Name of Sponsor/Company: CROLLL GmbH	Individual study table referring to part of the dossier not applicable	
Name of Finished Product: Exjade®	Volume	
Name of Active Ingredient: Deferasirox	Page	

Title of Study:

The Impact of Deferasirox on Non-Alcoholic-Steatohepatitis (NASH) - a prospective open-label phase I/II trial

Investigators:

Prof. Dr. med. Gerhard Treiber
Prof. Dr. med. Eckart Schott
Prof. Dr. med. Frank Lammert
Prof. Dr. med. Marcus Schuchmann
PD Dr. med. Matthias Dollinger
Prof. Dr. med. Dr. h.c. Peter Malfertheiner
PD Dr. Reiner Wiest
Prof. Dr. med. Stefan Zeuzem

Study centre(s): 9

001 - Balingen
002 - Berlin
003 - Homburg
004 - Mainz
006 - Halle
007 - Magdeburg
008 - Tübingen
009 - Regensburg
010 - Frankfurt

Previous related Publications (reference):

- Treiber G, Rotthauwe J, Heinrich U, Schulz HU, Fahlke J, Roecken C, Klauck S, Malfertheiner P. The Prevalence of Non-Alcoholic Fatty Liver Disease in HCC-Patients. Gastroenterology 2003; 124 (suppl S): A746
- Treiber G, Csepregi A, Klauck S, Roecken C, Malfertheiner P. Simple, low- cost, and non-invasive quantification of steatosis in patients with non-alcoholic fatty liver disease. Gastroenterology 2005; 128 (suppl 2): A543
- Twreiber G, Csepregi A, Klauck S, Roecken C, Wex T, Leucke M, Malfertheiner P. Multistep Approach for Treatment of Non-Alcoholic Fatty Liver Disease - Impact of Diet and Pioglitazone. Gastroenterology 2006 (suppl 1);

Studied period (years):	**Phase of development:**
Date of first enrolment July 27th 2010 **Date of last completed** March 13th 2012 The recruitment has been stopped prematurely in June 2011 by the sponsor after the enrolment of five patients because the enrollment pace was far beyond target.	I/II

Objectives:

To assess the clinical and biological activity of Deferasirox in patients with NASH and increased iron storage / disturbed distribution of iron on liver function and liver histology.

Methodology:

Open-label, uncontrolled, prospective

Number of Patients (planned and analysed):

Planned: Phase I: 10 (2 x 5) Phase II: 50

Analysed: Phase I: 5 Phase II: 0

Diagnosis and main criteria for inclusion:

Trial indication:
Patients with moderate to severe NASH and increased iron storage

Main inclusion criteria:

- Patients with elevated liver enzymes: transaminases (ALAT and or ASAT) ≥ 1.5 ULN and/or
  g-GT ≥ 1.5 ULN, max. 5 ULN
- Elevated serum ferritin: females > 300 ng/ml, males > 450 ng/ml
- Liver Histology consistent with a diagnosis of NASH (NAS Score ≥ 3), as evaluated by the
- NASH acitivity scoring system (NAS) according to Kleiner DE et al. Hepatology 2005
- Males and females of age ≥ 18 years
- Informed consent given

Main exclusion criteria:

- Established liver cirrhosis Child Pugh B or C
- Copresence of other causes of chronic liver disease
- Anemia < 10 g/dl
- Any elevation of ALAT, ASAT, and g-GT of > 5 ULN, any elevation of > 2.5 ULN for other liver enzymes, any elevation of bilirubin > 1.5 ULN
- Serum creatinine > 1.4 mg/dl or Ccr < 60 ml/min
- Hemochromatosis (defined as homozygous state for the C282Y mutation documented by molecular diagnostic testing)
- Patients with impaired coagulation

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

Test product and mode of administration: **Deferasirox/ICL670/Exjade®**, dispersible tablet for oral use

Dose: **max. 15mg/kg/d**

Batch numbers: **ICL670 125 mg (Batch No. S0008A)**
ICL670 250 mg (Batch No. S0036)
ICL670 500 mg (Batch No. S0050; Batch No. 0264)

Duration of Treatment:

12 weeks (Phase I); 48 weeks (Phase II) for all participating patients

Reference therapy, dose and mode of administration, batch number:

Not applicable

Criteria for evaluation

Efficacy:
Decrease in NAS of ≥ 1 at week 48 (during phase II)

Safety:
Safety assessments consist of evaluating adverse events and serious adverse events, laboratory parameters including hematology, chemistry, vital signs, and physical examinations according to NIH CTC.

