CLINICAL REVIEW

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Established Name	Deferasirox
(Proposed) Trade Name	Exjade
Therapeutic Class	Iron Chelator
Applicant	Novartis
Priority Designation	Priority
Formulation	Tablets
Dosing Regimen	20-30 mg/kg
Indication	Iron overload due to chronic transfusion
Intended Population	Patients with congenital anemias

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List of abbreviations

α1-M	α1- microglobulin
Ab	Antibody
ACE	Angiotensin-converting enzyme
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT/SGPT
ANC	Absolute neutrophils count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT/SGOT
AUC	Area under the curve
A-V	Atrio-ventricular
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
β2-M	β2- microglobulin
CI	Confidence Interval
CK	Creatine kinase
CL	Clearance
Cmax	Maximum plasma concentration
CP	Clincal pharmacology
CRF	Case Report/Record Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
CV	Coefficient of variation
DFO	Deferoxamine
dw	dry weight
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDM	Electronic Data Management
ELISA	Enzyme-Linked Immuno Sorbent Assay
EMEA	European Agency for the Evaluation of Medicinal Products
EOS	End of study
ERB	Ethical Review Board
FDA	Food & Drug Administration
Fe	Iron
GCP	Good Clinical Practice
GI	Gastrointestinal
Hb	Hemoglobin
HBcAg-IgM	Hepatitis-B-core-Antigen-Immunoglobulin M
HBeAg	Hepatitis-B-envelope-Antigen
HBsAg	Hepatitis-B-surface-Antigen
HCV	Hepatitis-C Virus
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
Ig G	Immunoglobulin G

IRB	Institutional Review Board
ITT	Intent To Treat
i.v.	Intravenous
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
LIC	Liver Iron Content
LLN	Lower Limit of Normal range (for laboratory values)
ml	milliliter
MRI	Magnetic Resonance
NAG	N-acetyl-β-glucosaminidase
NIE	Net Iron Excretion
NOAEL	No Adverse Effect Level
PD	Pharmacodynamics
PK	Pharmacokinetics
PP-1	Per-protocol 1 (population)
PP-2	Per-protocol 2 (population)
PSB	Program Safety Board
RBC	Red Blood Count
RBP	Retinol Binding Protein
SAE	Serious Adverse Event
SD	Standard deviation
s.c.	Subcutaneous
SGOT	S-glutamic oxaloacetic transaminase
SGPT	S-glutamic pyruvic transaminase
SMC	Study Monitoring Committee
SOC	(Body) system organ class
SQUID	Superconducting QUantum Interference Device
TBI	Total Body Iron
TBIE	Total Body Iron Excretion
t1/2	elimination half life
tmax	maximum plasma
TRF	Transferrin
ULN	Upper Limit of Normal range (for laboratory values)
UPCR	Urine protein / creatinine ratio
WBC	White Blood Count
WHO	World Health Organization
Ww	Wet weight

1. EXECUTIVE SUMMARY

Please refer to separate Advisory Committee Summary.

1 INTRODUCTION AND BACKGROUND

1.1 Product Information

Exjade (deferasirox, ICL-670) is a tridentate iron chelating agent that is proposed to be employed in patients with congenital and acquired anemias who have developed excessive total body iron stores (hemosiderosis) due to chronic transfusion therapy. It is available as a dissolvable tablet in strengths containing 125 mg, 250 mg or 500 mg of active pharmaceutical ingredient. It is a new molecular entity of the N-substituted bis-hydroxyphenyl triazole family.

Chemically, Exjade is 4-(3,5-Bis-(2-hydroxy-phenyl)-1,2,4) triazol-1-yl)-benzoic acid and has a molecular weight of 373.4. Its molecular structure is
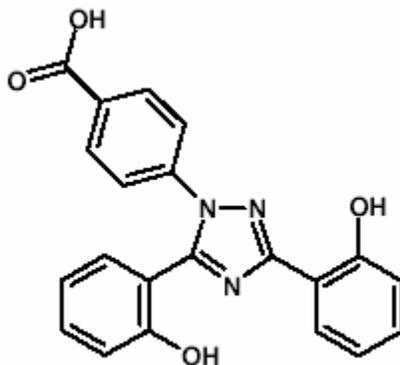
Inactive ingredients in the drug product include Lactose monohydrate (NF), crospovidone (NF), povidone (K30) (NF), sodium lauryl sulphate (NF), microcrystalline cellulose (NF), silicon dioxide (NF), and magnesium stearate (NF).

1.2 Currently Available Treatment for Indications

Deferoxamine (Desferal, DFO) is the only alternative therapy for the current indication. Deferoxamine, although effective in reducing iron stores in the body, suffers from the need for parenteral administration and a short pharmacological half life. These features necessitate long term (10-12 hour) subcutaneous or intravenous (via catheter) infusions by pump daily for 5-7 days a week. Compliance with this regimen has led to a limitation in its use.

1.3   Availability of Proposed Active Ingredient in the United States

Exjade is not currently marketed in the United States.

1.4   Important Issues With Pharmacologically Related Products

The only other approved iron chelator is Desferal (deferoxamine). The molecular structure of deferoxamine is not related to the molecular structure of Exjade.

1.5   Presubmission Regulatory Activity

Following is a chronological regulatory history for Exjade.
- June 30, 1999. IND 58554 opened. A phase I dose escalation study (0101) had been done in Italy. The IND opening study (0104 which combined proposed protocols 0102 and 0103) was a randomized, double blind, placebo controlled, multiple dose study in patients with β-thalassemia to study Exjade's safety, tolerability and effects on iron balance. Subsequently, the sponsor submitted a protocol for Study 0105, a phase II study to study the safety, tolerability and efficacy of Exjade compared to DFO in patients with ß-thalassemia, as well as Study 0106, a phase II study to compare the safety, tolerability and efficacy of Exjade to DFO in pediatric patients.
- June 19, 2001. Recommendations from the Division to sponsor regarding conduct of animal toxicity and carcinogenicity studies.
- June 3, 2002. End of Phase II Meeting. There was a discussion of Fast Track and Orphan Drug applications as well as a Proposed Pediatric Study Request. Additional preclinical neonatal, cardiovascular safety pharmacology and ocular toxicity studies were recommended. The sponsor wished to broaden the indication to all patients with transfusional hemosiderosis. The Division replied that labeling would reflect the population in which the drug was studied. In the proposed phase III study, a binary endpoint of "success" or "failure" was suggested by the Division as being desirable. The Division recommended that information on dose proportionality in the proposed dose range, *in vitro* and *in vivo* data on chelation of other constituents, drug-drug interactions with commonly administered drugs in the target population and secretion of Exjade into human milk be submitted in the NDA.
- January 30, 2003. Special Protocol Assessments for Studies 0107, 0108 and 0109 performed by the Division. For all three studies, the following applied. Patient numbers were acceptable. Liver iron concentration (LIC) determined by liver biopsy was accepted as the standard measure of LIC. The Division sought data regarding the validation of the use of a superconducting quantum interference device (SQUID) as an assessment tool to measure LIC. The dose of Exjade was acceptable. LIC was accepted as the primary measure for determining clinical efficacy. It was acceptable to measure the efficacy of Exjade by total body iron elimination rate in addition to measuring LIC. The Per Protocol population was accepted for primary efficacy analysis. There was an agreement in principle that final approved labeling would not require LIC determination by liver

biopsy or SQUID and should recommend the usual clinical monitoring tests for body iron status, but that the exact monitoring recommended in the label would depend on the data obtained. A recommendation was made to obtain PK data in patients with various degrees of hepatic impairment. There was concern expressed by the Division that there be a significant number of pediatric patients enrolled in the trials if there were to be claims in the final approved labeling.

For 0107 and 0109, DFO was accepted as the active comparator. There was no question asked by the sponsor in regard to the non-inferiority margin of -15%, but the statistical review of the protocol indicated that "the assessment of the external evidence will remain an issue when the results of the study are reviewed".

For 0108, since there was no control arm, the Division recommended use of an historical control as a comparator. Analysis on the basis of intention to treat, with missing data considered as failure, was acceptable.

- February 21, 2003. Fast Track Designation granted.
- August 1, 2003. Preclinical study in neonatal and juvenile animals reviewed and recommendations made. A follow up teleconference was held on these issues on October 30, 2003.
- October 23, 2003. Industry Meeting. There was a discussion regarding recruitment to Study 0109 and the number of pediatric patients to be entered into the trial. The Division again expressed concern about the use of SQUID to measure LIC. The sponsor agreed to provide information to address the correlation between various measures of total body iron stores (liver biopsy, SQUID, MRI, serum biomarkers).
- January 5, 2004. Denial of a Proposed Pediatric Study Report to qualify for exclusivity.
- January 5, 2004. The Division states that the proposed trade name of "Exjade" is acceptable.
- October 1, 2004. Pre-NDA Meeting. Application accepted into the Pilot 1 program. There was discussion of a Priority Review, eNDA submission, stability and shelf life issues and the adequacy of preclinical and Exjade-digoxin interaction studies. The Division indicated that its review of the information provided by the sponsor in reference to the measurement of LIC by SQUID showed that the methodology might not be useful for that purpose. The Division agreed to review the data on the utility of measuring the serum ferritin in providing dosing recommendations in the product label. The Division stated that evidence of a reduction in morbidity/mortality related to diminished body iron stores was required and the sponsor agreed to provide data that reduction of an elevated LIC was a predictor of these clinically important events. The sponsor was asked to provide historical evidence for the effectiveness of the comparator in order to support the assumptions of the non-inferiority analysis.
- October 13, 2004. The Division informs the sponsor that reducing the threshold for liver biopsy dry weight to determine LIC from 1 g to 0.5 g is unacceptable.
- November 9, 2004. Telecon with Sponsor. The sponsor proposed to prospectively amend the definition of the population for the primary analysis of non-inferiority prior to database lock. The rationale for this change was that the sponsor believed from initial

information that it would not be successful in meeting its originally proposed primary efficacy objective because doses of Exjade of 5-10 mg/kg/d were ineffective in reducing LIC when baseline LIC was <7 mg Fe/g dw. The sponsor stated that this was owing to the underestimation of LIC by SQUID which led to an underdosing in the Exjade arm but not in the deferoxamine arm. The Division expressed grave reservations about this strategy. The Division stated that this proposal would restrict the applicability of Exjade to only the analyzed group of patients.

- May 5, 2005. Sponsor requests approval of Treatment Protocol to allow the treatment of up to 3000 patients with Exjade until drug approvability is determined. The Division grants approval of the Treatment Protocol.

1.6   Other Relevant Background Information

The drug is not approved in any country.

2   SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

2.1   CMC (and Product Microbiology, if Applicable)

The CMC review has noted some problems in solubility and dispersability. The drug is poorly soluble in water but reasonably soluble in lipids. Oral administration of the drug is preceded by dispersion of the tablets in either water or orange juice to minimize particle size and improve absorption from the gastrointestinal tract. There were several minor additional problems addressed in the CMC review but the Chemistry Reviewers (Drs. Raymond Frankovich and Liang Zhou) did not believe that these were a basis for non-approvability. For more details, please refer to the Chemistry review.

2.2   Animal Pharmacology/Toxicology

Animal studies were based on the oral and intravenous administration of Exjade to mice, rats and marmoset monkeys. In some studies, juvenile rats and mice were used. Fertility/reproductive studies were performed in rats. Genotoxic and carcinogenetic studies were performed

Target organs demonstrating toxic effects at various doses of Exjade included the following:
- Kidneys. Tubular degeneration, vacuolization of tubular cells and necrosis of tubular cells.
- Eye. Cataract development.
- Heart. Myocytolysis.
- Gastrointestinal tract. Ulceration.

- Gall bladder/bile duct. Inflammation and cellular degeneration.
- Lymphocyte depression in the spleen and thymus in juvenile animals.

For more details, please refer to the Pharmacology/Toxicology review.

3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

3.1 Sources of Clinical Data

The sponsor performed a number of trials of Exjade that included initial dosing, pharmacokinetic/pharmacodynamic, tolerability, QT/QTc, drug/drug interaction, fasting/food interaction and clinical studies in populations of interest. The clinical studies are listed in tabular form immediately below. Some of the studies remain ongoing. The sponsor submitted the data in electronic form.

3.2 Tables of Clinical Studies

Exjade Clinical Studies

Study Number	Purpose	Design	Size	Duration/Dose	Status
0101	Safety, tolerability and PK of ascending doses of Exjade	Double blind, placebo controlled, randomized, parallel group	25 healthy Caucasian males, ages 18-32	2 escalated doses (2.5-80 mg/kg) or placebo and a single dose 3 groups	Completed
0104	Safety, tolerability and iron balance of multiple doses of Exjade	Double blind, placebo controlled, randomized, parallel group	24 β-thalassemia patients, ages 18-50 12 males, 12 females	12 days 3 groups 10-40 mg/kg/d	Completed
0105	Safety, tolerability and effect on LIC (SQUID) of multiple doses of Exjade compared to DFO	Randomized, open label 2:1 ratio of Exjade/DFO	71 β-thalassemia patients, ages 17-50 26 males, 45 females	48 weeks Exjade, 10-20 mg/kg/d. DFO, 40 mg/kg/d s.c.	Completed
0105E1	Extension study for patients enrolled in 0105. Provision of treatment. Effect on LIC by SQUID.	Open label	67/71 patients from Study 0105	12 months Exjade, 10-20 mg/kg/d with dose adjustment up to 40 mg/kg/d. DFO 40 mg/kg/d s.c. with adjustment up to 50 mg/kg/d.	Completed
0105E2	Non-comparative extension study for patients enrolled in 0105E1. Provision of Exjade treatment. Effect on LIC by SQUID, liver biopsy and MRI.	Open label	59/71 patients from Study 0105	3 years Exjade, 10-20 mg/kg/d with dose adjustment up to 40 mg/kg/d. No patients on DFO.	Ongoing

0106	Safety, tolerability, PK and effect on LIC by SQUID	Open label	40 pediatric patients with β-thalassemia 17 males, 23 females Age 2 to <12 years, 20 patients. Age 12-17 years, 20 patients .	48 weeks Exjade, 10 mg/kg/d with dose adjustment up to 40 mg/kg/d.	Completed
0107	Pivotal efficacy. Effect of Exjade compared to DFO on LIC by biopsy or SQUID.	Multi-center, open label, parallel group, non-inferiority of Exjade compared to DFO Phase III, Pivotal	591 patients with β-thalassemia. 285 males,306 females. Mean age, 17.2 years (range, 2-53).	1 year Exjade, 5-30 mg/kg/d. DFO, 20-60 mg/kg/d	Completed
0108	Efficacy and safety of Exjade on LIC by biopsy or SQUID	Multi-center, open label, single arm, non-comparative	184 patients with transfusion dependent chronic anemias, unable to be treated with DFO.	1 year Exjade, 5-30 mg/kg/d with dose adjustment up to 40 mg/kg/d	Completed
0109	Safety, tolerability, PK and effects on LIC by SQUID (sub-study with MRI and liver biopsy) of Exjade compared to DFO	Multi-center, open label, randomized, parallel group compared to DFO	195 patients with sickle cell disease and hemosiderosis 80 males, 115 females Mean age, 19.2 years (range, 3-54) Exjade:DFO ratio 2:1	1 year Exjade, 5-30 mg/kg/d with dose adjustment up to 40 mg/kg/d DFO, 20-60 mg/kg/d s.c.	Ongoing
0106E1, 0107E1, 0108E1, 0109E1	Extension studies for patients who have completed respective studies	Open label	Available to all patients completing protocol	Up to 3 years Exjade, 5-30 mg/kg/d	Ongoing

During the IND, a consultation was obtained from Dr. Charles Ho, Biomedical Engineer, CDRH, ODE/DCD/CEMB to evaluate the use of the SQUID Biosusceptometer to determine LIC. Dr. Ho advised that the sponsor had not proven that the methodology was sensitive to LIC and LIC alone. The measurement could be compromised because of noise from iron concentrations in the heart and spleen, and the magnetic fields of the heart and brain.

During the NDA review, Exjade was the subject of an Advisory Committee.

3.3   Review Strategy

All of the trials submitted by the sponsor were reviewed for safety and efficacy. Study 0107 was the pivotal trial in the series and special attention was focused on it. Literature provided by the sponsor as well as that independently obtained was incorporated into the review.

3.4   Data Quality and Integrity

Data collection.
Designated investigator staff entered the information required by the protocol into the

Novartis eCRFs using a Novartis-supplied computer loaded with fully validated software that conforms to FDA requirements for electronic data capture. During any down-time with the system, the data was recorded in source documents and was later transferred to eCRFs. Automatic validation programs checked for data discrepancies in the eCRFs and by generating appropriate error messages, allowed modification or verification of the entered data before transfer to Novartis via a secure internet link. The Investigator certified that the data were complete and accurate. Initially this was performed by applying an electronic signature to the eCRF. During the study a new standard EDM process was introduced in which the e-signature was no longer required and paper forms confirming completeness and accuracy were sent to the site to be signed and stored in site files. For archiving of the patient data at the investigational site a CD-Rom was sent once the laptops were retrieved from site – as the clinical data of the extension study CICL670A0107E is being entered on the same laptops, archiving will not be performed until extension has locked.

All eCRFs sent to Novartis by investigational sites were reviewed upon receipt for any SAEs.

 <u>Database management and quality control.</u>
Data items were entered directly into the study database or indirectly from source data documents by designated Novartis-trained investigator staff using single data entry with electronic verification. Novartis staff reviewed the data for completeness and accuracy and instructed the site personnel to make any required corrections or additions. Queries were generally sent to the investigational site using an electronic data query system which provided an automatic audit trail of the corrections made by designated investigator staff.
Occasionally, when queries were sent on a Data Query Form, the signed, original and resolved Data Query Form was kept at the investigator site and a copy sent to Novartis so the resolutions could be entered centrally into the database.
Concomitant medications entered into the database were coded using the WHO Drug Reference List which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and AEs were coded using the Medical dictionary for regulatory activities (MedDRA) terminology.
Laboratory samples were processed centrally through, BARC NV, Industriepark 7B bus 3, B-9052 Gent, Belgium and the results were sent electronically to Novartis.
When the database was declared to be complete and accurate, it was locked and unblinded. Any changes to the database after that time could only be made by joint written agreement between the Clinical Trial Leader, the Trial Statistician and the Data Manager.

The Division of Scientific Investigation reviewed source data from 3 sites (The New York Hospital-Cornell Center, Children's Hospital of Oakland and Children's Hospital of Philadelphia). These institutions were selected because they had contributed a reasonably large number of patients to the trials (although no institution accounted for more than a small fraction of all patients) and they had contributed patients to all of the larger trials.

The findings of the DSI are pending.

3.5   Compliance with Good Clinical Practices

All trials were conducted in compliance with Good Clinical Practices, with applicable local regulations and with the ethical principles in the Declaration of Helsinki and its revisions. After the completion of   Novartis received information that
had had his   suspended in   for "practicing while
impaired"   Board of Registration in Medicine. After that action,
moved to   where he became a sub-investigator for these studies at center.   was
licensed to practice medicine in   while he functioned as a sub-   . sponsor states that
no disbarred investigators were involved in the trials submitted in support of the application.

3.6   Financial Disclosures

The sponsor has submitted a statement, dated April 22, 2005, that one investigator (
who enrolled patients on to   holds financial interests in the sponsor. The
states that no payments were made to the investigator nor would the value of the interests be affected by the outcome of the study.

4   CLINICAL PHARMACOLOGY

4.1   Pharmacokinetics

After oral administration of Exjade at doses of 5-30 mg/kg to β-thalassemia patients, peak plasma levels are achieved at 1-4 hours and are dose-proportional. The mean $t_{1/2}$ is 7 to 16 hours after multiple dose administration. The accumulation ratio expressed as the ratio of the average AUC between day 15 and 360 to day 1 is 1.433 (90% CI 0.88, 1.729). The oral bioavailability is ~70%. Exjade is 99% bound to plasma proteins, mostly albumin. Metabolism by CYP enzymes is low, accounting for <10% of the dose. Glucuronidation accounts for the majority of the metabolism with the production of acyl- and phenol-glucuronides. Exjade and its iron complex are eliminated primarily by hepatobiliary excretion with some enterohepatic circulation. Renal excretion accounts for <8% of the dose. A drug-drug study with digoxin was negative for interaction.

The effect of renal impairment on the metabolism of Exjade is not known since patients with serum creatinine values above the upper limit of normal (ULN) were not enrolled in the studies. The effect of hepatic dysfunction on the metabolism of Exjade is not known. However, patients with serum transaminases up to 5x the ULN were enrolled in the trials and treated with the same doses as those without hepatic impairment. Safety, efficacy and trough parameters in these patients were similar to those in the overall population.

Females have a moderately lower (by 17.5%) apparent clearance than males. Age is associated with a directly proportional exposure to the drug with children from age 2 to 6 exhibiting an exposure of half that of adults. Ethnic origin does not affect the PK of Exjade. The PK of Exjade has not been systematically studied in persons over the age of 65.

The PK of Exjade has been studied only in patients with β-thalassemia and has not been evaluated in patients with other forms of anemia.

4.2   Pharmacodynamics

Two molecules of Exjade bind a single atom of iron from the soluble iron pool in the plasma and this complex is excreted primarily in the stool. A short term (12 days) study of iron balance (Study 0104) performed in 23 patients with β-thalassemia demonstrated that Exjade in doses of 10-40 mg/kg/d was able to increase iron excretion above iron intake in a dose dependent manner as shown in the following table:

Table 3-2	Pharmacodynamic parameters in study 0104	
ICL670 dose (mg/kg)	Iron excretion rate (mean ± SD) (mg/kg/day)	Efficiency of chelation (%)
0	0.038 ± 0.057	-
10	0.119 ± 0.060	16
20	0.329 ± 0.104	22
40	0.445 ± 0.282	15

Source: [CP study 0104 – appendix 6 – table 2.5]

Virtually all of the excreted iron was found in the stool.

Reviewer's Comments. Based on the results of Study 0104, a 60 kg patient would excrete approximately 19.7 and 26.7 mg of iron daily at a dose of Exjade of 20 and 40 mg/kg/d, respectively. This would compensate for the transfusion of approximately 2-3 units of blood per month.

