due to high endogenous EPO levels) or EPO without benefit in the past
- no indication and/or no plans for cytostatic drugs
- no previous exposure to cytostatic drugs, thalidomide, lenalidomide, G-CSF or EPO or exposure to any of these drugs has been terminated since ≥ 8 weeks (4 weeks for G-CSF).
- no indication and/or no plans for stem cell transplantation
- stable or worsening cytopenia during the past 8 weeks. If in doubt, extend screening period to ≥ 8 weeks
- Patients of either gender and age > 18 years
- Life expectancy > 12 months
- Written informed consent by the patient

Test product, dose and mode of administration, batch number:

The starting dose of deferasirox is 10 mg/kg body weight /day, corresponding to dose level II. Oral administration.

Dose adjustments for deferasirox will be mainly based on the patient's serum ferritin levels, renal safety assessments as well as serial measurements of safety markers indicative of over chelation. It is planned that the majority of deferasirox dose adjustments will be performed in steps of 5 or 10 mg/kg/day. Dose levels are defined as

0 mg/kg/day	dose level 0
5 mg/kg/day	dose level I
10 mg/kg/day	dose level II (starting dose)
15 mg/kg/day	dose level III
20 mg/kg/day	dose level IV
30 mg/kg/day	dose level V (maximum dose)

Serum ferritin is measured every month during the first 3 months and less frequently thereafter according to the treatment plan and the dose of deferasirox is adjusted based on the trends in serum ferritin (see below). Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). Doses above 30 mg/kg are not recommended because there is only limited experience with doses above this level.

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Duration of treatment / treatment schedule:

- 104 weeks treatment with deferasirox

Reference therapy, dose and mode of administration, batch number: n.a.

1. Reference substance: n.a.
2. Reference substance: n.a.

Unblinding:
n.a.

Criteria for evaluation:

Evaluation of the possible efficacy, safety and tolerability of the iron chelator deferasirox in improving cytopenias in MDS patients. In parallel the efficacy of reducing the iron overload, as measured by serum ferritin, is monitored.

Efficacy:

- Reduction of iron overload, as measured by serum ferritin.
- Examining the percentage of patients with hematological improvement (Transfusion requirements, hematologic counts, bone marrow).
- Examining liver iron concentration using MRI R2 Methodology.

Safety:

Regular monitoring of hematology, blood chemistry, and regular measurement of vital signs and the performance of physical examinations. Additional assessments of ECG and auditory/ocular examinations are performed at baseline and as indicated during the study. Monthly safety assessments can be performed locally, when intervals beween study visits are scheduled less frequently (from visit 6 onwards).

Statistical methods:

- descriptive statistics

Summery – Conclusions:
2 Pat included
age: between 40 and 50 years
sex: 1 male, 1 female

Pat 01_01: duration of treatment: 6 weeks
Pat 01_02: duration of treatment: 15 weeks active treatment

Efficacy Results:

Serum ferritin
Was reduced to normal in patient 01_02.

Safety Results:
Pat. 01_01:
9 AE documented (see also case-report).
None of the AEs was considered to be related to the study drug.

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2 SAE:
SAE1: pneumonia (start 23.11.2010, end 29.11.2010)
SAE2: AML (start 30.12.2012), judged to be related to the natural course of the disease and not to the study drug.

Pat. 01_02:
9 AE documented (see also case-report).
No SAE.

Conclusion:
One patient showed a rapid and sustained decrease of serum ferritin. No unexpected adverse events occurred. Due to insuffcient patient recruitment, the trial had to be stopped early. No significant conclusions can be drawn from this trial, because only two patients were included.

Date of the report:
June 27, 2013

Exjade-Early-Trial

Protocol No.: CICL670ADE06T

EudraCT number: 2008-006268-12

CASE REPORT

Patient ID: 01_01
Age: 45y
Sex: male
Weight: 75 kg
Study medication: deferasirox

Date of informed consent:	29.10.2010
Serum ferritin level before start of deferasirox treatment:	1097 µg/l
Duration deferasirox treatment:	6 weeks
Date started:	05.11.2010
Date stopped:	20.12.2010
Dose:	750 mg (=10 mg/kg body weight /day) no modification of dose
Premature discontinuation of study:	30.12.2010
Reason for end of study:	SAE, development of acute leukemia

9 AEs were documented, 2 of them were SAEs: no relationship to the study drug suspected

AE Description	Date started	Date stopped	serious	severity grade	Outcome	Relationship to study drug	Action taken
pain back	19.10.2010	11.11.2010	no	moderate	completely recovered	not suspected	no action taken
multiple petechiae	11.11.2010	02.12.2010	no	mild	completely recovered	not suspected	no action taken
multiple hematomae	29.10.2010		no	mild	NK	not suspected	no action taken
multiple thrombophlebitis	11.11.2010		no	mild	NK	not suspected	no action taken
fatigue	29.10.2010		no	mild	Nk	not suspected	no action taken
dyspnea	29.10.2010		no	mild	Nk	not suspected	no action taken
depression	29.10.2010		no	mild	Nk	not suspected	no action taken
pneumonia	23.11.2010	29.11.2010	yes	severe	completely recovered	not suspected	no action taken
AML	30.12.2010		yes	severe	condition still present and unchanged	not suspected	**trial drug permanently discontinued due to this AE**

Exjade-Early-Trial

Protocol No.: CICL670ADE06T

EudraCT number: 2008-006268-12

CASE REPORT

Patient ID: 01_02
Age: 40y
Sex: female
Weight: 70 kg
Study medication: deferasirox

Date of informed consent:	23.11.2010
Serum ferritin level before start of deferasirox treatment:	731 µg/l
Duration of treatment:	15 weeks
Date started:	03.12.2010
Date stopped:	24.03.2011
Starting Dose deferasirox:	750 mg (=11 mg/kg body weight /day); dose level II; from 03.12.2010 to 30.01.2011.
Dose adjustment:	500 mg (= 7,1 mg/kg body weight /day); dose level I; from 31.01.2011 to 24.03.2011.
Discontinuation of treatment:	24.03.2011
Reason for discontinuation of treatment:	serum ferritin < 150 µg/l

According to protocol deferasirox treatment has to be restarted at serum ferritin levels > 150 µg/l. The ferritin levels remained low until end of study, therefore no restart of deferasirox treatment.

9 AEs were documented, no SAEs: no relationship to the study drug suspected

AE Description	Date started	Date stopped	serious	severity grade	Outcome	Relationship to study drug	Action taken
tibia right wound	18.11.2010	NK.01.2012	no	moderate	completely recovered	not suspected	no action taken
nausea	20.12.2010	NK.04.2011	no	mild	completely recovered	not suspected	no action taken
pyrosis	20.12.2010	NK.04.2012	no	mild	completely recovered	not suspected	no action taken
gastric spasm	20.12.2010	NK.04.2011	no	mild	completely recovered	not suspected	no action taken
fatigue	30.12.2010		no	mild	condition still present and unchanged	not suspected	no action taken
hypertension			no	mild	condition still present and unchanged	not suspected	no action taken
mental stress	30.12.2010		no	mild	condition still present and unchanged	not suspected	no action taken
foot pain	07.10.2011	12.01.2012	no	mild	completely recovered	not suspected	no action taken
gingiva bleeding	06.05.2011	07.10.2011	no	mild	completely recovered	not suspected	no action taken