Statistical methods:

Simon II stage design

Summary - Conclusions

The study was intended as an open label single arm Phase I (n=10) and Phase II (n=50) trial. All patients fulfilled the inclusion criteria for NASH as predefined. As patient enrollment into the first cohort (n=5) took about one year and was mainly accomplished by one participating trial site, it was concluded to stop the trial because of insufficient recruitment.
Judging efficacy from MRI, liver enzymes and clinical data, it appeared that 2/5 patients had a clear improvement while increasing from 5 to 10 mg/kg/d of Deferasirox. There was no clear predictor from baseline for treatment success. There was one complex, clinically important SAE, possibly / in part related to Deferasirox; appearing at the 10 mg/kg/d dose level on week 11 of treatment, all other AEs were minor and in general the treatment was well tolerated.

Efficacy Results:

Demographics at Baseline (BL): 4/5 patients had moderate NASH with a NAS score of 4-5. Mean BARD score was 2.2, Mean grading on ultrasound was 4.4, and mean BMI 33.2, mean body fat was 37.2%. Each patient had at least 2 features of the metabolic syndrome. Mean (median) serum levels were 797 (767) ng/ml for ferritin, 548 (595) U/l for g-GT, 86 (82) U/l for ALAT, and 63 (58) U/l for ASAT. All other liver enzymes were within normal limits.

During Treatment: One patient received only 5mg/kg/d for 12 wks and had no MRI, the other 4 pts. were treated/monitored according to the protocol. Pts. had no changes over time in general physical appearance, e.g. BMI, body fat, blood pressure, heart rate. Significant laboratory parameter decreases were seen in 2/5 pts., becoming significant for the whole group for ferritin (BL vs. wk 12: $p<0.001$), g-GT (BL vs wk 12 and 16: $p<0.05$), and uric acid (wk 8 vs. wk 12: $p<0.05$). Metabolic changes seen did not correlate with liver enzymes or MRI results. Intrahepatic lipid contents as seen on MRI decreased by 81%, 49%, and 16%, while an increase was seen in one patient (21%). T2 increased in all 4 pts. between 16 and 34%. Relative increases in T2* were minor.
Until End of Follow-up: in most cases parameters returned to baseline during the 12 week period, thus no sustained drug effect after withdrawal could be noticed.

Safety Results:

An exceptional vote was given for 3 pts. at baseline to become included into the trial because of too high liver enzymes (n=2) and borderline elevated creatinine (n=1). All of these had improvements over time in their abnormal values. We saw 15 events with CTC grade 1, such as bronchitic infect, peripheral lower leg edema, dizziness, nausea, Herpes labialis, tooth pain, diarrhea. One patient had a prolonged episode starting with headache associated with a cold. Then the patient progressed with nausea and emesis and became dehydrated. Finally the patient was somnolent and hypoglycemic. The interpretation was that the earlier rise in ALAT/ASAT despite further decrease in g-GT could have been associated with Deferasirox. However, the prolonged intake of metformin and injection of insulin together with dehydration due to lack of sufficient fluids may better explain metabolic acidosis, prolonged hypoglycemia, and prerenal insufficiency, becoming fully reversible after stopping Deferasirox, metformin, insulin, and substitution of fluid. Otherwise, there were especially no eye or ear side effects, and quality of life indices had improved over time.

Conclusion

Due to premature study termination due to slow accrual, patient numbers are too low to come to a definite conclusion about efficacy and safety results in the predefined NASH population. MRI results imply that there may be a subpopulation that will profit even from a short-termed Deferasirox treatment. 5-10 mg/kg/d are effective in decreasing serum ferritin to the target level of 150 ng/ml over 12 weeks. After drug withdrawal, all changes seen tend to return to baseline levels.

Date of report

4th of march, 2013

Substantial Protocol Amendments

Amendment 1:
Omission of week 24 liver biopsy; deletion of atomic absorption spectrometry measurement for changes in hepatic iron content and distribution; definition of ULN mean for liver enzymes; extension of permitted period for baseline biopsy; safety update concerning new data for the IMP (new Summary of product characteristics).

Amendment 2:
To simplify the MRI measurement for phase I and II of the clinical trial. For phase I the MRI will be optional.