A long term (48 weeks) study of iron balance (Study 0105 substudy) performed in 71 patients with β-thalassemia suggested that Exjade in a dose of 10 mg/kg/d could maintain LIC at a stable concentration, while Exjade at a dose of 20 mg/kg/d decreased LIC to the same approximate degree as did deferoxamine at a dose of 40 mg/kg/d as shown in the figure below.

Figure 3-1   Change in LIC by SQUID in study 0105

Actual initial doses administered, mean ± SD
Source: [study 0105 – PT table 9.1-3]
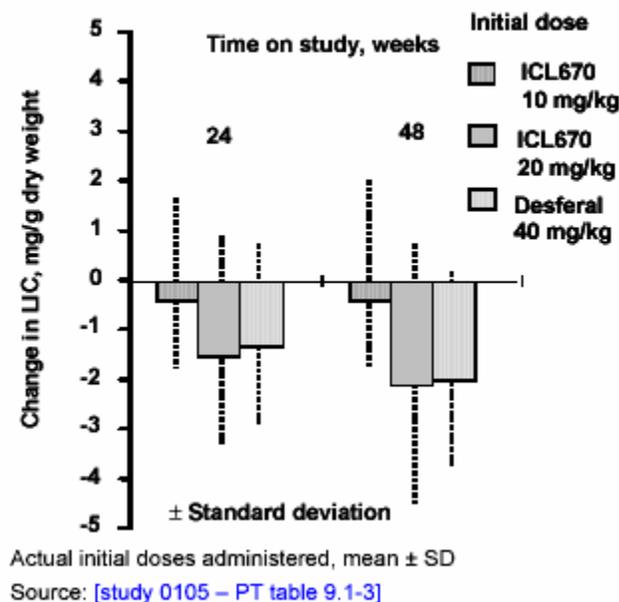
A QT/QT$_c$ study showed no effect of Exjade on the QT interval.

Reviewer's Comments. The LIC in Study 0105 was measured by SQUID. This method is not validated and the sponsor has concluded that LIC using SQUID is considerably lower than LIC measured by liver biopsy. Also, the three SQUID devices used in the trial provided three different relationships to LIC as measured by biopsy. The relatively long half-life of the drug permits once a day dosing.

4.3   Exposure-Response Relationships

Based on the above studies, there appears to be a linear exposure/response relationship. Lower doses may stabilize LIC in patients with mild or moderately increased LIC while high doses may be necessary to produce a diminution in LIC over time.

Reviewer's Comments. Unfortunately, when the clinical trials described below were planned, a decision was made to use doses of Exjade that from these studies might not have been sufficient to stabilize or reduce LIC. In addition, LIC measured by SQUID was subsequently determined to have underestimated LIC by a factor of 2 and, since the initial dosing of Exjade was based on LIC, many patients, particularly children, received suboptimal doses. Better understanding of dose-response relationships would have improved the design of succeeding clinical trials.

5 INTEGRATED REVIEW OF EFFICACY

5.1 Indication

The proposed indication is for: The treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients as young as two years of age.

Reviewer's Comments. The proposed indication is overly broad based on the studies performed to date. Most of the patients included in the studies have had β-thalassemia. Very few patients with other anemias (e.g., sickle cell disorders, myelodysplastic syndrome, aplastic anemia, Blackfan Diamond syndrome, refractory anemia, etc) that necessitate chronic transfusion therapy have been studied. In the United States, patients with β-thalassemia would be a minority of the proportion of patients requiring chronic transfusion therapy who might develop hemosiderosis. The permitted indication should reflect the populations studied.

5.1.1 Methods

The review of efficacy was based on the results from Studies 0105, 0106, 0107, 0108 and 0109 (see 4.2 for a listing of studies). The sponsor's pivotal study was 0107. Study 0109 is ongoing but data from the study are used in the review of safety.

Study 0107 will be discussed in greatest detail. The other studies will be used in a supportive manner.

5.1.2 General Discussion of Endpoints

Iron balance in the body is maintained by an equilibrium between the oral intake of iron (5-15 mg/d of which approximately 1 mg is absorbed) and the small losses that occur when iron containing cells (skin, GI mucosa, etc.) are sloughed from the body. The proportion of iron ingested is increased in persons who are iron deficient and in patients with various anemias. The normal daily loss is approximately 1 mg (menstrual blood loss and pregnancy increase this amount in women). Total body iron is approximately 50 mg/kg in adult men and 35 mg/kg in menstruating women. Since iron is carefully conserved by the body, any additional intake adds to body iron stores. The accumulation of iron to excess in the human body is clearly associated with significant morbidity and early mortality, although the exact mechanism by which excess iron causes tissue damage is not known. The total amount of iron normally present in the body is approximately 3-5 grams (1). The amount of excess iron that needs to be present to produce morbidity is variable and depends on individual response and the target organ. Although any organ in the body is capable of being affected, organ dysfunction is primarily seen in the liver,

heart, pancreas, joints and endocrine organs. Most of the morbidity and mortality is the result of iron overload of the heart.

Hemochromatosis is an inherited disorder in which excess iron is absorbed from the gastrointestinal tract. This condition, when recognized, is most easily treated with periodic phlebotomy. In contrast, in patients with chronic anemias, particularly when congenital and requiring lifelong transfusion therapy, iron present in the transfused cells cannot be removed by phlebotomy and cannot be excreted by the body. There is approximately 1 mg of iron in each ml of transfused red cells (therefore, there is approximately 200 mg of iron in each unit of packed red cell transfusion).

Chronic transfusion therapy has become the standard of care for patients with β-thalassemia major because it prevents much of the developmental retardation and excess cardiac work associated with the anemia. In sickle cell anemia, certain events, particularly cerebrovascular accidents, often lead to chronic transfusion therapy. Monthly transfusional requirements of 2-3 units of packed red cells are typical and each year of transfusions may add 5-8 gm of iron to total body stores. The onset of organ dysfunction is variable and not necessarily related to the degree of iron overload. Subclinical cardiac abnormalities with diminished left ventricular contractility may occur when as little as 20 g of total body iron has been reached (2).

There are several studies in chronically transfused patients with β-thalassemia that suggest that chelation of excess iron using DFO reduces morbidity and increases longevity, particularly when patients are compliant with therapy and maintain a serum ferritin below 2500 µg/L (3).

The optimal method of determination of the degree of iron overload in the body is not certain and various indicators have been used. These include:
- Direct chemical determination of iron content of biopsied tissue (4). The liver is the only organ that has been studied for iron content during life because of the availability of tissue by biopsy. Normal liver iron content (LIC) is less than 1.5 mg Fe/g dry weight (dw). In patients with hemosiderosis, LIC exceeds 2 mg Fe/g dw and may reach levels of 55 mg Fe/g dw or higher. There is a reasonable degree of correlation between the lifetime amount of blood transfused and the LIC. There is also a degree of correlation between LIC and the total body iron stores in thalassemia (total body iron stores in mg/kg body weight = 10.6 x (LIC in mg Fe/g dw) (5). There is an imperfect relationship between LIC and the likelihood of developing cirrhosis. There is some evidence that cirrhosis can be reversed by decreasing LIC.

    However, there are several problems associated with the use of the LIC as a measure of disease burden and response to therapy. These include:
    - The need for repetitive invasive biopsy to determine progression or regression in LIC. Clinically, this would be very cumbersome.
    - The LIC is not necessarily reflective of the degree of iron overload in other tissues, particularly in the heart. Hemosiderosis of the heart is a more common

- o The size of the liver biopsy required for adequate LIC should be ≥1 gm dw (5). Often, the liver biopsy obtained is smaller and multiple attempts at biopsy lead to greater complications.
- o Liver biopsy is a blind procedure and it is well documented that LIC of several biopsies of a liver performed at the same time can have different measurement of LIC. The variability of iron dispersion in the liver is also suggested by magnetic resonance imaging studies (6).

Despite these drawbacks, at the present time, the standard measurement of the degree of excess iron in the body is LIC by biopsy.

In the trials performed by the sponsor, LIC by biopsy was performed prior to and after treatment with Exjade. In most of the studies, the initial dose of Exjade was determined by the degree of LIC by biopsy. However, in some patients, particularly children and those with sickle cell disease, LIC at baseline and after completion of therapy with Exjade was determined not by biopsy but by SQUID (vide infra). There was no validation of SQUID prior to its use in the studies, and retrospective comparisons made by the sponsor between LIC determined by biopsy and SQUID showed that SQUID underestimated the true LIC by a factor of about 2.

- Measurement of iron levels in the blood. The standard measures of iron metabolism in the blood include the serum iron (Fe), total iron binding capacity (TIBC) and the serum ferritin. Serum Fe is raised and TIBC becomes saturated very quickly after relatively small amounts of iron have been administered and render these tests unusable for determining the need for, and efficacy of, iron reduction therapy. Clinically, because it requires a simple blood sample, serum ferritin has been used most extensively to estimate the degree of iron overload. The main drawback of serum ferritin is related to the fact that ferritin is an acute phase reactant, and its level in the blood may not always reflect the degree of body iron overload. Nonetheless, studies in patients with β-thalassemia suggest that multiple measures over long periods are related to body iron content and to the morbidity and mortality associated with transfusional hemosiderosis.

- Various forms of imaging. In several of the sponsor's studies, a superconducting quantum interference device (SQUID) (7) was used to estimate the degree of iron overload, the initial dose of Exjade and the response to therapy. This methodology depends on the inherent ability of iron to generate a magnetic field that is proportional to its concentration in an organ such as the liver. Problems with this method of measurement include:
    - The methodology has not been validated.
    - Other organs within the body containing iron (e.g., heart, spleen, bone marrow) affect the signal.

- Both the heart and the brain are sources of a magnetic field independent of their iron content.
- The unavailability of the equipment. There are fewer than five SQUID devices in the world that have been used for clinical purposes.
- The sponsor's own analysis of the relationship between LIC simultaneously measured by biopsy and by SQUID. The data indicate that LIC by SQUID underestimates LIC by biopsy by a factor of 2. Additionally, a comparison of the 3 SQUIDs that were used in the trials indicates that the correlation among the results of the devices was poor (The Turin center gave results that were about 20% lower than the Hamburg and Oakland centers).

Both computed tomographic (CT) and magnetic resonance (MR) imaging have been used to determine iron content in various tissues. Although early studies proved to be unsuccessful, recent development of specific computer programs may allow non-invasive evaluation of body iron excess in the future (8).

- Estimation of body iron excess based on the number of transfusions received. Since almost none of the iron administered in the form of transfused red cells is eliminated from the body, one can theoretically calculate the degree of iron excess from the number of transfusions administered. Problems arising from this method include faulty record keeping, multi-institutional transfusions, inaccurate measures of the exact amount of red cells per transfusion, and uncertainty of the degree of external blood loss (menses, other bleeding, diagnostic phlebotomy, etc.).

Reviewer's Comments. The agreed upon endpoint between the sponsor and the Division was LIC by biopsy. This was and continues to be the standard for determining total body burden of iron despite its deficiencies. The use of SQUID for this purpose was not acceptable to the Division. Consultation from Dr. Charles Ho (CDRH, ODE/DCD/CEMB) dated August 31, 2004 indicated that " the sponsor has not proven that the SQUID susceptometer used by the sponsor is sensitive to LIC and LIC alone". The sponsor's own studies indicate that there was an underestimation of LIC by a factor of 2 when SQUID LIC was directly compared to biopsy LIC. Therefore, patients in whom SQUID only was employed to measure LIC cannot be adequately evaluated for efficacy.

This reviewer realizes that there is little likelihood that LIC by biopsy to determine the dosing of Exjade and its efficacy will be adopted by the physician/patient community. The procedure is too invasive when there is a body of literature that involves serum ferritin as a clinically acceptable surrogate for total body iron burden. Although measurement of serum ferritin was deemed unacceptable for a rigorous clinical trial for efficacy, the sponsor has provided data comparing long term changes in serum ferritin and changes in LIC by biopsy. These will be given careful scrutiny since serum ferritin is likely to be used clinically to guide dosing and to follow the course of therapy if the agent is approved.

5.1.3 Studies submitted by the Sponsor. The following studies were submitted by the sponsor in support of its application for the approval of Exjade.

Study 0107.   Pivotal Study

Objective:

The primary objective was to demonstrate the non-inferiority of Exjade to DFO in terms of effects on LIC assessed by liver biopsy after one year of treatment in patients with β-thalassemia and transfusional hemosiderosis.

Multiple secondary objectives were:
- To evaluate the tolerability profile of Exjade in comparison with DFO in patients treated for at least one year.
- To estimate the absolute and relative change of LIC and total body iron excretion (TBIE) rate for subgroups, defined by baseline LIC (2-<7, and ≥7 mg Fe/g dw) and age.
- To evaluate the relationship between LIC and potential surrogate markers for efficacy such as serum ferritin, serum iron, transferrin (TRF) and TRF saturation for the dose titration of Exjade as well as safety markers indicative of possible signs of over chelation.
- To evaluate the relationship between pharmacokinetic (PK), pharmacodynamic (PD) and safety variables in patients receiving Exjade treatment (results are reported separately in the [CP study 0107]).
- To explore the potential of magnetic resonance imaging (MRI) as a method for non-invasive assessment of LIC in a subset of patients (results not included in this report).
- To identify genetic factors related to iron stores in patients with β−thalassemia and transfusional hemosiderosis which may predict a) response to treatment with Exjade, b)relative susceptibility to drug-drug interactions, or c) genetic predisposition to serious adverse events (SAEs) (results not included in this report).
- To collect proteomic data for biomarker identification (results not included in this report).
- To assess health care resource utilization and patient global assessment of satisfaction with treatment (results not included in this report).
- To assess drug usage for both treatments.

Reviewer's Comments. The primary endpoint is acceptable and was agreed to by the Division in the Special Protocol Assessment. It should be remembered, however, that the LIC is a surrogate marker and that the effects of Exjade on morbidity/mortality, which are the truly important clinical endpoints, are not likely to be demonstrated in this short trial.   The secondary endpoints seem reasonable.

Study Design.

The study was a Phase III, multicenter, randomized, open label, active comparator (DFO) controlled, parallel group trial. Patients with β-thalassemia who met the inclusion and exclusion criteria were randomized in a 1:1 ratio to either an oral Exjade arm or to a subcutaneous (s.c.) DFO arm after a 28 day run-in period during which DFO (most patients recruited into the study were already receiving DFO) was discontinued (wash out of 5 days) and the patient had a liver biopsy performed. LIC was measured by flame absorption spectrophotometry after digestion of the biopsy specimen. In patients < age 18 years, SQUID LIC was permitted in place of biopsy after approval had been granted by the sponsor. In 48 patients, LIC was measured by both biopsy and by SQUID. LIC was measured at baseline and at the end of the study. In the substudy in which SQUID LIC was compared to LIC by biopsy, an additional SQUID LIC was obtained at 24 weeks of treatment. In patients receiving Exjade, PK/PD studies were performed on blood samples obtained at weeks 24 and 52.

In addition to the primary efficacy assessments, a number of secondary efficacy assessments were made, some on all enrollees and some on subsets of enrollees. These included:
- Iron balance
- Surrogate markers (Serum ferritin, iron and iron binding capacity)
- Liver pathology for iron staining, fibrosis and hepatitis
- Safety assessments
- Pregnancies
- Laboratory evaluations (hematology, chemistry, hepatitis serology, renal function, ECGs, echocardiograms, audiometry, liver echography, ocular examinations, developmental characteristics for children, pharmacogenetic studies, proteomics, health care utilization, drug levels and PK assessments)

The schedule of visits and evaluations appears below.

	Run-in Day -28 - -6	Run-in Day -5 - -1	Day 1	1	2	3	4	5	6	7	8	9	10	11	12	13
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Randomization			X													
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Physical examination	X			X			X			X			X			X
Medical history/Current medical conditions	X															
Liver function history	X															
LIC Liver biopsy	X															X
LIC SQUID subgroup	X								X							X
LIC MRI subgroup	X								X							X
Liver pathology	X															X
Liver echography	X								X							X
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X					X			X			X				X
Echocardiography	X															X
Urinalysis		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Renal function	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ocular exam/audiometry	X					X			X			X				X
Hemoglobin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, biochemistry, iron metabolism	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis serology	X															
Cystatin C	X	X	As necessary													
Blood/urine for proteomics			X			X			X			X				X
Blood for pharmacogenetics			X													
Health care resource utilization				X	X	X	X	X	X	X	X	X	X	X	X	X
Global assess. of satisfaction	X		X						X							X
PK trough samples			X			X			X							X
PK profile samples, subgroup									X							X
Concomitant medication	X	As necessary														
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pediatric patients additional evaluations																
Body height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stature assessment	X		X			X			X			X				X
Growth velocity assessment									X							X
X-ray (bone age evaluation)	X															X
Pubertal staging	X		X			X			X			X				X
School attendance evaluation			X	X	X	X	X	X	X	X	X	X	X	X	X	X
School performance evaluation	X															X

Reviewer's Comments. The design of the study was agreed to by the EMEA through Protocol Assistance and with the FDA through a Special Protocol Assessment. Although the reluctance to

perform liver biopsies on pediatric patients was *understandable, the use of an unvalidated method of measuring LIC (SQUID) was inappropriate.*

Study Patients.

Patients with transfusion dependent β-thalassemia who either had been previously treated with DFO or were naïve to DFO were eligible for enrollment. LIC values of ≥2 mg Fe/g dry weight (dw) of liver were considered adequate to commence chelation therapy.

Inclusion criteria were:
- Outpatients of either sex aged ≥2 years with β-thalassemia and transfusional hemosiderosis
- Patients already treated with DFO at a mean daily dose of 20-60 mg/kg/day for five consecutive days each week for at least four weeks before entering screening and still suitable for treatment with DFO, or patients never treated with an iron chelator and without contra-indications to either trial medication
- Suitable for treatment with s.c. DFO at a dose range between 20 and 60 mg/kg/day.
- LIC ≥2 mg Fe/g dw, as assessed by liver biopsy.
- Regular blood transfusions as indicated by ≥8 transfusional events per year
- Female patients of childbearing potential had to use double-barrier contraception or must have undergone clinically documented total hysterectomy and/or ovariectomy, or tubal ligation.
- Written informed consent by the patient if an adult
- Written informed consent by a guardian if "pediatric" according to local legislation

Exclusion criteria were:
- Transfusion-dependent anemias other than β-thalassemia
- Non-transfusional hemosiderosis
- Documented poor response to DFO
- Contraindications to DFO and/or documented unacceptable DFO toxicity
- Clinical evidence supporting the need for intensive chelation, based on the judgment of the investigator
- Patients with mean levels of ALT or AST >250 U/L during the 12 months before randomization (at least four determinations during the 12-month period preceding enrollment, including measurements during the run-in) and patients with ALT or AST variations >300% (CV of mean value) during 12-months preceding enrolment
- Serological evidence of chronic hepatitis B (presence of HBe Ag, HBsAg, HBcAb-IgM, in the absence of HBsAb)
- Clinical evidence of active hepatitis C (liver pathology, HCV total antibody positive and abnormal liver transaminase levels; if no liver biopsy is performed, HCV RNA (PCR) positive).
- A history of HIV seropositivity
- Uncontrolled systemic hypertension

- Serum creatinine above the upper limit of normal (ULN) at screening
- Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 (mg/mg) in a second void urine sample taken at both Visits 1 and 2. A third sample was to be taken from patients in whom one ratio was > 0.5 (mg/mg) and one was ≤ 0.5 (mg/mg). Patients in whom the ratio was > 0.5 (mg/mg) in two of the three samples were excluded.
- History of nephrotic syndrome
- Patients with 2nd or 3rd degree A-V block, clinically relevant Q-Tc interval prolongation and patients requiring treatment with digoxin and drugs which induce prolongation of the A-V conduction time or Q-Tc interval
- Fever and other signs of infection in the ten days before Day 1
- Clinically relevant cataract or a history of relevant ocular toxicity related to iron chelation
- Systemic diseases (cardiovascular, renal, hepatic, etc.) which would prevent the patient from undergoing any of the treatment options
- Psychiatric or addictive disorders preventing giving informed consent or undergoing any of the treatment options
- Pregnant or breast-feeding patients
- Patients unable to undergo audiometry, liver echography, ocular examinations
- Medical contra-indication to percutaneous liver biopsies
- Patients treated with systemic investigational drug within the past four weeks or topical investigational drug within the past seven days
- Any other surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of any drug. The investigator should be guided by evidence of any of the following: history of inflammatory bowel disease, gastritis, ulcers, gastrointestinal (GI) or rectal bleeding, history of major GI surgery such as gastrectomy, gastroenterostomy or bowel resection, history of pancreatic injury or pancreatitis, indications of impaired pancreatic function/injury as indicated by abnormal lipase or amylase, history or presence of impaired renal function as indicated by creatinine or BUN values above the upper limit of normal or history of urinary obstruction or difficulty in voiding
- History of non-compliance to medical regimens and patients who are considered potentially unreliable and/or uncooperative
- 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 washout
- Exclusion criterion for pediatric patients: Patient body weight which prevented the use of the smallest tablet strength for dosing

Withdrawal from the Study
Premature withdrawal from the study occurred for the following reasons:
- Adverse events (AEs)
- Abnormal laboratory values
- Abnormal test procedure results
- Unsatisfactory therapeutic results

- Patient's condition no longer required therapy
- Protocol violation
- Withdrawal of consent
- Lost to follow up
- Administrative problems
- Death

Reviewer's Comments. Inclusion criteria are acceptable. Exclusion criteria are extensive and eliminate a substantial proportion of the population likely to be candidates for Exjade treatment. The exclusion criteria will have to be considered in the final labeling. The rationale for withdrawals is acceptable.

Study Drugs

For patients randomized to Exjade, the initial daily oral dose was dependent on the LIC as follows:
- Patients with a screening LIC of 2 - 3 mg Fe/g dw received 5 mg/kg
- Patients with a screening LIC of >3 - 7 mg Fe/g dw received 10 mg/kg
- Patients with a screening LIC of >7-14 mg Fe/g dw received 20 mg/kg
- Patients with a screening LIC of >14 mg Fe/g dw received 30 mg/kg

No dose adjustment was made during the 1 year trial unless safety and efficacy markers indicated that a dose adjustment was necessary.

Exjade tablets were available at dose strengths of 125, 250 and 500 mg. Correct dosing was accomplished by using the proper number of tablets from each strength to achieve the weight dependent dose. The minimum daily dose was 125 mg. The dose was to be taken in the morning 30 minutes before breakfast. Tablets were to be dispersed in a glass of water by stirring for 1-3 minutes until the tablet had fully disintegrated, whereupon the entire glass of liquid was to be drunk.

For patients randomized to DFO, the initial dose was dependent on the LIC as follows:
- Patients with a screening LIC of 2 - 3 mg Fe/g dw received 20-30 mg/kg/day (but patients previously receiving DFO could remain on the previous dose)
- Patients with a screening LIC of >3 - 7 mg Fe/g dw received 25-35 mg/kg/day (but patients previously receiving DFO could remain on the previous dose)
- Patients with a screening LIC of >7-14 mg Fe/g dw received 35-50 mg/kg/day
- Patients with a screening LIC of >14 mg Fe/g dw received ≥50 mg/kg/day

DFO was administered as s.c. infusions for ≥8 hrs for 5 consecutive days a week as a 10% solution using a Microject Crono pump. No dose adjustment was made during the 1 year trial unless safety and efficacy markers indicated that a dose adjustment was necessary.

Dose adjustments for both Exjade and DFO were mainly based on the combined evaluation of safety markers indicative of over- or under-chelation. Where applicable, secondary efficacy parameters (potential surrogate markers such as serum ferritin) were also considered. It was planned that for Exjade, the majority of dose adjustments would be performed in steps of 10 mg/kg/day up to a maximum of 40 mg/kg/day. In individual cases, such as in pediatric patients, if prompted by safety concerns, or where baseline LIC levels had been close to 2 mg Fe/g dw, dose adjustment by steps of 5 mg/kg/day was also permitted. Dose adjustments for DFO were prescribed in steps of 5 or 10 mg/kg/day. Dose adjustments had to be approved in writing from Novartis.

During the course of the trial, only medications that had been commenced prior to entry could be continued, unless the patient received permission from the physician for other medications. Blood transfusions were continued as necessary to maintain the hemoglobin ≥9 g/dl.

Reviewer's Comments. Patients assigned to the DFO arm were allowed to remain on the dose of DFO they were receiving prior to study entry even when their LIC was relatively low. In retrospect, the sponsor believes that this decision biased the trial against Exjade particularly in those persons whose LIC was determined by SQUID since SQUID LIC was eventually found to be approximately 50% that of simultaneous LIC by biopsy. In contrast to the fixed initial dosing for Exjade that assigned many of these patients to low dose Exjade, patients already receiving DFO (the majority) were allowed to continue on higher doses (and usually did) even when LIC was relatively low.

Protocol Amendments

Amendment 1. (May 7, 2003). This amendment changed the exclusion based on absolute levels of urinary protein to a urinary protein/creatinine ratio >0.5 (mg/mg) and dictated Exjade discontinuation and redosing based on the protein/creatinine ratio.

Amendment 2. (Nov 28, 2004). This amendment changed the dosing regimen for different age groups based on changes in serum creatinine.

Amendment 3. (Sep 2, 2004). This amendment added QT/QTc analysis to comply with ICH Guideline E14. More importantly, it changed the acceptable weight threshold for analysis of liver biopsies from 1.0 to 0.5 gm, reduced the number of stains to two and eliminated the need for a second pathological opinion.

Other Changes

Because of discrepancies in the results of LIC by biopsy compared to SQUID in the first 14 patients, enrollment was suspended temporarily until the issue could be addressed. This caused some of the already randomized patients to have a run-in period that lasted up to 182 days. As a

result, in 27 patients the baseline liver biopsy occurred between 57 to 92 days prior to treatment initiation.

Six adult patients had baseline LIC determined by SQUID only because the liver biopsy specimen was too small or was lost. In some patients, the first liver biopsy was too small for adequate interpretation, so the determination of LIC was based on a second biopsy.

A guideline for dose changes required to manage skin reactions was introduced on June 30, 2003. This instructed investigators on the methods of decreasing or temporarily suspending, and then increasing, the dose of Exjade to control dermatological reactions to the drug.

After enrollment had closed, a review of the baseline LIC values indicated that the LIC values based on SQUID were approximately 50% of LIC values based on biopsy. Therefore, an analysis was performed on patients in a sub-study who had undergone SQUID, biopsy and MRI LIC determinations. This analysis confirmed the difference in LIC between SQUID and biopsy. The Program Safety Board and the Study Monitoring Committee were made aware of the analysis and a decision was made to continue the study as formulated because this did not seem to pose a safety risk. Some unspecified members of the Novartis team were also informed of the results.

Between December, 2003 and February, 2004, a problem in the measurement of serum ferritin was detected related to high serum ferritin (immunocomplex aggregates) and improper control of the assay that precluded detection of the measurement error. These were corrected by March, 2004, at which time all previously collected duplicate samples from the beginning of the study were reanalyzed.

Reviewer's Comments. The amendments do not compromise the interpretation of the study. The changes are more problematic because they focus on the validation problems with SQUID and because they call into question the accuracy, precision and reproducibility of the measurement of serum ferritin. If the sponsor has difficulty with measurements during a rigidly conducted clinical trial, who will be able to vouch for the validity of serum ferritins performed in multiple laboratories using different analytical methods if serum ferritin is to be used as a measure of initial dosing and long term efficacy of Exjade if it is approved?

Primary Endpoint.

The primary efficacy variable was either the success or failure of therapy in each arm of the trial. The definition of success was dependent on the difference in the LIC between baseline and the end of study as shown in the following table:

Definition of Success

LIC at baseline	Success
2-<7 mg Fe/g dw	Maintain LIC within the same range
≥7 mg Fe/g dw	Reduce LIC to <7 mg Fe/g dw
≥10 mg Fe/g dw	Reduce by at least 3 mg Fe/g dw

As noted above, there were multiple secondary efficacy endpoints.   One of the secondary endpoints for success analyzed at the request of the Division was an increase of <1 mg Fe/g dw in patients whose baseline LIC was 2-<7 mg Fe/g dw.

Reviewer's Comments. Although accepted by the Division, the primary endpoint is a surrogate endpoint since it does not necessarily address clinically significant morbidity or mortality. The main mortality in β-thalassemia is due to cardiac dysfunction whose etiology in β-thalassemia is probably multifactorial. Nonetheless, most of the literature in β-thalassemia has used LIC as a marker for morbidity for other organ involvement and as a surrogate for mortality. There is some information, however, that LIC does not completely correlate to the extent of cardiac hemosiderosis, the primary cause of mortality. Obviously, repetitive biopsy of the myocardium to measure iron concentrations in the heart is not acceptable. Newer MRI techniques seem promising but at present I believe that most persons in the field would accept LIC by biopsy as the standard for evaluation of efficacy in this clinical situation. It should be noted that the Division was in agreement with the primary endpoint planned by the sponsor.

Statistical Methods

All data were analyzed by treatment group (Exjade vs. DFO). Additional analyses were performed by age, sex, race, initial dose, baseline LIC and iron intake categories.

The primary objective of the study was to demonstrate non-inferiority of Exjade to DFO in decreasing LIC as assessed by liver biopsy after one-year treatment in β-thalassemia patients with transfusional hemosiderosis. The primary analysis was based on the success rate as defined in the primary endpoint above. Non-inferiority was defined to be established if the two sided 95% CI of the difference in success rate between the two arms of the trial was above –15%.

The sample size was selected to show non-inferiority at a 2-sided alpha level of 0.05 if the success rates of the DFO and Exjade treatment arms (p= 0.5) had maximal variance. Thus, 468 patients were required (234 per arm) to achieve a power of 90%. A sample size of 500 patients was selected in order to show non-inferiority to DFO and to achieve the secondary efficacy objectives of absolute and relative changes in LIC by having subgroups of adequate size.

Four populations were analyzed:
- **Intent to treat (ITT).** All randomized patients.
- **Safety.** All patients who received at least one dose of study medication.
- **Per Protocol 1 (PP-1).** All patients who received study drug who had an LIC (by the same methodology) at baseline and at study's end including those who discontinued study drug prematurely because of adverse events, an abnormal laboratory value, an abnormal test procedure or an iron overload related death.
- **Per Protocol 2 (PP-2).** All patients who had an LIC (by the same methodology) at baseline and at study's end.

Background and demographic characteristics were summarized by treatment group in the standard manner. Subgroups were based on dose cohort, age and country. Previous iron status was described. Multiple variables of Exjade dosing were established and analyzed. Prior and concomitant therapies were summarized.

Reviewer's Comments. The statistical methods and the populations analyzed appear acceptable. Please refer to the Statistical Review for additional information. The Division (via the statistical review in the October 1, 2004 pre-NDA meeting) had indicated that the efficacy of DFO would have to be established and that the margin of -15% would have to be justified in the NDA.

Safety Evaluation

The assessment of safety was based mainly on the frequency of AEs and on the number of laboratory values that fell outside of pre-determined ranges. Other safety data (e.g. ECGs, vital signs and special tests, particularly related to the liver, the kidneys, hearing and vision) were obtained in all patients. All safety data are presented in the safety population.

Safety was based on the following observations:
- Adverse events
- Laboratory evaluations
- Physical examinations
- ECGs, echocardiograms
- Auditory, ophthalmological tests
- Pediatric development tests

Patient narratives were provided for all patient deaths, SAEs believed related to study drug, and SAEs involving the kidney, heart, liver, skin, bone marrow, eyes and ears.

Safety evaluations were done by treatment group and for multiple subgroups.

No interim safety analyses were performed. The PSB reviewed all safety data at regular intervals.

Reviewer's Comments. The safety evaluation seems appropriate in light of the findings noted in preclinical studies. Developmental analysis is important in light of the fact that a prime target for the drug is the pediatric population.

Patients Studied

A total of 591 patients were randomized (297 Exjade, 294 DFO) and 586 (296 Exjade, 290 DFO) patients were treated (5 never commenced therapy). Ninety five percent (95%) of patients in each arm completed the trial. The reasons for discontinuation are listed in the table below.

Patient disposition

Disposition	ICL670 N=296 n (%)	DFO N=290 n (%)	All patients N=586 n (%)
Completed	279 (94.3)	278 (95.9)	557 (95.1)
Discontinued	17 (5.7)	12 (4.1)	29 (4.9)
Adverse events	7 (2.4)	1 (0.3)	8 (1.4)
Death	1 (0.3)	3 (1.0)	4 (0.7)
Protocol violation	2 (0.7)	2 (0.7)	4 (0.7)
Withdrawal of consent	7 (2.4)	6 (2.1)	13 (2.2)

Source: Reviewer table based on sponsor's submission

More patients in the Exjade arm discontinued study drug because of adverse events than did those in the DFO arm. There was no clear relationship between the dose of Exjade and its discontinuation. Discontinuation from the study because of withdrawal of consent was similar in both arms.

Protocol violations are shown in the following table and did not lead to discontinuation from the trial. Most violations were related to a non-evaluable post-treatment LIC. There were somewhat more protocol violations in the Exjade arm than in the DFO arm.

Number (%) of patients with protocol violations by treatment
Intention-to-treat population

Selection criteria	ICL670 N=297 n (%)	Deferoxamine N=294 n (%)	All patients N=591 n (%)
Pt. has not received treatment	1 (0.3)	4 (1.4)	5 (0.8)
No eval. 52 wk LIC and no safety disc.	20 (6.7)	13 (4.4)	33 (5.6)
Not evaluable post-Baseline LIC	26 (8.8)	17 (5.8)	43 (7.3)
Not evaluable 52 week LIC	28 (9.4)	17 (5.8)	45 (7.6)

Source: Sponsor submission page 198

The analysis populations are listed in the following table.

Number (%) of patients in analysis populations

Analysis Population	ICL670 N=297 n (%)	DFO N=294 n (%)	All patients N=591 n (%)
Intent-to-treat (ITT) population	297 (100.0)	294 (100.0)	591 (100.0)
Safety population	296 (99.7)	290 (98.6)	586 (99.2)
PP-1 population	276 (92.9)	277 (94.2)	553 (93.6)
PP-2 population	268 (90.2)	273 (92.9)	541 (91.5)

Source: Sponsor submission page 63

In an analysis of the subgroup by dose cohort compared to the average planned dose category, there was a difference in the intensity of administration of the two study drugs. Proportionally more patients in the DFO arm received higher than protocol specified doses of DFO compared to those in the Exjade arm than would have been expected. This was owing to the protocol that allowed patients already receiving DFO to continue their previous dose of drug irrespective of LIC, whereas patients in the Exjade arm were assigned to doses of the drug that were based exclusively on LIC. Forty seven patients in the Exjade arm and 43 patients in the DFO arm had LIC determined by SQUID only, mostly patients between the ages of 6-16 years of age. The sponsor has conducted a study of the relationship between the LIC measured by both SQUID and biopsy, and it is now known that SQUID underestimates the true LIC by a factor of approximately 2 as measured by biopsy. These subgroup analyses are shown in the following tables.

Number (%) of patients in analysis subgroups

Subgroup	ICL670 N=296 n (%)	DFO N=290 n (%)	All patients N=586 n (%)
Dose cohort (based on initial dose)			
5 mg/kg ICL / <25 mg/kg DFO	15 (5.1)	7 (2.4)	22 (3.8)
10 mg/kg ICL / 25-<35 mg/kg DFO	78 (26.4)	40 (13.8)	118 (20.1)
20 mg/kg ICL / 35-<50 mg/kg DFO	84 (28.4)	119 (41.0)	203 (34.6)
30 mg/kg ICL / ≥50 mg/kg DFO	119 (40.2)	124 (42.8)	243 (41.5)
Average planned dose category			
<7.5 mg/kg ICL / <25 mg/kg DFO	11 (3.7)	5 (1.7)	16 (2.7)
7.5-<15 mg/kg ICL / 25-<35 mg/kg DFO	85 (28.7)	48 (16.6)	133 (22.7)
15-<25 mg/kg ICL / 35-<45 mg/kg DFO	101 (34.1)	95 (32.8)	196 (33.4)
≥25 mg/kg ICL / ≥45 mg/kg DFO	99 (33.4)	142 (49.0)	241 (41.1)

Source: Sponsor submission page 64

Table 7-5 Number (%) of patients by age and baseline LIC method (PP-1 population)

LIC at baseline	ICL670			DFO			Total
	Biopsy	SQUID	Biopsy + SQUID	Biopsy	SQUID	Biopsy + SQUID	
	n (%)	n (%)	n (%)	n (%)	n (%)	N (%)	n (%)
Age < 6 years							
<7 mg Fe/g dw	4 (14.3)	1 (3.6)	5 (17.9)	4 (14.3)	2 (7.1)	6 (21.4)	11 (2.0)
>=7 mg Fe g/dw	20 (71.4)	3 (10.7)	23 (82.1)	19 (67.9)	3 (10.7)	22 (78.6)	45 (8.1)
Total	24 (85.7)	4 (14.3)	28 (100.0)	23 (82.1)	5 (17.9)	28 (100.0)	56 (10.1)
Age 6-<12 years							
<7 mg Fe/g dw	7 (11.1)	11 (17.5)	18 (28.6)	7 (10.5)	18 (26.9)	25 (37.3)	43 (7.8)
>=7 mg Fe g/dw	38 (60.3)	7 (11.1)	45 (71.4)	38 (56.7)	4 (6.0)	42 (62.7)	87 (15.7)
Total	45 (71.4)	18 (28.6)	63 (100.0)	45 (67.1)	22 (32.8)	67 (100.0)	130 (23.5)
Age 12-<16 years							
<7 mg Fe/g dw	8 (14.0)	17 (29.8)	25 (43.9)	8 (16.3)	9 (18.4)	17 (34.7)	42 (7.6)
>=7 mg Fe g/dw	30 (52.6)	2 (3.5)	32 (56.1)	30 (61.2)	2 (4.1)	32 (65.3)	64 (11.6)
Total	38 (66.7)	19 (33.3)	57 (100.0)	38 (77.6)	11 (22.5)	49 (100.0)	106 (19.2)
Age >= 16 years							
<7 mg Fe/g dw	34 (26.6)	3 (2.3)	37 (28.9)	36 (27.1)	3 (2.3)	39 (29.3)	76 (13.7)
>=7 mg Fe g/dw	88 (68.8)	3 (2.3)	91 (71.1)	92 (69.2)	2 (1.5)	94 (70.7)	185 (33.5)
Total	122 (95.3)	6 (4.7)	128 (100.0)	128 (96.2)	5 (3.8)	133 (100.0)	261 (47.2)

LIC at baseline	ICL670			DFO			Total
	Biopsy	SQUID	Biopsy + SQUID	Biopsy	SQUID	Biopsy + SQUID	
	n (%)	n (%)	n (%)	n (%)	n (%)	N (%)	n (%)
All Patients							
<7 mg Fe/g dw	53 (19.2)	32 (11.6)	85 (30.8)	55 (19.9)	32 (11.6)	87 (31.4)	172 (31.1)
>=7 mg Fe g/dw	176 (63.8)	15 (5.4)	191 (69.2)	179 (64.6)	11 (4.0)	190 (68.6)	381 (68.9)
Total	229 (83.0)	47 (17.0)	276 (100.0)	234 (84.5)	43 (15.5)	277 (100.0)	553 (100.0)

Source: Sponsor submission page 65-66

Reviewer's Comments. There was a high rate of completion by patients in the trial. More patients in the Exjade arm discontinued from the study because of adverse events. The primary protocol violation was the absence of an evaluable liver biopsy at the end of the study and there were slightly more such patients in the Exjade arm than in the DFO arm. Because of the use of SQUID in children, the dosing of Exjade may have been sub-optimal in that population, and this bias in favor of DFO may have been compounded by the allowance in the protocol for a continuation of the pre-existing dose of DFO in patients assigned to the DFO arm.

Patient demographics

Patient age, sex, race and weight were equally distributed in the safety population as shown in the table below.

Patient demographics

Variable Statistic	ICL670 N=296	Deferoxamine N=290	All patients N=586
Age (years)			
n	296	290	586
Mean ± SD	17 ± 9.47	17.3 ± 9.96	17.2 ± 9.71
Median	15	15.5	15
Min - Max	2 - 49	2 - 53	2 – 53
Age group (years)			
<6	30(10.1%)	28 (9.7%)	58 (9.9%)
6 - <12	67 (22.6%)	68 (23.4%)	135 (23.0%)
12 - <16	57 (19.3%)	49 (16.9%)	106 (18.1%)
16 - <50	142 (48.0%)	144 (49.7%)	286 (48.8%)
50 - <65	0 (0.0%)	1 (0.3%)	1 (0.2%)
Sex			
Male	140 (47.3%)	142 (49.0%)	282 (48.1%)
Female	156 (52.7%)	148 (51.0%)	304 (51.9%)
Race			
Caucasian	263 (88.9%)	251 (86.6%)	514 (87.7%)
Black	2 (0.7%)	1 (0.3%)	3 (0.5%)
Oriental	9 (3.0%)	10 (3.4%)	19 (3.2%)
Others	22 (7.4%)	28 (9.7%)	50 (8.5%)
Height (cm)			
n	295	290	585
Mean ± SD	145 ± 20.94	144.9 ± 21.37	144.9 ± 21.13
Median	150	150	150
Min - Max	84 - 186	84 - 181	84 – 186
Weight (kg)			
n	295	290	585
Mean ± SD	43.1 ± 16.65	42.9 ± 16.65	43 ± 16.64
Median	44.3	46.1	45
Min - Max	11.4 - 87.9	12 - 90.2	11.4 - 90.2
Weight group (kg)			
<15	7 (2.4%)	8 (2.8%)	15 (2.6%)
15 - <35	91 (30.7%)	88 (30.3%)	179 (30.5%)
35 - <55	120 (40.5%)	116 (40.0%)	236 (40.3%)
55 - <75	69 (23.3%)	73 (25.2%)	142 (24.2%)
>=75	8 (2.7%)	5 (1.7%)	13 (2.2%)

Source: Sponsor submission page 67

The frequencies of a history of hepatitis B (6.8%), hepatitis C (24.6%), both hepatitis B and C (3.8%), splenectomy (32.6%), splenomegaly (4.8%), hepatomegaly (3.1%), hypogonadism (13.8%), hypothyroidism (7.8%) and cardiac disorders (3.9%) were similar in both treatment groups. Only 24.7% of all patients had a history of an elevated blood iron. Only 1 patient had a history of an elevated transaminase. Diabetes mellitus was present in 4.1% of patients, hemosiderosis in 6.5%, osteoporosis/osteopenia in 21.9 % and amenorrhea in 5.8%. These were generally equally distributed between both treatment arms.

Reviewer's Comments. The patients in each arm of the trial were reasonably well matched for demographics and medical backgrounds. There are almost no black patients in the study but this might reflect the low frequency of β-thalassemia in this population in the countries where the trial was performed.

Medication Exposure

The initial dose assignments are shown in a previous table. The average daily dose for the safety population is shown in the following table.

Table 8-2 Average daily dose during study – by LIC dosing category

| | Baseline LIC in mg Fe/g dw (regardless of method) | | | |
	<=3	>3-7	>7-14	>14
ICL670 (N=296)	N=15	N=78	N=84	N=119
Protocol proposed dose	5 mg/kg	10 mg/kg	20 mg/kg	30 mg/kg
Average daily dose (mg/kg/day)				
Mean ± SD	6.2 ± 1.6	10.2 ± 1.2	19.4 ± 1.7	28.2 ± 3.5
Median	5.0	10.0	20.0	30.0
Minimum-Maximum	4.3 – 8.7	5.6 – 16.3	9.9 – 21.4	11.0 – 30.0
DFO (N=290)	N=14	N=79	N=91	N=106
Protocol proposed dose	20-30 mg/kg	25-35 mg/kg	35-50 mg/kg	>=50 mg/kg
Average daily dose (mg/kg/day)				
Mean ± SD	33.9 ± 9.9	36.7 ± 9.2	42.4 ± 6.6	51.6 ± 5.8
Median	30.0	35.0	40.8	51.0
Minimum-Maximum	23.0 – 52.6	20.0 – 75.6	21.0 – 70	30.0 – 66.1

Source: Sponsor submission page 70

In the PP-1 population, 85 patients in the Exjade arm and 87 patients in the DFO arm had LIC values <7 mg Fe/g dw at baseline. Of those, 15/85 (17.6%) patients in the Exjade arm initially received the lowest daily dose of Exjade (5 mg/kg) and the remaining 70/85 (82.4%) patients received 10 mg/kg. No patient with an LIC <7 mg Fe/g dw received more than 10 mg/kg. In the group with an LIC of <7 mg Fe/g dw enrolled in the DFO arm, 4/87 (4.6%) patients received the lowest DFO dose (<25 mg/kg), 35/87 received 25-<35 mg/kg and the remaining 48/87 (55.2%) patients received a dose of ≥35 mg/kg.

Study drug interruptions, average daily dose and relative dose intensity are shown in the following table. For both Exjade and DFO, the relative dose intensity was approximately 1, indicating that the expected and actual dosing were nearly identical.

Study drug interruptions, average daily dose and relative dose intensity

Study drug administration	ICL670 N=296	DFO N=290	All patients N=586
Number of interruptions n (%)			
0	233 (78.7%)	236 (81.4%)	469 (80.0%)
1	40 (13.5%)	37 (12.8%)	77 (13.1%)
2	16 (5.4%)	13 (4.5%)	29 (4.9%)
3	3 (1.0%)	1 (0.3%)	4 (0.7%)
>3	4 (1.4%)	3 (1.0%)	7 (1.2%)
Total length of interruptions (days)			
1 interruption			
n	40	37	77
Mean ± SD	10.4 ± 14.53	7.2 ± 9.58	8.8 ± 12.43
Minimum - Maximum	1 - 63	1 - 56	1 – 63
Median	5	4	5
2 interruptions			
n	16	13	29
Mean ± SD	16.1 ± 16.82	20.8 ± 31.92	18.2 ± 24.37
Minimum - Maximum	2 - 67	3 - 125	2 – 125
Median	10	12	11
Average daily dose (mg/kg/day)			
Mean ± SD	19.9 ± 8.29	43.8 ± 9.73	31.7 ± 15
Minimum – Maximum	4.3 - 30	20 - 75.6	4.3 - 75.6
Median	20.0	44.1	30.0
Relative dose intensity			
Mean ± SD	0.98 ± 0.144	1.0 ± 0.1	0.99 ± 0.125
Minimum - Maximum	0.37 - 1.75	0.68 - 1.86	0.37 - 1.86
Median	1.0	1.0	1.0

Source: Sponsor submission page 69

The frequency and characteristics of drug interruptions were similar for the 2 drugs. Dose adjustments during the trial occurred in 63% of patients in the Exjade arm and in 67% of patients in the DFO arm. Dose adjustment because of AEs or laboratory abnormalities was twice as common in the Exjade arm as in the DFO arm, mostly because of protocol required changes when the serum creatinine level rose. Dose increases due to lack of efficacy were more common in the Exjade arm and occurred in 7/15 patients on the 5 mg/kg dose and in 10/78 patients on the 10 mg/kg dose. Dose decreases were more common in the Exjade arm in patients treated with higher doses because of changes in serum creatinine and skin rashes. The reasons for dose adjustments are shown in the following table.

Table 8-4 Reasons for dose adjustments

Dose adjustment	ICL670 N=296	DFO N=290	All patients N=586
Dose increase due to lack of efficacy (patients)	18	4	22
Time to dose increase (weeks on treatment)	19.3-63.0	12.1-15.3	12.1-63.0
Dose decrease due to AE/lab test abnormality (patients)	33	4	37
Interruptions due to AE/lab test abnormality (patients)	63	52	115
Interruptions due to AE/lab test abnormality (episodes)	132	77	209

Source: Sponsor submission page 72

The duration of study drug exposure was ≥48 weeks in about 95% of patients in both arms. However, there were 8 patients in the Exjade arm who received the drug for 12-<24 weeks while this shortened duration was experienced by only a single patient in the DFO arm.

Concomitant medications were taken by approximately 90% of all patients in each arm of the trial with the most frequent being analgesics, mucolytics, corticosteroids, antibiotics, alimentary agents, folic acid and ophthalmological agents.

Blood transfusions were administered to patients in both arms of the study at a similar frequency with the average of one transfusion every three weeks. Similar amounts of blood (mean ± SD, 7.93 ml/kg ± 2.55) per transfusion were given to both groups of patients. There was an inverse relationship between age and the average amount of blood in ml/kg given per transfusion.

Reviewer's Comments. The two arms of the trial appear reasonably balanced in regard to drug exposure but several points should be emphasized:
- *The initial dose of Exjade for persons with low LIC (many determined by SQUID and mostly in pediatric patients) was that included in the protocol. The rationale for the low dose of Exjade (5-10 mg/kg/d) was that the sponsor was concerned that for patients with a low LIC there might be a danger of over-chelation of iron even though the dose was in the range that had been shown in other studies to be ineffective in reducing LIC. The initial dose of DFO was generally higher than that included in the protocol because patients were allowed to remain on the pre-existing dose of DFO regardless of the LIC.*
- *Dose increases for efficacy reasons and dose interruptions or decreases for AEs occurred more often in Exjade treated patients than in DFO treated patients.*
- *Eight patients in the Exjade group received study drug for 12-<24 weeks while this shortened treatment period occurred in only 1 patient receiving DFO.*

Efficacy Results

Primary endpoint.
Exjade was to be declared non-inferior to DFO if the lower limit of the 2-sided 95% CI for the difference in the percentage of treatment success between Exjade and DFO in the PP-1 population was above -15%. For the entire PP-1 population, this goal was not achieved. This

led the sponsor to segment the PP-1 population into multiple subcategories to determine whether or not non-inferiority could be achieved for any subgroup. The following table shows the efficacy analyses on the entire PP-1 population and its subcategories.

Table 9-1 Success rates based on change in LIC (PP-1 population)

	ICL670 5 mg/kg N=15	ICL670 10 mg/kg N=70	ICL670 20 mg/kg N=79	ICL670 30 mg/kg N=112	ICL670 All pts N=276	DFO All pts N=277
Biopsy & SQUID	N=15	n=70	n=79	n=112	n=276	n=277
Success rate (n (%))	6 (40.0)	28 (40.0)	29 (36.7)	83 (74.1)	146 (52.9)	184 (66.4)
95% CI	[16.3, 67.7]	[28.5, 51.5]	[26.1, 47.3]	[66.0, 82.2]	[47.0, 58.8]	[60.9, 72.0]
Difference and 95% CI					-13.5 [-21.6, -5.4]	
LIC < 7 mg Fe/g dw	N=15	n=70			n=85	n=87
Success rate (n (%))	6 (40.0)	28 (40.0)			34 (40.0)	72 (82.8)
95% CI	[16.3, 67.7]	[28.5, 51.5]			[29.6, 50.4]	[74.8, 90.7]
Difference [95% CI]					-42.8 [-55.9, -29.7]	
LIC ≥ 7 mg Fe/g dw			n=79	n=112	n=191	n=190
Success rate (n (%))			29 (36.7)	83 (74.1)	112 (58.6)	112 (58.9)
95% CI			[26.1, 47.3]	[66.0, 82.2]	[51.7, 65.6]	[52.0, 65.9]
Difference [95% CI]					-0.3 [-10.2, 9.6]	
Biopsy	n=8	n=45	n=64	n=112	n=229	n=234
Success rate (n (%))	0 (0.0)	12 (26.7)	22 (34.4)	83 (74.1)	117 (51.1)	147 (62.8)
95% CI	[0, 36.9]	[13.7, 39.6]	[22.7, 46.0]	[66.0, 82.2]	[44.6, 57.6]	[56.6, 69.0]
Difference [95% CI]					-11.7 [-20.7, -2.8]	
LIC < 7 mg Fe/g dw	n=8	n=45			n=53	n=55
Success rate (n (%))	0 (0.0)	12 (26.7)			12 (22.6)	42 (76.4)
95% CI	[0, 36.9]	[13.7, 39.6]			[11.4, 33.9]	[65.1, 87.6]
Difference [95% CI]					-53.7 [-69.6, -37.8]	
LIC ≥ 7 mg Fe/g dw			n=64	n=112	n=176	n=179
Success rate (n (%))			22 (34.4)	83 (74.1)	105 (59.7)	105 (58.7)
95% CI			[22.7, 46.0]	[66.0, 82.2]	[52.4, 66.9]	[51.4, 65.9]
Difference [95% CI]					1.0 [-9.2, 11.2]	
SQUID	n=7	n=25	n=15	n=0	n=47	n=43
Success rate (n (%))	6 (85.7)	16 (64.0)	7 (46.7)	-	29 (61.7)	37 (86.0)
95% CI	[42.1, 99.6]	[45.2, 82.8]	[21.4, 71.9]	-	[47.8, 75.6]	[75.7, 96.4]
LIC < 7 mg Fe/g dw	n=7	n=25			n=32	n=32
Success rate (n (%))	6 (85.7)	16 (64.0)			22 (68.8)	30 (93.8)
95% CI	[42.1, 99.6]	[45.2, 82.8]			[52.7, 84.8]	[85.4, 100]
LIC ≥ 7 mg Fe/g dw			n=15	n=0	n=15	n=11
Success rate (n (%))			7 (46.7)	-	7 (46.7)	7 (63.6)
95% CI			[21.3, 73.4]	-	[21.3, 73.4]	[30.8, 89.1]

Source: Sponsor submission page 77

The sponsor wishes to concentrate on a segment of the table above that is extracted by me in the table below. These are the PP-1 patients whose LIC ≥7 mg Fe/g dw was determined by biopsy (not by SQUID) and were therefore treated with Exjade at a dose of 20 mg/kg (64 patients) or with Exjade at a dose of 30 mg/kg (112 patients). When these 2 subgroups are combined (176

patients) and then compared to all similar patients (179 patients) who were treated with DFO at doses of 35-≥50 mg/kg, the success rates are 59.7% (105/176 patients) and 58.7% (105/179 patients) , respectively. The 95% CI (-9.2, 11.2) of the point estimate for this subset of patients, therefore, is within the CI of the delta margin of -15 and establishes the non-inferiority of Exjade compared to DFO for this subset of patients.

Success rates for patients with biopsy documented LIC ≥7 mg Fe/g dw

ICL Dose	20 mg/kg	30 mg/kg	All ICL	DFO
LIC ≥ 7 mg Fe/g dw	n=64	n=112	n=176	n=179
Success rate (n (%))	22 (34.4)	83 (74.1)	105 (59.7)	105 (58.7)
95% CI	[22.7, 46.0]	[66.0, 82.2]	[52.4, 66.9]	[51.4, 65.9]
Difference [95% CI]			1.0 [-9.2, 11.2]	

Source: Sponsor submission page 77

Non-inferiority could also be demonstrated in the subgroup of patients whose LIC was ≥7 mg Fe/g dw whether LIC was determined by biopsy or SQUID as shown in the following segment of the table.

Success rates for patients with biopsy or SQUID documented LIC ≥7 mg Fe/g dw

ICL Dose	20 mg/kg	30 mg/kg	All ICL	DFO
LIC ≥ 7 mg Fe/g dw	n=79	n=112	n=191	n=190
Success rate (n (%))	29 (36.7)	83 (74.1)	112 (58.6)	112 (58.9)
95% CI	[26.1, 47.3]	[66.0, 82.2]	[51.7, 65.6]	[52.0, 65.9]
Difference [95% CI]			-0.3 [-10.2, 9.6]	

Source: Sponsor submission page 77

Non-inferiority of Exjade compared to DFO was also achieved in the ITT and PP-2 populations when these same subgroups were analyzed. Non-inferiority could not be established for the entire ITT or PP-2 populations.

The sponsor argues that the inability to achieve non-inferiority of Exjade compared to DFO can be attributed to SQUID (because it underestimates LIC by a factor of 2) and the leniency of the protocol (because it allowed patients who were receiving DFO to remain on their pre-existing dose of DFO rather than receiving the lower dose that was specified by the protocol for DFO naïve patients).

Reviewer's Comments. These results are problematic. Analyses should be prespecified, not retrospective. The identification of a subgroup in which efficacy is demonstrated would usually suggest that a new prospective study be performed in that population. However, the sponsor's argument has merit even though the sponsor's predicament is of its own devise. Almost all patients enrolled in the study had been receiving DFO prior to enrollment (289/296 patients in the Exjade arm, 282/290 patients in the DFO arm). It was believed unethical to reduce the dose of DFO in patients assigned to DFO who appeared to be responsive to a pre-existing dose of DFO. Therefore, most patients received more DFO than specified by the protocol in all 4 LIC

groups assigned to the DFO arm. However, for patients assigned to Exjade, initial dosing was based entirely on LIC, even for those whose LIC was determined by SQUID. As noted before, LIC by SQUID is approximately 50% of that by biopsy. Additionally, the secondary endpoint of the change in LIC in the subgroup of patients whose LIC was ≥7 mg Fe/g dw had been prespecified by the sponsor as noted in the next immediate paragraph.

Secondary endpoints.
1. Liver iron concentrations. Mean LICs at baseline in the PP-2 population were markedly different based on whether the determination was made by biopsy or by SQUID. SQUID LICs (6.0-6.3 mg Fe/g dw) were less than 50% of biopsy LICs (14.5-15.7 mg Fe/g dw) as shown in the following table.

Liver iron concentration (mg Fe/g dw) at baseline (PP-2 population)

Statistics	ICL670 N=268	DFO N=273
Biopsy	**N=224**	**N=230**
Mean ± SD	15.7 ± 10.11	14.5 ± 9.56
Minimum – Maximum	2.1 - 48.1	2.2 - 55.1
P25 - P75	7.3 - 22.0	7.3 - 19.5
Median	13.8	12.4
SQUID	**N=44**	**N=43**
Mean ± SD	6.0 ± 2.77	6.3 ± 3.31
Minimum – Maximum	2.4 - 13.2	2.1 - 16.4
P25 - P75	4.3 - 8.0	4.0 - 7.7
Median	5.5	5.6

Source: Sponsor submission page 79

In patients with a baseline LIC ≥7 mg Fe/g dw determined by biopsy, there was a significant difference between LIC from baseline to end of study in patients treated with either Exjade (-5.6 ± 8.21mg Fe/g dw) or DFO (-4.4 ± 5.98 mg Fe/g dw). There was no difference in change in LIC from baseline to end of study between the Exjade arm and the DFO arm. A change from baseline to end of study could not be demonstrated in either Exjade or DFO patients when the SQUID measurement of LIC was ≥7 mg Fe/g dw. These are shown in the following table.

Table 9-3 Change in LIC in patients with LIC greater or equal to 7 mg Fe/g dw at baseline (PP-2 population)

Statistics	ICL670 N=185	DFO N=186	Difference (ICL670-DFO) adjusted on baseline
Biopsy & SQUID			
n	185	186	
Mean ± SD	-5.3 ± 8.04	-4.3 ± 5.83	-0.56 ± 0.623
95% CI			[-1.79, 0.66]
p-value	p<0.001 (S)*		p=0.367 (NS)**
Biopsy			
n	172	175	
Mean ± SD	-5.6 ± 8.21	-4.4 ± 5.98	-0.65 ± 0.661
95% CI			[-1.95, 0.65]
p-value	p<0.001 (S)*		p=0.325 (NS)**
SQUID			
n	13	11	
Mean ± SD	-1.5 ± 3.69	-2.9 ± 2.32	1.19 ± 1.342
95% CI			[-1.60, 3.98]
p-value	p=0.160 (NS)*		p=0.386 (NS)**

Source: Post-text Table 9.2-16
* t-test for one sample (one sided): if p<0.025, significant difference (S) of the change from baseline in the ICL670 group.
** Covariance analysis with baseline as covariate: if p<0.05, significant difference(S)in changes between the 2 groups at EOS.
NS = not significant

There was a direct relationship (with a fairly wide scatter) between LIC on biopsy and serum ferritin both at baseline and at end of study. For patients receiving Exjade (5-10 mg/kg/d) whose baseline LIC was ≤7 mg Fe/g dw, there was an increase in both mean LIC and serum ferritin at study's end. For patients with baseline LIC >7-14 mg Fe/g dw, mean LIC and serum ferritin were unchanged at end of study (all of these patients received an initial daily dose of Exjade of 20 mg/kg). For patients with LIC >14 mg Fe/g dw, mean LIC (24.2 ± 7.82 fell to 15.3 ± 9.38) and serum ferritin (3769 ± 2379 fell to 2858 ± 2092) declined at the end of study (all of these patients had received an initial daily dose of 30 mg/kg). For patients receiving DFO whose baseline LIC was ≤7 mg Fe/g dw, there was no change in mean LIC or serum ferritin. For patients with baseline LIC >7-14 mg Fe/g dw, mean LIC and serum ferritin were slightly decreased at the end of study. . For patients with LIC >14 mg Fe/g dw, mean LIC (23.9 ± 8.06 fell to 17.0 ± 8.66) and serum ferritin (3627 ± 2451 fell to 2544 ± 1911) declined at the end of study. This is summarized in the following table.

Table 9-4 LIC and serum ferritin in patients with biopsy (PP-2 and Safety population)

		ICL670			DFO		
		Baseline	EOS	Change	Baseline	EOS	Change
LIC ≤ 3	LIC	2.5 ± 0.21	10.4 ± 1.75	7.8 ± 1.9	2.7 ± 0.28	3.1 ± 1.12	0.4 ± 1.26
	Ferritin	1370 ± 904	2525 ± 1107	1155 ± 339	1366 ± 660	1476 ± 756	167 ± 501
LIC >3-7	LIC	4.9 ± 1.08	10.1 ± 4.21	5.1 ± 3.93	5.2 ± 1.22	5.6 ± 2.63	0.4 ± 2.76
	Ferritin	1707 ± 771	2560 ± 1208	864 ± 857	1523 ± 701	1512 ± 832	-21 ± 447
LIC >7-14	LIC	10.6 ± 2.08	10.5 ± 4.72	-0.1 ± 4.86	10.6 ± 2.03	8.8 ± 2.99	-1.8 ± 2.96
	Ferritin	2136 ± 1049	2108 ± 1095	-42 ± 673	2124 ± 874	1824 ± 892	-316 ± 573
LIC >14	LIC	24.2 ± 7.82	15.3 ± 9.38	-8.9 ±8.07	23.9 ± 8.06	17.0 ± 8.66	-6.5 ± 6.95
	Ferritin	3769 ± 2379	2858 ± 2092	-926 ± 1416	3627 ± 2451	2544 ± 1911	-1001 ± 1435

Source: Sponsor submission page 80

The changes in LIC determined by biopsy for patients receiving either Exjade or DFO are demonstrated in the next 2 figures.

Figure 9-2 Change in LIC (Biopsy) by dose of ICL670 (PP-2 population)
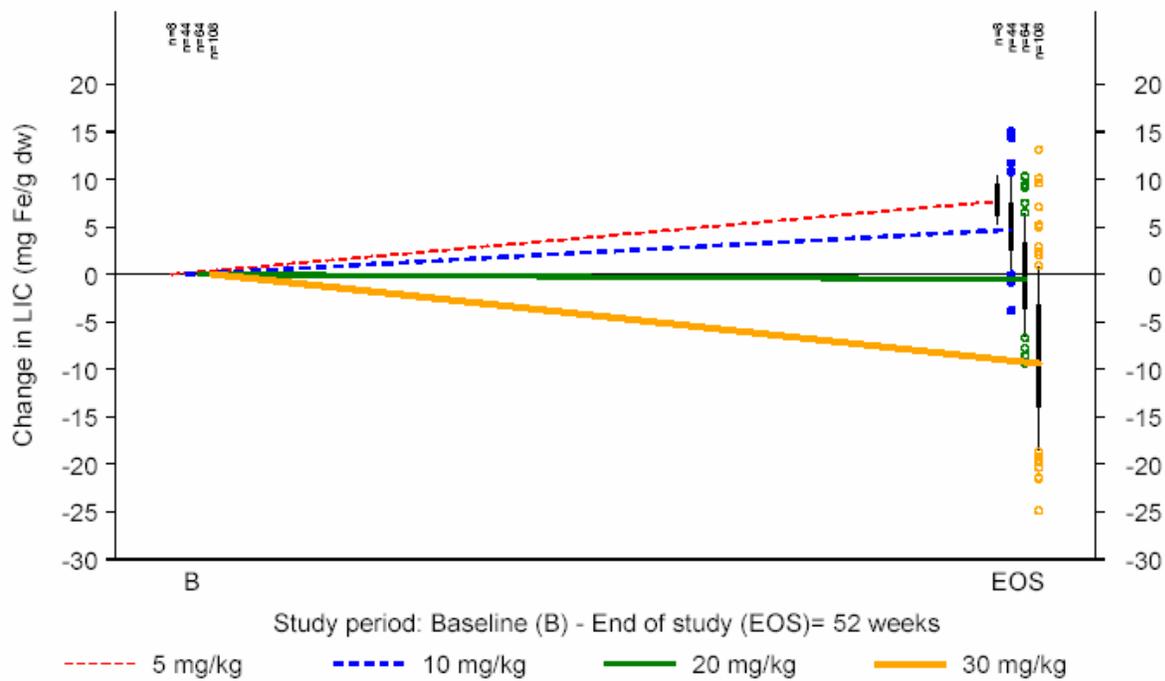
Source: Sponsor submission page 81

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Figure 9-4 Change in LIC (Biopsy) by dose of DFO (PP-2 population)

Source: Sponsor submission page 82
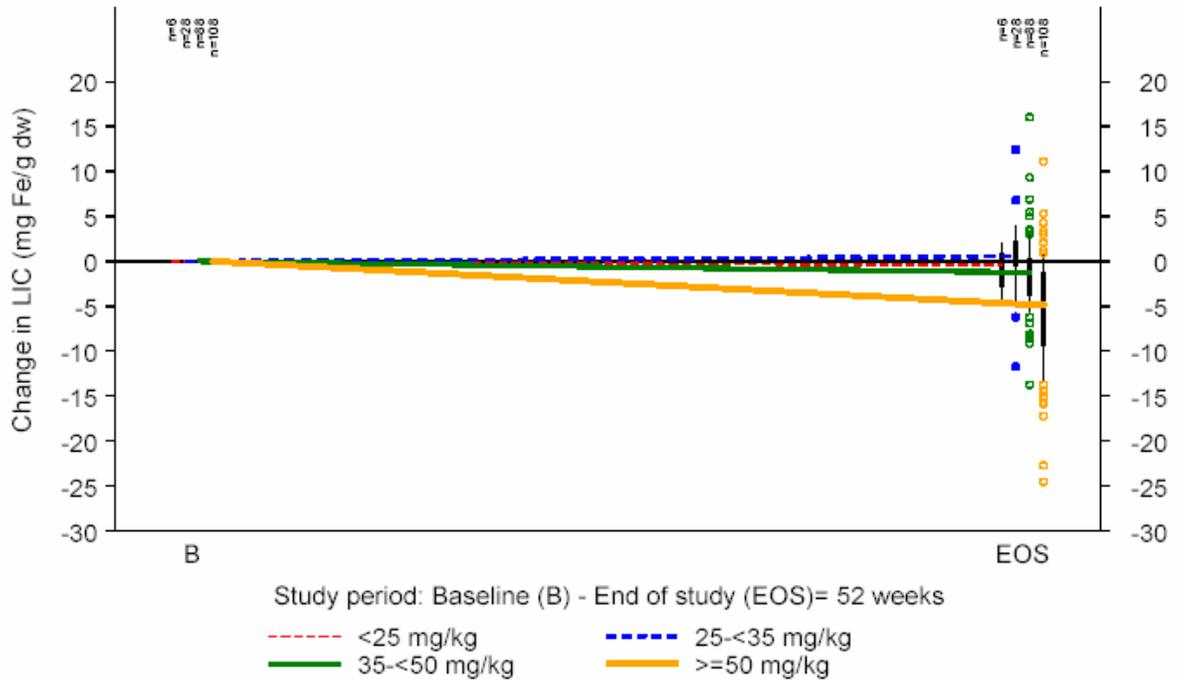
The change in LIC by biopsy for both Exjade and DFO by dose administered is presented in the following table. The data indicate that Exjade at a low dose (5-10 mg/kg) is not capable of stabilizing or decreasing LIC, but Exjade at a dose of 20 mg/kg does stabilize LIC and at a dose of 30 mg/kg decreases LIC. These results are consistent with the earlier PD studies of dose/response effect in patients being chronically transfused. In contrast, DFO was able to stabilize LIC at low doses and to decrease LIC at higher doses. The data are presented in the following table.

Table 9-5 Change in LIC (Biopsy) by dose (PP-2 population)

Statistics	ICL670 N=224	DFO N=230	Difference (ICL670-DFO) adjusted on baseline
Dose cohort: 5 mg/kg ICL/ <25 mg/kg DFO			
n	8	6	
Mean ± SD	7.8 ± 1.9	-0.9 ± 2.52	6.85 ± 1.219
95% CI			[4.17, 9.53]
Dose cohort: 10 mg/kg ICL670/ 25 - <35 mg/kg DFO			
n	44	28	
Mean ± SD	5.1 ± 3.93	0.6 ± 4.12	4.24 ± 0.95
95% CI			[2.34, 6.13]
Dose cohort: 20 mg/kg ICL670/ 35 - <50 mg/kg DFO			
n	64	88	
Mean ± SD	-0.1 ± 4.86	-1.4 ± 4.02	1.34 ± 0.717
95% CI			[-0.07, 2.76]
p-value	p=0.844 (NS)*		p=0.063 (NS)**
Dose cohort: 30 mg/kg ICL670/ ≥50 mg/kg DFO			
n	108	108	
Mean ± SD	-8.9 ± 8.07	-5.8 ± 6.26	-2.03 ± 0.923
95% CI			[-3.85, -0.21]
p-value	p<0.001 (S)*		p=0.029 (S)**

Source: Post-text Table 9.2-12

* t-test for one sample (one sided): if p<0.025, significant difference (S) of the change from baseline in the ICL670 group.

** Covariance analysis with baseline as covariate: if p<0.05, significant difference (S) in changes between the 2 groups at EOS.

NS = not significant

Exjade at a dose of 30 mg/k/d appeared to cause a greater decrease in LIC by biopsy (-8.9 ± 8.07 mg Fe/g dw) than did DFO at doses in excess of 50 mg/kg/d (-5.8 ± 6.26 mg Fe/g dw) (p=0.029).   However, one subgroup of patients who responded more favorably to the administration of DFO than to Exjade, even at high dose, was the subgroup of patients less than age 6 years.

Reviewer's Comments. Analysis of this secondary endpoint reprises the analysis of the primary efficacy endpoint, but provides data to support a significant dose-response effect for Exjade. Exjade appears not to be beneficial at doses of 5-10 mg/kg/d even in patients whose LIC by biopsy was <7 mg Fe/g dw, suggesting that at those doses, chronic transfusion therapy overwhelms Exjade's ability to eliminate iron. Exjade at a dose of 20 mg/k/d appears to be able to maintain homeostasis of iron balance in transfused patients, but it is only at a dose of 30 mg/kg/d that Exjade matches the ability of DFO to induce a

negative iron balance in the face of repeated transfusion. Therefore, it appears that even for patients whose LIC is <7 mg Fe/g dw, the dose of Exjade would have to be at least 20 mg/k/d or even 30 mg/kg/d to prevent progressive overloading of iron. Since some of the adverse events associated with Exjade are dose related, the safety experience in this trial may not be predictive of the true incidence of these adverse events when effective doses of Exjade are employed. An important point to consider in the use of the drug is that, even at doses of 20-30 mg/k/d, Exjade may not be as therapeutically effective as DFO in children aged 6 years or younger. This pediatric population is an important target group and is likely to benefit from chelation therapy.

2. Iron Balance. The average iron intake for the safety population (exclusive of dietary iron) from blood transfusion was 0.40 ± 0.113 mg/kg. Iron excretion in the PP-2 population was based on changes in LIC at baseline and at end of study and then determining total body iron stores (TBIS) at each period by the formula ($TBIS_{in\ mg/kg} = 10.6 \times LIC_{in\ mg\ Fe/g\ dw}$) (5). The average daily iron excretion rate for patients whose LIC was determined by liver biopsy was 0.45 ± 0.252 mg/kg in the Exjade treated patients and 0.47 ± 0.194 mg in the DFO treated patients. Iron balance, calculated as the ratio of excretion/intake, was dose dependent for both drugs but more so for Exjade than DFO as shown in the following table.

Table 9-9 Iron balance (based on biopsy) by dose (PP-2 population)

	Ratio Fe excretion/Fe intake	
	ICL670 N=224	DFO N=230
Dose cohort : 5 mg/kg ICL670/25-<35 mg/kg DFO		
N	8	6
Mean ± SD	0.32 ± 0.203	1.06 ± 0.215
Minimum - Maximum	0.1 - 0.68	0.82 - 1.31
Median	0.35	1.06
Dose cohort : 10 mg/kg ICL670/25-<35 mg/kg DFO		
N	44	28
Mean ± SD	0.55 ± 0.378	0.91 ± 0.378
Minimum - Maximum	-0.78 - 1.36	-0.34 - 1.63
Median	0.55	0.93
Dose cohort : 20 mg/kg ICL670/35-<50 mg/kg DFO		
N	64	88
Mean ± SD	1.01 ± 0.418	1.1 ± 0.377
Minimum - Maximum	0.0 - 2.08	-0.55 - 2.51
Median	1.0	1.07
Dose cohort: 30 mg/kg ICL670/≥50 mg/kg DFO		
N	108	108
Mean ± SD	1.67 ± 0.716	1.4 ± 0.511
Minimum - Maximum	0.1 - 4.47	0.04 - 3.78
Median	1.62	1.34

Source: Sponsor submission page 87

Reviewer's Comments. This secondary endpoint analysis is consistent with the findings of the LIC by biopsy. Doses of Exjade of 5-10 mg/kg/d are insufficient to maintain pace with the increasing iron burden from required blood transfusions. Exjade in a dose of 20 mg/kg/d maintains iron homeostasis, and in a dose of 30 mg/kg/d is capable of keeping pace with required blood transfusions and inducing iron loss that reduces extant excess body stores. DFO is able to maintain iron homeostasis over a wider range of doses but appears to be less able than Exjade to induce iron loss at the highest recommended doses of the two agents. Patients whose LIC was determined by SQUID are not included in this analysis.

3. Serum Ferritin. Serum ferritin levels mirror the changes in the LIC for patients treated with either Exjade or DFO, although there are extreme variations around the mean values. This is illustrated in the following table.

Table 9-11 Changes in serum ferritin from baseline (Safety population)

	ICL670 N=296	DFO N=290
Dose cohort: 5 mg/kg ICL670/ <25 mg/kg DFO		
N	15	6
Mean ± SD	1188.6 ± 700.17	-59.8 ± 480.35
Minimum - Maximum	370 – 3362	-581 - 852
P25 – P75	830 – 1478	-212 - -71
Median	892	-173.5
Dose cohort: 10 mg/kg ICL670/ 25-<35 mg/kg DFO		
N	73	40
Mean ± SD	832.8 ± 817.42	37.7± 572.75
Minimum - Maximum	-865 – 3609	-1377 – 1446
P25 – P75	374 – 1320	-294.5 – 326
Median	667	69
Dose cohort: 20 mg/kg ICL670/ 35-<50 mg/kg DFO		
N	80	117
Mean ± SD	-36.3 ± 721.08	-265.3 ± 828.25
Minimum - Maximum	-1865 - 1584	-5245 – 2906
Median	-41.5	-200
Dose cohort: 30 mg/kg ICL670/≥50 mg/kg DFO		
N	115	117
Mean ± SD	-926 ± 1416.09	-842.7 ± 1295.34
Minimum - Maximum	-7082 – 3169	-8259 – 1765
Median	-793	-671

Source: Sponsor submission page 91

Reviewer's Comments. Clinical reality will require that the dosing of Exjade be determined on a measure other than liver biopsy. At the present time, physicians rely primarily on serum ferritin to estimate excess body iron stores even though it is well known that there is an imperfect correlation between the two. Ferritin is an acute phase reactant and its serum level may be affected by the presence of other stimuli. However, levels of serum ferritin in excess of 1000-1500 ng/ml are almost never caused by anything other than an increase in body iron stores. Sequential serum ferritin measurement is likely to be the manner in which physicians will monitor the efficacy of any iron chelator. There is literature that indicates that patients with transfusion dependent β-thalassemia whose serum ferritin levels consistently remain below 2500 mg/L have longer survivals than those whose serum ferritin levels regularly exceed 2500 mg/dL (3) . The hazards of a chelator induced fall in serum ferritin to below 1000 mg/dL are not known.

4. Serum iron, transferrin and transferrin saturation. Serum iron was always raised. Transferrin levels and transferrin saturation were little changed during the trial.

> *Reviewer's Comments. As known from previous experience and literature, serum iron and transferrin saturation rise very early in states of iron overload and are not useful in dose selection or in the determination of efficacy.*

5. Liver pathology. Microscopic examination of liver biopsies at baseline and at end of study showed only small changes in histologic interpretation and in semi-quantitative assessment of liver iron stores at lower dose levels of both Exjade and DFO. Somewhat greater changes (improvement) were seen at high doses for both drugs.

> *Reviewer's Comments. Low doses of chelators would not be expected to change the histological interpretation of liver biopsies because they induce no diminution in LIC. High doses of chelators are associated with some improvement in the histological appearance of the liver biopsy. It is possible that the short duration (1 year) of the trial did not allow for sufficient time to observe significantly greater changes. The frequency of other hepatic injuries, especially infective, complicates the interpretation of the microscopic findings.*

Study 0105. Supportive

Primary Objective
The primary objective was to evaluate the safety and tolerability of Exjade after administration of multiple oral daily doses of 10 mg/kg or 20 mg/kg with dose adjustments within the range 5 – 40 mg/kg (titrated according to changes in LIC), in comparison with DFO, 40 mg/kg and of dose adjustments by steps ± 10 mg/kg and up to 50 mg/kg administered for 5 consecutive days each week by s.c. injection.

Secondary Objectives
- To determine the effects of Exjade on LIC measured by SQUID
- To evaluate the usefulness of serum ferritin in the titration of the dose of Exjade
- To measure the PK of Exjade
- To evaluate the relationship between the PK and PD of Exjade
- To measure the effects of food on Exjade PK

Study Design
This was a multicenter, randomized, open-label, exploratory, parallel group study in patients with transfusion-dependent iron overload previously treated with DFO who were randomized

1:1:1 to treatment with repeated oral doses of either Exjade 10 mg/kg or 20 mg/kg (given for seven days per week) or DFO 40 mg/kg s.c. for five consecutive days per week. The study lasted for 3 months with an additional nine month extension (Study 0105E1)as indicated in the following figure.

Figure 3-1 Study design

← Run-in period →		←———	Treatment and observation period							→
Screening	Washout			Core			E O S core	Extension		E O S ext
−14 to −6 days	−5 to −1	Day 1	Month* 1	Month* 2		Month* 3		Months* 4 to 12		
Visit 1	Visit 2	V3	V4 V5	V6	V7	V8 V9		Visits 10 to 27		
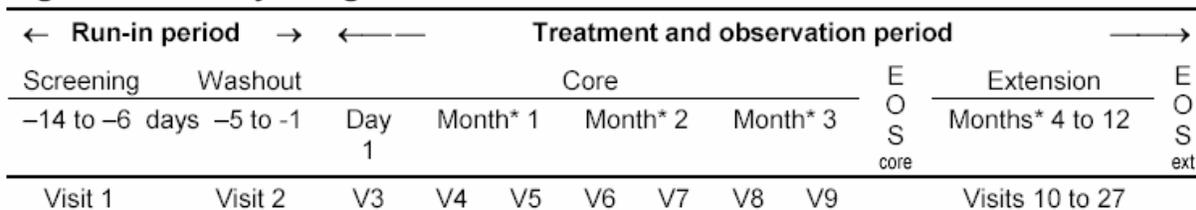
* 1 month = 4 weeks = 28 days

Source: Sponsor submission page 18

During the 2 week run–in period, the dose of DFO was adjusted to 40 mg/kg/d, and LIC by SQUID was determined. During the washout phase, DFO was withheld for 5 days. On day 1, either Exjade (at one of the two doses) or DFO was commenced and given for 3 months. During the extension period, each patient continued on the same treatment regimen as given during the first three months.

In the core phase, continuation of treatment was dependent on negative results from assessments of possible liver, renal or ocular toxicity performed every two weeks. During the extension phase of the comparative study, ocular examinations were performed fortnightly whereas hematology, blood chemistry and ECGs were performed at monthly intervals. Audiometry and liver echograms were performed every three months. After implementation of amendment 3 during the prolongation of the extension phase of the comparative study, ocular examinations, ECGs and audiometry were performed every 3 months. At the end of the core phase and subsequently every 3 months, the LIC was monitored by a SQUID assessment.
Study drug dose adjustments were directly correlated with the SQUID results and based on the degree of change in LIC. Blood sampling for PK was collected at trough times. A subpopulation of 10 patients had more frequent blood sampling for Exjade levels as well as for periodic 24 hour urine iron excretion determination.

Reviewer's Comments. This early comparative study of Exjade to DFO was designed primarily to evaluate safety and tolerability, to obtain PK/PD data and begin to evaluate SQUID as a measurement of LIC. The sponsor refers to a study (Starr TN, Fischer R, Ewing T, et al. A new generation SQUID biosusceptometer. In Nenonen J, Ilmoniemi RJ, Katila T (eds): Biomag 2000: Proceedings 12th Int Conf Biomagnetism) as an "established non-invasive method to monitor LIC during the course of treatment". In the article cited, there were only 4 persons whose livers were evaluated. It is clear from the cited reference that this methodology was far from established for this purpose.

Patients
Seventy one patients with β-thalassemia major (69) or β-thalassemia intermedia (2) were enrolled in the trial.

Inclusion criteria were:
- Consenting outpatients of either sex, aged ≥18 years, with transfusion-dependent hemosiderosis who had been treated with a mean daily dose of DFO of ≥30 mg/kg for ≥4 weeks prior to entering the screening period. Female patients of childbearing potential were to have been practicing an approved method of contraception.
- For admission to the screening period: Serum ferritin values were to have been in the range ≥2000 ng/mL to ≤8000 ng/mL confirmed by at least two determinations during 12 months prior to enrollment or previous SQUID LIC ≥5 mg/g dw to ≤15 mg/g dw performed in the previous year.
- For admission to the washout period: SQUID LIC was to be in the range ≥5 mg/g dw to ≤15 mg/g dw.
- Average post-transfusion hemoglobin levels (measured or calculated) in the range ≥10.5 to ≤ 13.5 g/dL (during 12 months prior to enrollment and including one measurement during the washout period).

Exclusion criteria were:
- Evidence of any significant hepatic or renal impairment.
- Patients with creatinine clearance <80 mL/min (measured and/or calculated according to the Cockcroft-Gault formula at Visit 2).
- Patients with hypertension or those with any degree of atrio-ventricular (A-V) block, clinically relevant Q-T interval prolongation or those requiring treatment with digoxin or similar compounds or antiarrhythmic drugs which may induce prolongation of A-V conduction.
- Patients with a diagnosis of cataract or a previous history of clinically relevant ocular toxicity related to iron chelation.

Treatments
Patients were initially randomized to one of three treatment arms.
- Exjade tablets dissolved in water, 10 mg/kg/d by mouth
- Exjade tablets dissolved in water, 20 mg/kg/d by mouth
- DFO, 40 mg/kg/d by continuous s.c.infusion 5/7 days weekly for 8-12 hours per infusion

In each treatment arm, the dose of drug could be changed based on followup SQUID LIC. Exjade dose could be changed in increments of ±5-10 mg/kg within the range of a total daily dose of 5-40 mg/kg. DFO dose could be changed by ±10 mg/kg/d with an upper daily limit of 50 mg/kg.

Treatment assignment was by central randomization. Use of concomitant medications to treat current medical conditions was permitted, but they were recorded and changes in medications had to be reported to the investigator. Blood transfusions were continued as necessary to

maintain a hemoglobin of $\geq 9 \pm 1$ g/dl. Treatment compliance was measured at each visit. The visit schedule is shown in the table below.

Table 3-1 Visit and evaluation schedule

VISIT	Screen Day -14 to -6 (1)	Washout Day -5 to -1 (2)	DAY 1 (3)	Core Month 1 (4 5)	Core Month 2 (6 7)	Core Month 3 (8)	EOS (9)	Extension Month 4 5 6 7-11 (10–27)	EOS Month 12
Informed consent	x								
Eligibility	x	x							
Medical history	x								
Hemoglobin	x	x						At each visit	
Transfusion		x						As required	
SQUID	x						x	3 monthly	
Pregnancy test	x						x		x
Physical examination	x			x					
Vital signs, ECG	x			x	x		x	Monthly	
Body weight/height	x/x	x	x					At each visit	
Hepatitis serology/HIV	x								
Urinalysis		x						At each visit	
Urinary creatinine, protein, NAG, β2-M		x						At each visit	
Creatinine clearance		x		x x				Monthly	
Ocular exams	x							At each visit	
Audiometry	x						x	3 monthly	
Liver echography	x						x	3 monthly	
Laboratory safety	x	x		x	x		x	Monthly	
Surrogate markers		x		x x	x x	x	x	At each visit	
PK blood sampling (troughs)				x x	x		x	3 monthly	
PK blood and urine sampling (profiles)			x	x x	x		x	3 monthly	
Conmed	x	x						As required	
Comments								As required	
Adverse events			x	x x	x x	x	x	At each visit	
Drug dispensing			x	x x	x x	x	x	At each visit	

Source: Sponsor submission page 23

Efficacy Assessments
These included LIC by SQUID, all performed at Turin University, serum ferritin, serum iron, transferrin, transferrin saturation and urinary iron excretion. LIC by SQUID was stated to be a direct measure of excess body iron stores. The other assessments were stated to be surrogate markers.

Safety Assessments

These included monitoring of AEs and SAEs, blood tests for hematology and chemistry, urine (total protein, beta-2 microglobulin, N-acetyl-β-glucosaminidase), creatinine clearances (originally by direct measure, subsequently by Cockcroft-Gault formula), physical examinations, audiometry, ocular examination, liver echography and ECGs.

Reviewer's Comments. This was a dose-response study with a comparator control. Its primary goal, however, was to assess the safety and tolerability of Exjade. Only 2 doses of Exjade were initially given, with adjustments in both the Exjade and DFO dose based on measures of changes in iron overload during the trial. The patient population with inclusions and exclusions is appropriate. Since this was an early study, patients with hepatic, renal, cardiac conduction and ocular dysfunction were excluded. Again, the problem is that SQUID was used as the measure of iron overload at baseline and LIC changes over the course of the trial.

Protocol Amendments

The protocol was amended on four occasions.

Amendment 1 (12 July 2001) was mainly for administrative reasons to provide some minor corrections and clarifications to the text of the protocol and specify a change in the procedure of treatment assignment.

Amendment 2 (28 March 2002. The following changes to the conduct of the study were made:
- Since the dropout rate during the first four months of the trial was lower than expected, patient enrollment was to be terminated after 71 patients had been recruited.
- Creatinine clearance was to be calculated using the Cockcroft-Gault formula.
- Dose adjustments of Exjade were permitted with dose changes of ±10 mg/kg (or ±5-10 mg/kg, if appropriate) and the maximum dose was increased from 30 to 40 mg/kg. Dose adjustments for Exjade were to be made on the basis of SQUID measurements using the underlying trend of LIC to determine liver iron concentrations. If LIC was extrapolated to fall below 2 mg/g dw within the next 3 months, a request for dose adjustment was to be made to the SMC.
- Provision was made to recruit patients to participate in the food interaction PK study.
- With the unanimous endorsement of the SMB, the following changes for clinically notable abnormalities were made:
  o The threshold for clinically notable creatinine clearance calculated using the Cockcroft Gault formula was set at <60 mL/min. An increase in plasma creatinine of >25% of basal levels was also considered clinically notable. The level for clinically notable urinary protein levels was increased from 0.2 g/24 hours to 0.4 g/24 hours, and the clinically notable level for β-2 M was set at >1000 µg/L. In addition, LIC levels of <2 mg/g dw or predicted levels of <2 mg /g dw within the next three months based on the extrapolated slopes of the SQUID measurements (confirmed by an additional SQUID within 28±10 days) were declared clinically notable.

- Provision was made for the inclusion of a cardiologist on the Safety Board and steps were taken to facilitate the process of accelerated decision making.
- The baseline used for evaluation of the urinary excretion values was redefined.

Amendment 3 (10 June 2002) described an additional extension (Study 0105E2) to the current study though none of the provisions of this amendment affected any aspect of the study phases of Studies 0105 or 0105E1.
The following changes to the conduct of the study (to be implemented only after patients had completed 12 months of therapy) were made:

- Patients who had completed 12 months of treatment were to continue to receive the same treatment to which they had been randomized until all patients participating in the study had completed 12 months therapy. In the event that the evaluation of the results of the first 12 months of therapy demonstrated no safety issues in patients randomized toExjade, consenting patients who had received therapy with DFO could then be switched to therapy with Exjade.
- Since some patients had demonstrated transient increases of β-2 M which were of unknown clinical significance, the following parameters of renal function were added to the schedule of evaluations: α1-microglobulin (β-2 M), retinol binding protein (RBP), epidermal growth factor (EGF) and prostaglandin E2 (Pg-E2).

Amendment 4 (30 Sep 2002) revoked the determination of EGF and Pg-E2 to be implemented in patients who had completed 12 months of treatment, according to amendment 3. None of the provisions of this amendment affected any aspect of the study phases described in this report.

Reviewer's Comments. These amendments do not appear to compromise the essence of the trial.

Statistical Methods
Data from all centers that participated in this protocol were to be combined, so that an adequate number of patients would be available for analysis. Data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and PK results.

Patients
Three populations were analyzed:

- Intent to Treat (ITT). All patients who had been randomized, received study drug and who had at least one scheduled post-baseline SQUID assessment.
- Per protocol (PP). All patients, who had been randomized, received study drug and who had post-baseline SQUID assessments at three months and at twelve months.
- Safety (SA). All randomized patients, who received at least one dose of study medication.

Data was collected on background and demographic characteristics, study medication, concomitant therapy, efficacy assessments and safety assessments. Since this was primarily a

safety study, no sample size was estimated, but the numbers of patients in the trial were such that toxicities with incidences greater than 15% were not likely to be unnoticed.

Reviewer's Comments. There is a minimal formality in the statistical plan as this was an exploratory study done mostly to determine safety and tolerability.

Patients Studied
Seventy one patients were enrolled into the trial (24 received Exjade at an initial daily dose of 10 mg/kg, 24 received Exjade at an initial daily dose of 20 mg/kg and 23 received DFO at an original dose of 40 mg/kg) and 67 completed the trial. Four patients discontinued therapy as shown in the following table.

Table 7-1 Patient disposition

Patient disposition Discontinuations	ICL670 10 mg/kg N=24 n (%)	ICL670 20 mg/kg N=24 n (%)	DFO 40 mg/kg N=23 n (%)	All treatments N=71 n (%)
Completed	24 (100.0)	22 (91.7)	21 (91.3)	67 (94.4)
Discontinued (total)	0 (0.0)	2 (8.3)	2 (8.7)	4 (5.6)
due to adverse events	0 (0.0)	1 (4.2)	2 (8.7)	3 (4.2)
due to unsatisfactory therapeutic effect	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)

Source: Sponsor submission page 36

Adverse events are discussed below. There were no protocol violations.

Demographics were similar in the 3 groups except that there was a somewhat greater proportion of females assigned to the Exjade 10 mg/kg dose, possibly because many of them were in their menstrual years. A majority of patients had a history of hepatitis (mostly hepatitis C) and about 50% had undergone splenectomy. These and other medical conditions were generally equally divided among the arms of the trial.

Medications
The average daily dose of study drugs in each arm of the trial was reasonably close to the randomized initial dose, as shown in the table below.

Table 8-1 Average daily dose of study medication

Randomized daily dose (mg/kg)	ICL670 10 mg/kg N=24	ICL670 20 mg/kg N=24	DFO* 40 mg/kg N=23
n	24	24	23
Mean±SD	11.7±2.12	19.0±4.10	28.6±1.06
Minimum	8.5	10.4	26.6
Median	11.0	20.0	28.7
Maximum	14.7	25.6	31.6

Source: Post-text Table 8.1-2
* Note this is the mean daily dose calculated for 7 days during a regimen of 40 mg/kg on 5 consecutive days each week

Dose adjustments occurred in almost half of the patients and were more common in patients receiving Exjade [most of the changes were for lack of efficacy (13/24 patients) in the 10 mg/kg group, and for AEs (11/24 patients) in the 20 mg/kg group] than with DFO (only 1 patient had an increase in dose for lack of efficacy and 5 patients required temporary interruption for AEs). The duration of exposure for all 3 arms was approximately the same with a mean exposure time of 332 days.

Pharmacokinetic data for Exjade was consistent with that obtained in previous studies. C_{max} was achieved at 1-2 hours and the elimination half-life was 8-16 hours. Some Exjade was always observed in the plasma at trough measurements at 24 hours. There was no accumulation over 12 months after steady state was achieved. No PK/PD relationship could be established. No observable amounts of iron were excreted in the urine.

Concomitant medication use was common (100%) in patients enrolled in the trial but was similar in type and rationale in all 3 treatment arms.

This study provided some information on the dose-response relation for Exjade. The dose of 10 mg/kg/d appears to have limited effectiveness since 13/24 patients at that dose level had an increase in dose during the course of the trial. There appears to be a narrow therapeutic window since 11/24 patients receiving Exjade at a dose of 20 mg/kg/d had an interruption or decrease in dose because of AEs.

Efficacy Results. Primary Endpoint
Changes in LIC by SQUID were minimal at 6 months and 1 year in patients treated with Exjade at a dose of 10 mg/kg/d. In patients treated with Exjade at a dose of 20 mg/kg/d or DFO, there appeared to be a decrease in LIC by SQUID at 6 months with a somewhat greater decrease at 12 months. These changes in LIC were seen even though the patients continued to receive transfusions that accounted for an average iron intake of 0.37 mg/kg/d (over a 1 year period, a 50 kg patient would have been administered approximately 6,750 mg iron). Changes in LIC measured by SQUID are shown in the following table.

Table 9-2   Changes in LIC (mg/g dw) at 6 and 12 months (ITT population)

	Statistic	ICL670 10 mg/kg	ICL670 20 mg/kg	DFO 40 mg/kg	All Treatments
Month 6	n	24	22	21	67
	Mean	-0.4	-1.5	-1.3	-1.0
	SD	1.7	2.2	1.8	2.0
	Min-Max	-3.1-2.9	-7.5-2.2	-5.2- 1.4	-7.5-2.9
	P10	-2.7	-3.3	-4.0	-3.1
	Median	-0.4	-1.0	-1.0	-0.9
	P90	1.9	0.0	0.3	1.3
Month 12	n	24	22	21	67
	Mean	-0.4	-2.1	-2.0	-1.5
	SD	2.2	2.6	2.0	2.4
	Min-Max	-4.1-4.9	-8.4-4.4	-6.1-2.4	-8.4-4.9
	P10	-2.4	-4.8	-4.6	-4.6
	Median	-0.6	-2.2	-1.7	-1.6
	P90	2.4	0.4	0.0	1.6

Source: Sponsor submission page 47

Reviewer's Comments. SQUID has not been validated as a measure of LIC. SQUID results suggest a decrease in LIC with a dose of Exjade of 20 mg/kg/d which is similar to that seen with DFO at a dose of 40 mg/kg/d. Exjade at a dose of 10 mg/kg/d seems to be ineffective in reducing LIC but maintained the stability of LIC over a 12 month period. This result is in contrast to that in Study 0107 in which LIC by SQUID continued to rise when patients were treated with Exjade at a dose of 10 mg/kg/d.

Efficacy Results. Secondary Endpoints

There was no useful information obtainable from changes in serum ferritin, serum iron, transferrin, transferrin saturation or urinary iron excretion. In general, there were no differences over time and there were no differences among the 3 arms of the trial. The only exception was a statistically insignificant rise in serum ferritin observed in the Exjade treated patients at both dose levels compared to a stable serum ferritin in DFO treated patients.

Reviewer's Comments. Study 0105 was primarily a trial to evaluate the safety and tolerability of Exjade in β-thalassemia patients. Efficacy was a secondary consideration. The major problem with the study, which makes the data for the primary endpoint of little useful value, is that the change in LIC was determined by SQUID. SQUID measurements of LIC are not acceptable. In addition, none of the secondary endpoints, which are admittedly surrogate endpoints, suggest any efficacy of the use of Exjade at the doses employed in these patients.

The data from Study 0105E2 is presented in Appendix 1.

Study 0106.   Supportive

Objectives

The primary objective of this trial was to evaluate the safety and tolerability of Exjade after multiple administrations of an initial dose of 10 mg/kg/d with subsequent dose adjustments in pediatric patients with β-thalassemia major.

The secondary objectives of the trial were:
- To evaluate the pharmacokinetic (PK) profile of Exjade in β-thalassemia major pediatric patients after single and multiple oral doses.
- To evaluate the effect of Exjade on liver iron content (LIC) measured by SQUID and on the total body iron stores.
- To evaluate the relationship between plasma PK of Exjade and pharmacodynamic (PD) variables (LIC) in β-thalassemia major pediatric patients.
- To evaluate the compliance with Exjade treatment (measured by means of the trough PK samples) in β-thalassemia major pediatric patients.
- To evaluate the role of serum ferritin and other surrogate markers of iron homeostasis as indicators for the safe dose titration of Exjade.
- To identify genetic factors related to iron stores in β-thalassemia major patients which may predict response to treatment with Exjade, predict relative susceptibility to drug-drug interactions, or predict genetic predisposition to serious side effects.
- To collect proteomic data on subjects receiving Exjade for biomarker development.

Study Design

This was a phase II, multicenter, open-label, non-comparative, exploratory study. Forty pediatric patients with transfusion dependent β-thalassemia previously treated with DFO were enrolled into 2 stratified age groups (2-<12 [Group 2] and 12-≤17 [Group 1] years of age). This was the first dosing of pediatric patients with Exjade, so the initial dose given was 10 mg/kg regardless of the degree of iron overload. After a DFO washout period of 5 days, patients were begun on Exjade which was to have been continued with possible adjustments based on AEs and measures of efficacy for a period of 48 weeks. The schedule was as follows.

Figure 3-1   Study design
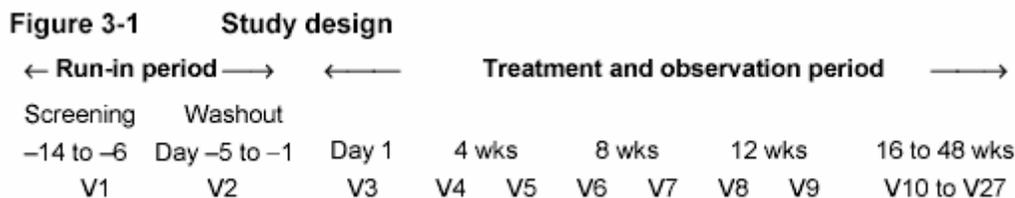
Source: Sponsor submission page 17

The study was primarily exploratory and was focused on safety and tolerability in the pediatric population. Extensive PK studies were the main assessments performed, but to these were added physical and laboratory assessments of potential AEs (mainly liver, kidney, cardiac, eye, ear and sexual development). The only PD study performed was a measure of urinary iron excretion in a subset of 10 patients. LIC was determined by SQUID at baseline and then at 4 and 12 weeks (to allow changes in dose) and at 48 weeks (end of study).

Patients Studied

Forty pediatric patients with transfusion dependent β-thalassemia previously treated with DFO were enrolled into 2 stratified age groups (2-<12 [Group 2] and 12-≤17 [Group 1] years of age). There were 20 patients allocated to each group.
Inclusion criteria were:

- For inclusion into patient Group 1: Adolescent outpatients of either sex aged 12 - ≤17 years at the screening visit, with transfusion-dependent β-thalassemia major. Female patients who had reached menarche must have been practicing an approved method of contraception, or must have undergone clinically documented total hysterectomy and/or ovariectomy, or tubal ligation.
- For inclusion into patient Group 2: Child outpatients of either sex aged 2 - <12 years at the screening visit, with transfusion-dependent β-thalassemia major.
- Previous treatment with DFO at a mean daily dose between 20 − 60 mg/kg for ≥4 weeks before screening.
- For admission to the Screening Period: Serum ferritin values ≥1000 ng/mL confirmed by at least two evaluations during 12-months prior to enrollment or LIC ≥2.5 mg Fe/g dw measured in the year prior to screening.
- For admission to the washout period: LIC ≥2.5 mg Fe/g dw as measured by SQUID.
- Regular transfusion of >50 mL/kg/year packed red cells during the last year.
- Written informed consent from the patient's parents or legal guardian in accordance with the national legislation.

Exclusion criteria were:
- Patients with sickle cell disease.
- Serological evidence of active hepatitis B or evidence of clinically active hepatitis.
- Patients with mean SGPT/ALT levels >250 U/L during the year before start of study treatment or patients with SGPT/ALT or SGOT/AST variations >300% (coefficient of variation (CV) of mean value) during the twelve months preceding enrollment or those with serum creatinine above the upper limit of normal (ULN).
- Patients with hypertension.
- Patients with any degree of A-V block, clinically relevant corrected QT interval prolongation or patients requiring treatment with any drug which may have induced prolongation of the A-V conduction time or QT interval
- Patients with a diagnosis of cataract or a previous history of clinically relevant ocular toxicity.
- Systemic diseases (cardiovascular, renal, hepatic, etc.) which would prevent the patient

from undergoing any of the treatment options.

- Patients treated with a systemic investigational drug within the past 4 weeks or topical investigational drug within the past 7 days.
- History of immunocompromise, including a positive HIV test result (ELISA and Western blot).

Reviewer's Comments. Pediatric patients are likely to be an important target population for Exjade. This study was designed to provide PK/PD and safety/tolerability data that would support Study 0107, 0108 and 0109. A major problem with the study was that it used SQUID to determine LIC. Exclusions included patients with raised transaminases, documented hepatitis, ocular abnormalities, cardiac conduction defects and various systemic diseases.

Treatments

All patients were treated with Exjade dissolving tablets (in water) before breakfast at an initial dose of 10 mg/kg/d. Dose adjustments were dependent on LIC by SQUID and were determined on a case by case basis at regular meetings of the Study Monitoring Committee. The main concern was that patients not be overdosed and, therefore, become iron deficient at which point an increased risk of AEs was believed to occur.

Regular medications required by patients were allowed to be continued for the duration of the trial. Those medications, and any others administered during the trial, were entered upon the case report form. Blood transfusions were continued to maintain the hemoglobin between 9-13 g/dl.

The visit schedule is shown in the following table.

Table 3-1 Visit schedule

	Screening	Washout	Day 1	\ Treatment and observation period (Day 1 – End of study)														EOS
Weeks				2	4	6	8	10	12	14	16	18	20	22	24	26	28–46	48
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17–26	27
Informed consent	x																	
In-/exclusion	x	x																
Medical history / prior medications	x																	
Vital signs	x			x			x			x			x			x		x
Hematology, Blood chemistry	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Renal function	x	x		x	x		x		x		x		x		x		x	x
Urinalysis		x		x	x		x		x		x		x		x		x	x
Physical exam.	x			x					x						x		#	x
SQUID	x			x					x						x		#	x
Liver echography	x			x					x						x		#	x
ECG	x			x			x		x						x		#	x
Ocular exam.	x								x						x		#	x
Audiometry	x								x						x		#	x
Pubertal staging / anthropometric assessments	x			x					x						x		#	x
Bone age / metaphys. growth	x																	x
PK sampling (trough levels)				x	x		x		x						x		#	x
PK sampling (profiles) + UIE			x	x	x													
Blood transfusions			As required to maintain hemoglobin ≥ 9g/dL															
Comments			As required															
Conc. medication			As required															
Adverse events			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Drug dispensing			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

\# = assessments to be performed at visit 21 (after 36 weeks of treatment)

Source: Sponsor submission page 34

Efficacy assessments included:
- Serial LIC measured by SQUID

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- Serum ferritin, serum iron, transferrin, transferrin saturation and urinary iron excretion

Safety assessments included:

- Monitoring of all AEs and SAEs
- Laboratory measurements of hematology, chemistry and urine parameters
- ECGs
- Creatinine clearance using the Schwartz formula
- Measurement of urinary N-acetyl-β-glucosaminidase (NAG), total protein, α_1-microglobulin (α-1 M), β_2-microglobulin (β-2 M) and retinol binding globulin (RBP)
- Regular monitoring of eye and ear function
- Liver echograms
- Developmental growth

PK assessments of trough levels were performed on all patients repetitively over the course of the trial. A subset population had PK assessments pre-dose, and at 0.5, 1, 2, 4, 8, and 24 hours on days 1 and 2 and at 4 weeks.

No significant amendments were made to the protocol.

Statistical Methods

Two populations were analyzed:

- Safety/Intent to Treat. All patients who received at least one dose of drug. This was the primary analysis population.
- Per Protocol (PP). All patients who received one dose of drug and who had an LIC by SQUID at baseline and at study's end. This population included patients who stopped medication for AEs, abnormal laboratory values, abnormal test procedures or suffered iron overload death. These patients were analyzed for the primary efficacy endpoint.

Secondary efficacy analyses were performed on the PP-2 population, a subset of the PP population that included patients who discontinued treatment for safety and counted as failures in the PP population.

A treatment success was based on the SQUID measured LIC at study's end compared to baseline as shown in the following table.

Table 6-1   Primary efficacy endpoint: success criteria (based on LIC)

LIC at baseline	Success, if LIC after 1 year	Failure, if LIC after 1 year
2 - <7 mg Fe/g dw	2 - <7 mg Fe/g dw	<2 mg Fe/g dw or ≥ 7 mg Fe/g dw
≥ 7 - <10 mg Fe/g dw	2 - <7 mg Fe/g dw	<2 mg Fe/g dw or ≥ 7 mg Fe/g dw
≥ 10 mg Fe/g dw	Decrease in LIC ≥3 mg Fe/g dw	Decrease in LIC ☐3 mg Fe/g dw

Source: Sponsor submission page 36

Patients who stopped medication were considered treatment failures. If no SQUID measurement of LIC was available at 48 weeks, the patient was considered a treatment failure.

Measurements of serum ferritin, serum iron, transferrin and transferrin saturation were analyzed.

Total body iron excretion (TBIE) is based on the amount of red cells transfused and on changes in total body iron (measured as noted above in Study 0107) from baseline to end of study.

Notable laboratory values for safety included values in the following table and succeeding paragraph.

Table 6-2   Definition of notable and extended ranges for selected laboratory parameters

Laboratory parameter	Criteria for notable and extended ranges
Platelet count	$<100 \times 10^9$/L
Absolute neutrophils	$<1.5 \times 10^9$/L
Serum creatinine	>33% increase from baseline (at two consecutive measurements) (extended range: >50% increase)
Urinary protein/creatinine ratio	≥1.0 (mg/mg) in a second-void morning urine sample
SGOT/SGPT	>5 x ULN (extended range: >10 x ULN)

Special renal function parameters, expressed as a ratio to urinary creatinine, were summarized as shift tables (baseline vs highest result during study) using the following ranges:

- Urinary protein / creatinine ratio: <0.2, 0.2 - <0.4, 0.4 - <0.6, ≥0.6 mg/mg
- Urinary β–2 M / creatinine ratio: <52, 52 - <156, 156 - <520, ≥520 µg/mmol
- Urinary α–1 M / creatinine ratio: <1.7, 1.7 - <3.4, 3.4 - <5.1, ≥5.1 mg/mmol
- Urinary RBP / creatinine ratio: <60, 60 - <120, 120 - <180, ≥180 µg/mmol
- Urinary NAG / creatinine ratio: <0.46, 0.46 - <0.92, 0.92 - <1.38, ≥1.38 U/mmol

Source: Sponsor submission page 38

Based on sample size and power calculations, the sponsor stated that toxicities with an incidence of >15% would not have gone unnoticed in the trial.

Reviewer's Comments. LIC was measured by SQUID only. Adjustments in dose, the TBIE calculation and efficacy were all based on SQUID measured LIC. Therefore, interpretation of the data is uncertain. The initial dose of Exjade administered is now known to be generally ineffective in stabilizing/lowering LIC in patients who require chronic transfusion therapy.

Patient Disposition
Forty patients were recruited into the trial. Only one patient was discontinued from the trial and this was because of the development of a skin rash on day 11 that was believed related to study medication. All other patients completed the study and are included in the analyses except for a single patient who did not have an LIC at study's end.

Protocol violations occurred in 2 patients. One was the child who discontinued medication because of drug rash. The other was a patient who did not have a SQUID measured LIC at 48 weeks, although he had had several post baseline LICs.

Therefore, the analysis populations are shown in the table below.

Table 7-3   Number (%) of patients in analysis populations

Analysis Population	Children <12 yrs N=20 n (%)	Adolescents ≥12 yrs N=20 n (%)	All patients N=40 n (%)
ITT population	20 (100.0)	20 (100.0)	40 (100.0)
Safety population	20 (100.0)	20 (100.0)	40 (100.0)
PP-1 population	19 (95.0)	20 (100.0)	39 (97.5)
PP-2 population	18 (90.0)	20 (100.0)	38 (95.0)
PP-3 population	19 (95.0)	20 (100.0)	39 (97.5)

Source: Sponsor submission page 41

Patient demographics are depicted in the table below.

Demographic summary

Variable / Statistic	Children <12 yrs N=20	Adolescents ≥12 yrs N=20	All patients N=40
Age (years)			
n	20	20	40
Mean ± SD	6.7 ± 2.83	14.1 ± 1.64	10.4 ± 4.37
Median	6.5	14	11.5
Min – Max	2 – 11	12 - 17	2 – 17
Age group (years)			
≥2 - <6	7 (35.0%)	0 (0.0%)	7 (17.5%)
6 - <12	13 (65.0%)	0 (0.0%)	13 (32.5%)
12 - <16	0 (0.0%)	16 (80.0%)	16 (40.0%)
16 - <18	0 (0.0%)	4 (20.0%)	4 (10.0%)
Sex			
Male	8 (40.0%)	9 (45.0%)	17 (42.5%)
Female	12 (60.0%)	11 (55.0%)	23 (57.5%)
Height (cm)			
n	20	20	40
Mean ± SD	114.5 ± 16.53	151.7 ± 7.14	133.1 ± 22.62
Median	114.5	151	141
Min – Max	84 – 146	138 - 165	84 – 165
Weight (kg)			
n	20	20	40
Mean ± SD	22.2 ± 9.23	45.4 ± 9.55	33.8 ± 14.99
Median	19.2	43.8	33
Min – Max	10.4 – 49	32 - 63.4	10.4 - 63.4
Weight group (kg)			
<15	3 (15.0%)	0 (0.0%)	3 (7.5%)
15 - <35	15 (75.0%)	3 (15.0%)	18 (45.0%)
35 - <55	2 (10.0%)	14 (70.0%)	16 (40.0%)
55 - <75	0 (0.0%)	3 (15.0%)	3 (7.5%)
BMI (kg/m2)			
n	20	20	40
Mean ± SD	16.3 ± 3.19	19.6 ± 2.78	18 ± 3.38
Median	15.4	19.4	16.7
Min – Max	13.4 - 28.6	15.9 - 24.8	13.4 - 28.6

Source: Sponsor submission page 42

There were somewhat more females than males in the trial. Two patients had a history of hepatitis C. Three patients, all in Group 2, had had a splenectomy.

Treatment Administered

The average daily dose of study drug and drug interruptions are shown in the following table. Dose interruptions occurred in almost half of all patients in each group, most often on a single occasion. The average daily dose was 11.3 ± 2.22 mg/kg. There were 21 dose escalations at a median time of 39 weeks for lack of efficacy. Fourteen patients had dose interruptions on 18 occasions for AEs.

Study drug interruptions and average daily dose			
Study drug administration	Children <12 yrs N=20	Adolescents ≥12 yrs N=20	All patients N=40
Number of interruptions			
0	11 (55.0%)	14 (70.0%)	25 (62.5%)
1	7 (35.0%)	4 (20.0%)	11 (27.5%)
2	2 (10.0%)	2 (10.0%)	4 (10.0%)
Total length of interruptions (days)			
1 interruption			
n	7	4	11
Mean ± SD	8.9 ± 5.05	4 ± 2.45	7.1 ± 4.81
Minimum - Maximum	1 – 15	1 - 7	1 - 15
Median	8	4	7
2 interruptions			
n	2	2	4
Mean ± SD	15 ± 14.14	24.5 ± 14.85	19.8 ± 13.05
Minimum - Maximum	5 – 25	14 - 35	5 - 35
Median	15	24.5	19.5
Average daily dose (mg/kg/day)			
n	20	20	40
Mean ± SD	11.2 ± 2.02	11.3 ± 2.47	11.3 ± 2.22
Minimum - Maximum	9.2 - 17.7	9.1 - 17.2	9.1 - 17.7
Median	10.8	10.0	10.3
Average daily dose group (mg/kg/day)			
7.5 - <15	18 (90.0%)	17 (85.0%)	35 (87.5%)
15 - <25	2 (10.0%)	3 (15.0%)	5 (12.5%)
Relative dose intensity			
n	20	20	40
Mean ± SD	1.1 ± 0.2	1.1 ± 0.25	1.1 ± 0.22
Minimum - Maximum	0.9 - 1.8	0.9 - 1.7	0.9 - 1.8
Median	1.1	1.0	1.0

Source: Sponsor submission page 44

The duration of exposure was comparable in both groups. Only one child was withdrawn for an AE. Overall patient exposure is shown in the following table.

Overall exposure

Duration of exposure (weeks)	Children <12 yrs N=20	Adolescents ≥12 yrs N=20	All patients N=40
<12 weeks	1 (5.0%)	0	1 (2.5%)
36 - <48 weeks	1 (5.0%)	0	1 (2.5%)
≥48 weeks	18 (90.0%)	20 (100%)	38 (95.0%)
n	20	20	40
Mean ± SD	47.1 ± 11.43	51.2 ± 2.25	49.2 ± 8.4
Min – Max	1.6 - 55.9	49.3 - 56.7	1.6 - 56.7
Median	48.4	49.9	49.9

Source: Sponsor submission page 46

Drug levels and PK data are reported in the Biopharmaceutics report.

All patients had received DFO prior to enrollment. The majority of patients received a number of drugs during the study that were typical of this patient population. These most frequently included analgesics, mucolytics, corticosteroids, anti-infectives and drugs acting on the gastrointestinal tract and the eyes.

During the study, patients continued to receive blood, with a mean number of transfusions over the 48 week period of 15.6 ± 3.61. The average blood transfusion contained 9.52 ± 2.55 ml RBC/kg. Therefore, the iron infused over the period of the study was approximately 150 mg/kg.

Reviewer's Comments. The patient population consisted of children and adolescents between the ages of 2 and 18 years. All were given an initial dose of 10 mg/kg/d and the mean daily dose was 11.3 mg/kg/d. There was a single dropout because of a skin rash. One child did not have an end of study LIC determination. The transfusion requirements were high, probably because of the age group of the patients.

Efficacy Results

Primary efficacy results were based on changes in LIC by SQUID over the course of the trial. Although it appears that there may have been a slight decline in LIC during the early months of the trial, by the end of the trial the LIC was on an upward trend. This is shown in the following table.

Table 9-1   Liver iron content (mg Fe/g dw) by SQUID – ITT population

Timepoint	Statistic	Children <12 yrs N=20	Adolescents ≥12 yrs N=20	All patients N=40
Baseline	n	20	20	40
	Mean ± SD	6.2 ± 2.51	5.7 ± 2.18	6 ± 2.34
	Minimum – maximum	2.8 – 13.4	2.6 - 10.9	2.6 - 13.4
	P25 - P75	4.3 - 8.1	4 - 7.1	4.3 - 7.5
	Median	5.9	5.2	5.6
Week 4	n	19	20	39
	Mean ± SD	6.2 ± 2.82	5.4 ± 2.21	5.8 ± 2.52
	Minimum – Maximum	2.6 – 13.5	2.5 - 9.9	2.5 – 13.5
	P25 - P75	3.7 – 8	3.5 - 6.7	3.5 - 7.3
	Median	5.9	5.2	5.3
Week 12	n	17	20	37
	Mean ± SD	6.1 ± 2.78	5.8 ± 2.33	5.9 ± 2.51
	Minimum – Maximum	2.8 – 14.1	2.6 - 11.5	2.6 - 14.1
	P25 - P75	4.2 - 7.3	4 – 7	4.1 - 7.1
	Median	5.1	5.5	5.1
Week 24	n	19	20	39
	Mean ± SD	6.6 ± 2.62	5.9 ± 2.69	6.3 ± 2.64
	Minimum – Maximum	2.4 – 13.7	2.1 - 12.2	2.1 - 3.7
	P25 - P75	4.8 - 8.4	3.9 – 7	4.6 - 8.3
	Median	5.8	5.9	5.8
Week 36	n	19	20	39
	Mean ± SD	7.4 ± 2.68	5.9 ± 2.11	6.6 ± 2.48
	Minimum – Maximum	3.9 – 14.7	2.7 - 10.5	2.7 - 14.7
	P25 - P75	5.5 - 8.9	4.8 - 7.2	5.2 - 8.5
	Median	6.1	5.8	5.9
End of Study	n	18	20	38
	Mean ± SD	7.9 ± 2.47	6.4 ± 2.08	7.1 ± 2.38
	Minimum – Maximum	4.4 – 13.5	3.3 - 10.2	3.3 - 13.5
	P25 - P75	6.7 - 9.7	4.6 - 7.5	5.5 - 8.7
	Median	7.4	6.8	7.1

Source: Sponsor submission page 49

Based on the definition of treatment success or failure, successes occurred almost entirely in those patients whose LIC at entry into the study was 2-<7 mg Fe/g dw (17/26), but in these patients the mean LIC rose but remained <7 mg Fe/g dw, during the year of the study. Only 2/12 patients whose LIC was ≥7 mg Fe/g dw achieved the definition of success.

Secondary efficacy results were as follows:
- Iron balance. The mean ratio of Fe excretion/Fe intake as defined was 0.93 ± 0.11 indicating that at the doses of Exjade given, there continued to be accumulation of iron in the body. This was consistent with the increases in LIC seen during the duration of the trial in both groups.
- Serum ferritin. Serum ferritin rose from a mean at baseline of 2006.8 ± 1119.1 to a mean at end of study of 2947.9 ± 1057.4 ng/ml in both groups.

Reviewer's Comments. This study was the first conducted with Exjade in a pediatric population. Clearly, this population is an important target for Exjade as prophylactic transfusion early in life is the standard of care for patients with β-thalassemia. All patients who were entered into the trial were already being treated with DFO but there is no information on the efficacy or safety of the use of DFO in these 40 patients, 20 of whom were age 2-12, and 20 of whom were age 12-17. Patients were begun on a low dose of Exjade for fear of inducing a state of iron deficiency in this vulnerable group. Dose adjustments (all increases) were necessitated by lack of efficacy in many of the subjects, and dose interruptions were occasioned because of adverse events in a substantial proportion. One child was withdrawn because of an AE (see safety review). Over the course of 48 weeks, there was a progressive increase in LIC and serum ferritin in both groups indicating a lack of efficacy in the population studied. "Treatment successes" were said to have occurred in a minority of patients but these were mostly patients who entered the trial with a LIC of 2-<7 mg Fe/g dw and remained in that band at the end of the trial even though their LICs were often greater at the end of the study than at baseline.

This study is difficult to evaluate because the primary mode of measurement of LIC was by SQUID and this method of measurement was not validated and is now known to be flawed. Therefore, although the data are noted and reviewed, they are unacceptable for efficacy evaluation. The data are useful for the purpose of evaluating safety in the pediatric population.

Study 0108. Supportive.

Primary Objective.
The primary objective was to evaluate the effects of Exjade treatment on LIC as assessed by liver biopsy, or by SQUID in patients with contraindications to liver biopsies, after one year of administration in patients with chronic anemia and transfusional hemosiderosis who were either β-thalassemia patients who could not be properly chelated with DFO, or patients with a variety of acquired or congenital rare anemias requiring chelation therapy.

The secondary objectives were:
- To evaluate the tolerability profile of Exjade in such patients treated for one year.
- To estimate the absolute and relative change in LIC and total body iron excretion (TBIE) rate for subgroups, defined by baseline LIC (2-<7, and ≥7 mg Fe/g dw), age and disease type.
- To evaluate the relationship between LIC and potential surrogate markers for efficacy such as serum ferritin, serum iron, transferrin (TRF) and TRF saturation for the dose titration of Exjade as well as safety markers indicative of possible signs of over chelation.
- To evaluate the relationship between the pharmacodynamics (PD) of Exjade and safety variables
- To identify genetic factors related to iron stores in patients with β−thalassemia and

transfusional hemosiderosis which may predict
  a) response to treatment with Exjade,
  b) relative susceptibility to drug-drug interactions, or
  c) genetic predisposition to serious adverse events (SAEs) (results not included in this report).
- To collect proteomic data for biomarker identification (results not included in this report).
- To assess Exjade drug usage.

Study Design.
This was a phase II, non-comparative, multicenter, open label, single arm trial to collect efficacy and safety data during one year of treatment with Exjade in patients with transfusional hemosiderosis who could not be satisfactorily treated with DFO. The plan was to enroll 100 patients with rare chronic anemias (Stratum 1) and 75 patients with β-thalassemia (Stratum 2). Patients were initially entered into the study for a run-in period that lasted up to 28 days, during which the patients were screened, LIC was measured by biopsy (or SQUID if there was a contraindication or impracticality to liver biopsy), baseline data was collected and deferiprone was discontinued in those who had been receiving it. This was followed by a treatment period of 1 year during which periodic assessments were made for safety and PD parameters. At study's end, LIC was determined using the same method as performed originally. In addition, in a subset of patients SQUID measurement of LIC was performed at 24 weeks of treatment.

The design was agreed to with the FDA through a Special Protocol Assessment.

A diagram of the time periods is shown in the following table.

Table 3-1 Study design

Run-in period		Treatment and observation period				
Screening	Washout					
-28 to -6 days	-5 to -1	Day 1	Week 4	Week 8	Week 12	Week 16 to 52
Visit 1	Visit 2	V3	V4	V5	V6	Visits 7 to 16 (EOS)

Source: Sponsor submission page 23

Reviewer's Comments. This non-comparative study enrolled patients with either β-thalassemia who for various reasons were not candidates for DFO treatment or patients with other anemias who had developed transfusion related hemosiderosis. This is the sponsor's first study that includes patients with iron overload for diseases other than β-thalassemia. The study was reviewed through the SPA program and recommendations made by the Division were incorporated into the protocol.

Primary Endpoint
The primary efficacy variable was defined as a binary outcome indicating success or failure of therapy. In order to be conservative, the initial dose of Exjade was based on LIC. Depending on

the LIC at baseline, different objectives had to be met to achieve success. For patients with baseline LIC within the range of 2-<7 mg Fe/g dw, the goal was to maintain LIC within this level. If the LIC was ≥7 mg Fe/g dw, the objective was to reduce LIC to <7 mg Fe/g dw and, if ≥10 mg Fe/g dw, to reduce it by at least 3 mg Fe/g dw. Thus, the baseline LIC determined the intensity of chelation and the objective to be met during the study. Exjade chelation therapy was to be considered efficacious if the overall success rate in the ITT population was significantly >50%. Surrogate markers for efficacy (serum ferritin, serum iron, transferrin and transferrin saturation) were made at 4 week intervals for comparison to LIC as determined by biopsy or SQUID.

Reviewer's Comments. This study of Exjade includes patients with hemosiderosis due to chronic transfusion therapy for anemias other than β-thalassemia as well as for β-thalassemia. Many patients had been treated with DFO and several had received deferiprone but were considered inadequately treated. LIC was determined by biopsy or SQUID. The primary efficacy endpoint was either "success" or "failure".

Patients.
Inclusion criteria were:
- Patients aged ≥2 years of either sex
- Patients with one of the following congenital or acquired chronic anemias and transfusional hemosiderosis, requiring chelation therapy:
  o Patients with β-thalassemia and documented non-compliance to DFO, defined as having taken less than 50% of the prescribed doses in the 12 months prior to study entry and an LIC≥ 14 mg Fe/g dw
  o Patients with β-thalassemia, inadequately chelated with DFO due to contra-indications and/or due to documented unacceptable toxicity of DFO, or documented poor response to DFO despite proper compliance, with an LIC ≥2 mg Fe/g dw
  o Patients with congenital or acquired chronic anemias other than β-thalassemia with an LIC ≥2 mg Fe/g dw
  o Patients with chronic anemias and transfusional hemosiderosis treated with deferiprone which was discontinued at least 28 days before Day 1 and an LIC ≥2 mg Fe/g dw
- Regular transfusion indicated by a blood requirement ≥ 8 blood transfusion per year
- Life expectancy of at least one year

Exclusion criteria were:
- Sickle cell disease
- β-thalassemia patients able to be adequately treated with DFO
- Patients with non-transfusional hemosiderosis
- Patients with mean ALT levels > 250 U/L during the year before enrollment in the study (at least four determinations during the 12-month period preceding enrollment and including the measurement during the run-in phase) and patients with ALT or AST

variations > 300% (CV of mean value) during twelve months preceding enrollment

- Serological evidence of chronic hepatitis B (presence of HBe Ag, HBsAg, HBbcAb-IGM, in the absence of HBsAb)
- Clinical evidence of active hepatitis C (liver pathology, HCV total antibody positive and abnormal liver transaminases level; if no liver biopsy was performed HCV RNA (Polymerase Chain Reaction) positive)
- Patients with a known history of human immunodeficiency virus seropositivity
- Patients with systemic uncontrolled hypertension
- Patients with serum creatinine above the upper limit of normal at screening
- Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 (mg/mg) in second-void urine samples taken at both Visits 1 and 2. A third sample was to be taken from patients in whom one ratio is > 0.5 (mg/mg) and one is ≤ 0.5 (mg/mg) and patients in whom the urinary protein/creatinine ratio is > 0.5 (mg/mg) in two of the three determinations were also to be excluded.
- History of nephrotic syndrome
- Patients with 2nd or 3rd A-V block, clinically relevant Q-T interval prolongation as well as patients requiring treatment with digoxin and similar compounds or drugs which may induce prolongation of the A-V conduction time or prolongation of the Q-T interval
- Fever and other signs/symptoms of infection requiring systemic antibiotics in the 10 days before study Day 1
- Patients with a clinically relevant cataract or a previous history of clinically relevant ocular toxicity related to iron chelation
- Systemic diseases (cardiovascular, renal, hepatic, etc.) which would prevent the patient from undergoing any of the treatment options
- Patients with psychiatric or addictive disorders which would prevent them from giving their informed consent or undergoing any of the treatment options
- Pregnant or breast-feeding patients
- Patients treated with systemic investigational drug within the past four weeks or topical investigational drug within the past seven days
- Any other surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of any drug. The investigator should be guided by evidence of any of the following:
  - history of inflammatory bowel disease, gastritis, ulcers, gastrointestinal (GI) or rectal bleeding
  - history of major GI surgery such as gastrectomy, gastroenterostomy, or bowel resection
  - history of pancreatic injury or pancreatitis; indications of impaired pancreatic function/injury as indicated by abnormal lipase or amylase
  - history or presence of impaired renal function as indicated by creatinine or BUN values above the upper limit of normal
  - history of urinary obstruction or difficulty in voiding
- Patients considered by the investigator as potentially unreliable and/or not cooperative with regard to the study protocol

- 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 phase
- Patients unable to undergo the following study examinations: audiometry, liver echography or ocular examination

Exclusion criteria for pediatric patients
- Patient body weight which prevented the use of the smallest tablet strength for dosing

Reviewer's Comments. Patients with β-thalassemia had a history of the use of DFO prior to entry into the study, but patients with other anemias did not. The exclusion criteria are numerous and include hepatitis C, renal dysfunction and cardiac conduction abnormalities. The exclusion criteria will affect the wording of the final product label.

Treatment
Exjade tablets are available in strengths of 125, 250 and 500 mg tablets. Prescribed doses were provided by selecting the appropriate combination of tablets to provide the necessary dose. Tablets were dissolved in water and then consumed 30 minutes before breakfast.

The initial Exjade dose was dependent on the LIC determined at screening:
- Patients with a screening LIC of 2 - 3 mg Fe/g dw received 5 mg/kg
- Patients with a screening LIC of >3 - 7 mg Fe/g dw received 10 mg/kg
- Patients with a screening LIC of >7-14 mg Fe/g dw received 20 mg/kg
- Patients with a screening LIC of >14 mg Fe/g dw received 30 mg/kg

The initial dose was to remain unchanged during the 1-year study period unless the evaluation of safety and efficacy markers indicated that dose adjustment was necessary. The minimum total daily dose of Exjade was 125 mg, being the smallest tablet strength. Dose adjustments, when made, were planned to be in increments of 10 mg/kg/d except in some pediatric patients, in whom dose adjustments could be made in increments of 5 mg/kg/d. Dose adjustments had to be approved by the sponsor after consultation with the Study Monitoring Committee.

Medications to treat concomitant conditions could be continued during the study and additional drugs could be used during the study, but all medications were to be entered on to the CRF.

Blood transfusions were to be given as necessary to maintain the hemoglobin ≥8 g/dl.

The visit schedule is shown in the following table.

Table 3-2 Visit schedule and evaluations

	Run-in		Treatment and observation													
	Day	Day	Day 1	4-weekly period												
	-28 - -6	-5 - -1		1	2	3	4	5	6	7	8	9	10	11	12	13
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Randomization			X													
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Physical examination	X			X			X			X			X			X
Medical history/Current medical conditions	X															
Liver function history	X															
LIC — Liver biopsy	X															X
LIC — SQUID	X								X							X
Liver pathology	X															X
Liver echography	X								X							X
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X				X				X			X				X
Echocardiography	X															X
Urinalysis		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Renal function	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ocular exam/audiometry	X				X				X			X				X
Hemoglobin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, biochemistry, iron metabolism	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Source: Sponsor submission page 32

Efficacy Assessments
The primary efficacy assessment was LIC measured by biopsy or SQUID.

Secondary efficacy assessments were:
- Absolute and relative changes in liver iron concentration
- Iron balance
- Surrogate markers and non-invasive methods for LIC assessment (serum ferritin, serum iron, transferrin and transferrin saturation)
- Liver pathology
- Safety assessments (laboratory hematology and chemistry, ECG, echocardiogram, physical examination, audiometry, liver echography, ocular examination).
- In pediatric patients, stature, growth velocity assessment, bone age and metaphyseal changes, pubertal stage, and school attendance and performance were to be observed.

Amendments and Other Changes

Amendment 1 (23-May-03) revised the exclusion criterion for the permitted level of proteinuria. Instead of being based on absolute levels of urinary protein, the new criterion excluded patients with urinary protein/creatinine ratios >0.5 (mg/mg) in a minimum of two urine samples. In addition, the amendment specified that treatment with Exjade was to be temporarily discontinued if the urinary protein/creatinine ratio increased to >1.0 (mg/mg) at consecutive visits. A 50% dose reduction was stipulated for patients in whom proteinuria of this severity recurred after restarting Exjade at the same dose. The protocol was also amended to more clearly state that patients with rare transfusion dependent anemias were eligible for inclusion whether or not they could be treated with DFO.

Amendment 2 (24-Nov-03) introduced dose adjustments for patients on Exjade in whom serum creatinine levels increased by >33% from baseline values at ≥2 consecutive visits. For patients ≥15 years, dose reductions were performed as shown in Table 4-1 and were made even if the creatinine levels remained within the normal range. No dose adjustments were performed if creatinine values from a subsequent visit were <33%. For patients <15 years, dose reductions were to be performed only if consecutive creatinine levels were >33% of baseline and were also above the age-adjusted ULN.

Table 4-1 ICL670 dose reductions in patients with increased serum creatinine

Current dose of ICL670	Reduced dose of ICL670
10 mg/kg/day	5 mg/kg/day
20 mg/kg/day	15 mg/kg/day
30 mg/kg/day	20 mg/kg/day
40 mg/kg/day	30 mg/kg/day

Source: Sponsor submission page 39

Amendment 3 (2-Sep-04) retrospectively addressed minor changes to the liver biopsy procedures. Most importantly, the sample weight threshold for the analysis of liver biopsies was reduced from 1g dw to 0.5 g dw. The number of stains used in the pathology analysis was reduced to three and a review by a second pathologist was eliminated.

In addition, the following minor discrepancies in the protocol were clarified:
- No photographs of the lens were to be taken during the eye examinations since no centralized review was planned
- All pregnancy tests were to be performed at the central laboratory

Other changes included the following:
- Because of a discrepancy between LIC measured by biopsy compared to SQUID, there was a temporary hold on the trial while the issue was resolved. This led to an extension

of the run-in phase for some patients (up to 57 days) and to the modifications listed in Amendment 3.

- A new rash management guideline was instituted to deal with the development of this AE. The change formalized the variations in dose based on the status of the rash and the use of oral steroids in the management of the rash.
- A reanalysis of all duplicate blood samples from all visits for serum ferritin was performed in April, 2004. These results were communicated to the investigators immediately. The reason for the reanalysis was that there was a problem with linearity of the ferritin test at concentrations of >1500µg/ml. The problem was corrected before the reanalysis of specimens was performed.

Reviewer's Comments. A number of the changes introduced by the amendments related to safety, particularly as regards the kidney. Concern was expressed by the Division over the size of the liver biopsy considered sufficient for the accurate determination of LIC. The reduction in the permissible size of the liver biopsy to be included in the analysis was objected to by the Division (see above).

Statistical Methods

The primary objective of the study was to evaluate the effects of Exjade on LIC as assessed by biopsy or SQUID after one year of treatment. Effective chelation with Exjade with either β-thalassemia unable to be adequately treated with DFO or with rare anemias was considered established if the success rate was >50%.

The following populations were analyzed:
- Intent to Treat. All patients who had received at least one dose of study drug
- Safety. Identical to the ITT population
- Per Protocol-1. Those that had received study drug and who had LIC at baseline and at study's end, including those who permanently discontinued study medication for an AE, abnormal laboratory value, abnormal test procedure or an iron overload death.
- Per Protocol-2. Those that had an LIC at study's end.

Statistical analysis included background and demographic characteristics, planned and actual dose of study medication, compliance and concomitant medications.

The primary analysis was based on the success rate in the ITT population which was calculated based on LIC by liver biopsy at baseline and after one year as defined in the following table.

Table 6-1 Primary efficacy endpoint: success criteria (based on LIC)

LIC at baseline	Success, if LIC after 1 year	Failure, if LIC after 1 year
2 - < 7 mg Fe/g dw	1 - < 7 mg Fe/g dw	< 1 mg Fe/g dw or ≥ 7 mg Fe/g dw
≥ 7 - < 10 mg Fe/g dw	1 - < 7 mg Fe/g dw	< 1 mg Fe/g dw or ≥ 7 mg Fe/g dw
≥ 10 mg Fe/g dw	Decrease in LIC ≥ 3 mg Fe/g dw	Decrease in LIC < 3 mg Fe/g dw

Source: Sponsor submission page 45

Subjects with no LIC result at 1 year were counted as failures in the ITT and PP-1 populations, as were those who discontinued study drug for safety reasons.

Secondary efficacy analyses included:
- Modified success criteria were added after an SPA by the Division. This is defined in the following table.

Table 6-2 Secondary efficacy endpoint: modified success criteria

LIC at baseline	Success, if LIC after 1 year	Failure, if LIC after 1 year
2 - < 7 mg Fe/g dw	1 - < 7 mg Fe/g dw and increase <1 mg Fe/g dw	< 1 mg Fe/g dw or ≥ 7 mg Fe/g dw or increase ≥ 1 mg Fe/g dw
≥ 7 - < 10 mg Fe/g dw	1 - < 7 mg Fe/g dw	< 1 mg Fe/g dw or ≥ 7 mg Fe/g dw
≥ 10 mg Fe/g dw	Decrease in LIC ≥ 3 mg Fe/g dw	Decrease in LIC < 3 mg Fe/g dw

Source: Sponsor submission page 46

- Absolute and relative changes in LIC
- Iron balance
- Surrogate markers. Serum ferritin, serum iron, transferrin and transferrin saturation
- Modeling for LIC and serum ferritin
- Liver pathology

Safety evaluation included AEs, laboratory examinations (hematology, chemistry, urinary), physical examination, ECGs, audiometry, eye examinations, liver echograms and echocardiograms. Pediatric developmental assessments were made in the pediatric population.

Subgroups analyzed included each stratum, age, sex, race, country, dose cohort, baseline LIC by method and others.

There was no formal interim analysis.

The size of the trial was determined to demonstrate at the one-sided alpha level of 0.025 that the success rate was greater than 50% provided that the expected success rate is 65%. One hundred and thirteen (113) patients were required to achieve a power of 90%, so a total of 175 patients were planned to be recruited.

Reviewer's Comments. The analysis plan appears acceptable for an uncontrolled study. A success rate of 50% in patients who are not successfully treated with DFO seems reasonable but this group would only include the patients with β-thalassemia, since patients in the category of other rare anemias did not require a history of the previous use of DFO to be eligible for entry into the trial.

Patient Disposition

A total of 184 patients were recruited into the trial of whom 85 had β-thalassemia and 99 had other rare anemias. Details of patient disposition at the end of the study are given in the following table.

Table 7-1 Patient disposition

Disposition Reason	β-thalassemia N=85 n (%)	Rare anemias N=99 n (%)	All patients N=184 n (%)
Completed	77 (90.6)	75 (75.8)	152 (82.6)
Discontinued	8 (9.4)	24 (24.2)	32 (17.4)
Adverse events	4 (4.7)	9 (9.1)	13 (7.1)
Death	-	5 (5.1)	5 (2.7)
Study drug no longer required	-	4 (4.0)	4 (2.2)
Withdrawal of consent	4 (4.7)	6 (6.1)	10 (5.4)

Source: Sponsor submission page 55

Adverse events were the most common cause for premature discontinuation of study drug, and occurred more often in patients with rare anemias. Reasons for no longer requiring study drug included bone marrow transplant and a fall in the need for transfusion. Death occurred in 4 patients with myelodysplastic syndrome (MDS) and 1 patient with Diamond-Blackfan syndrome (DBS). Six patients with MDS withdrew consent as did 4 with β-thalassemia.

Protocol violations occurred in 37 patients (9 with β-thalassemia and 28 with rare anemias) because they did not have end of study LICs and were excluded from the PP-2 population. Of these 37, 32 discontinued from the study. The remaining 5 completed the study but did not have an end of study LIC.

Reviewer's Comments. In this trial, a greater proportion of patients with β-thalassemia discontinued from the trial compared to Study 0107 (9.4% [8/85 patients] compared to 5.7% [17/296 patients]). The main cause for discontinuation was adverse events. The discontinuation rate for adverse events in rare anemias is greater than that for β-thalassemia.

Based on these data, the groupings for analysis are shown in the following table.

Table 7-3 Number (%) of patients in analysis populations

Analysis Population	β-thalassemia N=85 n (%)	Rare anemias N=99 n (%)	All patients N=184 n (%)
Intent-to-Treat (ITT) population	85 (100.0)	99 (100.0)	184 (100.0)
Safety population	85 (100.0)	99 (100.0)	184 (100.0)
PP-1 population	80 (94.1)	85 (85.9)	165 (89.7)
PP-2 population	76 (89.4)	71 (71.7)	147 (79.9)

Source: Sponsor submission page 56

The number of patients in analysis subgroups is shown in the following table.

Table 7-5 Number (%) of patients in analysis subgroups

Subgroup	β-thalassemia N=85 n (%)	Rare anemias N=99 n (%)	All patients N=184 n (%)
Disease group			
β-thalassemia	85 (100.0)	-	85 (46.2)
MDS	-	47 (47.5)	47 (25.5)
Diamond-Blackfan	-	30 (30.3)	30 (16.3)
Other anemias	-	22 (22.2)	22 (12.0)
Dose cohort (based on initial dose)			
5 mg/kg ICL	2 (2.4)	5 (5.1)	7 (3.8)
10 mg/kg ICL	8 (9.4)	11 (11.1)	19 (10.3)
20 mg/kg ICL	22 (25.9)	30 (30.3)	52 (28.3)
30 mg/kg ICL	53 (62.4)	53 (53.5)	106 (57.6)
Average planned dose category			
<7.5 mg/kg ICL	2 (2.4)	6 (6.1)	8 (4.3)
7.5-<15 mg/kg ICL	9 (10.6)	15 (15.2)	24 (13.0)
15-<25 mg/kg ICL	25 (29.4)	39 (39.4)	64 (34.8)
≥25 mg/kg ICL	49 (57.6)	39 (39.4)	88 (47.8)
Average iron intake category			
None	-	5 (5.1)	5 (2.7)
>0-<0.4 mg/kg/day	61 (71.8)	57 (57.6)	118 (64.1)
0.4- ≤0.5 mg/kg/day	16 (18.8)	25 (25.3)	41 (22.3)
>0.5 mg/kg/day	8 (9.4)	12 (12.1)	20 (10.9)
Baseline LIC method			
Biopsy	67 (78.8)	53 (53.5)	120 (65.2)
SQUID	18 (21.2)	46 (46.5)	64 (34.8)
Baseline LIC category (by method)			
<7 mg Fe/g dw (Biopsy)	6 (7.1)	1 (1.0)	7 (3.8)
<7 mg Fe/g dw (SQUID)	4 (4.7)	14 (14.1)	18 (9.8)
≥7 mg Fe/g dw (Biopsy)	61 (71.8)	52 (52.5)	113 (61.4)
≥7 mg Fe/g dw (SQUID)	14 (16.5)	32 (32.3)	46 (25.0)
Baseline LIC dosing category			
≤3 mg Fe/g dw	2 (2.4)	5 (5.1)	7 (3.8)
>3-7 mg Fe/g dw	8 (9.4)	10 (10.1)	18 (9.8)
>7-14 mg Fe/g dw	22 (25.9)	30 (30.3)	52 (28.3)
>14 mg Fe/g dw	53 (62.4)	54 (54.5)	107 (58.2)
Baseline liver enzymes			
≤2.5xULN	61 (71.8)	81 (81.8)	142 (77.2)
>2.5xULN	24 (28.2)	18 (18.2)	42 (22.8)
Hepatitis B and/or C			
Yes	30 (35.3)	9 (9.1)	39 (21.2)
No	55 (64.7)	90 (90.9)	145 (78.8)

Source: Sponsor submission page 58

Reviewer's Comments. Almost half of the patients with rare anemias had LIC determined by SQUID and the distribution of LIC values above and below 7 mg Fe/g dw suggest an underestimation of LIC by SQUID compared to LIC by biopsy. The initial dose of Exjade was

based on LIC and was 5-10 mg/kg/d in patients with an LIC of <7 mg Fe/g dw. The average iron intake was greater in the rare anemia subgroup.

The demographic characteristics of the patients by disease group in the safety population are shown in the following table.

Patient demographics

Variable/Statistic	β-thalassemia N=85	Rare anemias N=99	All patients N=184
Age (years)			
Mean ± SD	24.7 ± 10.03	43.7 ± 26.13	35 ± 22.4
Median	23	49	27
Min - Max	4 - 59	3 - 81	3 - 81
Age group (years)			
<6	2 (2.4%)	9 (9.1%)	11 (6.0%)
6 - <12	5 (5.9%)	6 (6.1%)	11 (6.0%)
12 - <16	8 (9.4%)	5 (5.1%)	13 (7.1%)
16 - <50	69 (81.2%)	30 (30.3%)	99 (53.8%)
50 - <65	1 (1.2%)	19 (19.2%)	20 (10.9%)
>=65	-	30 (30.3%)	30 (16.3%)
Sex			
Male	42 (49.4%)	51 (51.5%)	93 (50.5%)
Female	43 (50.6%)	48 (48.5%)	91 (49.5%)
Race			
Caucasian	56 (65.9%)	89 (89.9%)	145 (78.8%)
Oriental	11 (12.9%)	4 (4.0%)	15 (8.2%)
Other	18 (21.2%)	6 (6.1%)	24 (13.0%)
Height (cm)			
Mean ± SD	154.4 ± 15.41	154.6 ± 21.44	154.5 ± 18.85
Median	156	160	159.5
Min - Max	99 - 175	93 - 184	93 - 184
Weight (kg)			
Mean ± SD	51.1 ± 14.09	57.8 ± 20.81	54.7 ± 18.28
Median	53.2	60	55.2
Min - Max	13 - 84.4	13 - 93	13 - 93
Weight group (kg)			
<15	1 (1.2%)	3 (3.0%)	4 (2.2%)
15 - <35	10 (11.8%)	11 (11.1%)	21 (11.4%)
35 - <55	38 (44.7%)	25 (25.3%)	63 (34.2%)
55 - <75	33 (38.8%)	37 (37.4%)	70 (38.0%)
>=75	3 (3.5%)	23 (23.2%)	26 (14.1%)

Source: Sponsor submission page 62

The study enrolled 85 patients with β-thalassemia, 47 patients with MDS (which accounted for much of the difference in age of the rare anemia group since most of these patients were elderly), 30 patients with DBA and 22 patients with other types of rare anemia, which according to the investigators were: aplastic anemia (n=5), α-thalassemia (n=3), sideroblastic anemia (n=3), myelofibrosis (n=2), pure red cell aplasia (n=2), pyruvate kinase deficiency (n=2), autoimmune hemolytic anemia (n=1), Fanconi's anemia (n=1), hereditary sideroblastic anemia (n=1), erythropenia (n=1), and unspecified anemia (n=1).

Patients with Blackfan-Diamond syndrome were similar in age to patients with β-thalassemia. Patients with rare anemias were less likely to have a history of hepatitis C and splenectomy. The median serum ferritin was approximately 3000 µg/ml in patients with β-thalassemia compared to approximately 2000 µg/ml in patients with rare anemias.

Reviewer's Comments. Combining a disparate group of patients whose commonality is transfusion related hemosiderosis makes analysis of efficacy more difficult, particularly when the numbers are small. Generalizations to a wider population may be limited. The fact that 5/99 patients in the rare anemia group died of their underlying disease during the year of the study suggests that even though the drug may decrease iron content of tissues, it has a limited clinical relevance in this population since none of the patients appear to have died from the effects of hemosiderosis.

Treatment

The average daily dose and the relative dose intensity (ratio of actual dose/planned dose) of Exjade are shown in the following table. These were similar between the 2 groups.

Average daily dose and relative dose intensity

Study drug administration	β-thalassemia N=85	Rare anemias N=99	All patients N=184
Average daily dose (mg/kg/day)			
Mean ± SD	23.8 ± 7.18	21.5 ± 7.74	22.6 ± 7.55
Minimum - Maximum	5 - 30	4.9 - 30	4.9 - 30
Median	26.9	21.0	23.4
Relative dose intensity			
Mean ± SD	0.96 ± 0.078	0.94 ± 0.187	0.95 ± 0.147
Minimum - Maximum	0.61 - 1.0	0.52 - 2.0	0.52 - 2.0
Median	1.0	1.0	1.0

Source: Sponsor submission page 66

Dose adjustments, the reasons for adjustment and the duration of exposure in the 2 groups are shown in the following 3 tables.

Table 8-4 Dose adjustments

Dose changes	β- thalassemia N=85 n (%)	Rare anemias N=99 n (%)	All patients N=184 n (%)
Any dose adjustment			
No	47 (55.3)	48 (48.5)	95 (51.6)
Yes	38 (44.7)	51 (51.5)	89 (48.4)
Reason for dose adjustment			
AE/lab test abnormality	38 (44.7)	47 (47.5)	85 (46.2)
Lack of efficacy	-	3 (3.0)	3 (1.6)
AE/lab test abn. after increase	-	1 (1.0)	1 (0.5)
Other	-	1 (1.0)	1 (0.5)

Source: Sponsor submission page 68

Table 8-9 Reason for dose adjustments

Dose adjustment	β-thalassemia N=85	Rare anemias N=99	All patients N=184
Dose increase due to lack of efficacy (patients)	-	3	3
Time to dose increase (weeks on treatment)	-	37.4-38.0	37.4-38.0
Dose decrease due to AE/lab abnormality (patients)	15	13	28
Interruptions due to AE/lab test abnormality (patients)	29	40	69
Interruptions due to AE/lab test abnormality (episodes)	40	75	115

Source: Sponsor submission page 70

Table 8-10 Duration of exposure

Duration of exposure (weeks)	β-thalassemia N=85	Rare anemias N=99	All patients N=184
Exposure			
<12 weeks	1 (1.2%)	7 (7.1%)	8 (4.3%)
12 - <24 weeks	3 (3.5%)	9 (9.1%)	12 (6.5%)
24 - <36 weeks	3 (3.5%)	7 (7.1%)	10 (5.4%)
36 - <48 weeks	2 (2.4%)	7 (7.1%)	9 (4.9%)
>=48 weeks	76 (89.4%)	69 (69.7%)	145 (78.8%)
Mean ± SD	51.2 ± 9.92	44.3 ± 16.26	47.5 ± 14.08
Minimum - Maximum	1.3 - 61.6	0.7 - 66.9	0.7 – 66.9
Median	53.1	52.1	52.6

Source: Sponsor submission page 70

Reviewer's Comments. Increases in dosing were rare. Dose decreases and interruptions occurred in almost half of all patients entered into the trial and most of these were the result of adverse events or a notable laboratory abnormality. Patients with rare anemias generally had a shorter exposure to Exjade compared to patients with β-thalassemia because of a greater frequency of discontinuation due to death, adverse events and cessation of need for Exjade in patients with rare anemias.

Virtually all patients received concomitant medications. These frequently included analgesics, supplements, vitamins, anti bacterials, folic acid and sex hormones.

Blood transfusions were given to all patients during the trial except for 5 patients with rare anemias. The amount of blood given varied immensely from zero to >24 transfusions.

Reviewer's Comments. There is considerable heterogeneity between the patients with β-thalassemia and other rare anemias.

Efficacy Results
The primary efficacy endpoint was the success rate as defined in the protocol (final LIC compared to initial LIC). Success rates for the PP-1 and the ITT populations are shown in the following table.

Table 9-1 Success rates based on change in LIC (ITT and PP-1 population)

	PP-1 population			ITT population
	β-thalassemia N=80	Rare anemias N=85	All patients N=165	All patients N=184
Biopsy & SQUID	n=80	n=85	n=165	n=184
Success rate (n (%))	45 (56.3)	48 (56.5)	93 (56.4)	93 (50.5)
95% CI	[45.4, 67.1]	[45.9, 67.0]	[48.8, 63.9]	[43.3, 57.8]
p-value (1-sided, alpha=2.5%)			p=0.051 (NS)	p=0.441 (NS)
LIC <7 mg Fe/g dw	n=10	n=13	n=23	n=25
Success rate (n (%))	2 (20.0)	8 (61.5)	10 (43.5)	10 (40.0)
95% CI	[2.5, 55.6]	[31.6, 86.1]	[23.2, 65.5]	[21.1, 61.3]
LIC ≥7 mg Fe/g dw	n=70	n=72	n=142	n=159
Success rate (n (%))	43 (61.4)	40 (55.6)	83 (58.5)	83 (52.2)
95% CI	[50.0, 72.8]	[44.1, 67.0]	[50.3, 66.6]	[44.4, 60.0]
p-value (1-sided, alpha=2.5%)			p=0.022 (S)	p=0.289 (NS)
Biopsy	n=64	n=46	n=110	n=120
Success rate (n (%))	39 (60.9)	28 (60.9)	67 (60.9)	67 (55.8)
95% CI	[49.0, 72.9]	[46.8, 75.0]	[51.8, 70]	[46.9, 64.7]
p-value (1-sided, alpha=2.5%)			p=0.011 (S)	p=0.101 (NS)
LIC <7 mg Fe/g dw	n=6	n=0	n=6	n=7
Success rate (n (%))	-	-	-	-
95% CI	[0, 45.9]	-	[0, 45.9]	[0, 41.0]
LIC ≥7 mg Fe/g dw	n=58	n=46	n=104	n=113
Success rate (n (%))	39 (67.2)	28 (60.9)	67 (64.4)	67 (59.3)
95% CI	[55.2, 79.3]	[46.8, 75.0]	[55.2, 73.6]	[50.2, 68.4]
p-value (1-sided, alpha=2.5%)			p=0.002 (S)	p=0.024 (S)
SQUID	n=16	n=39	n=55	n=64
Success rate (n (%))	6 (37.5)	20 (51.3)	26 (47.3)	26 (40.6)
95% CI	[13.8, 61.2]	[35.6, 67.0]	[34.1, 60.5]	[28.6, 52.7]
LIC <7 mg Fe/g dw	n=4	n=13	n=17	n=18
Success rate (n (%))	2 (50.0)	8 (61.5)	10 (58.8)	10 (55.6)
95% CI	[6.8, 93.2]	[31.6, 86.1]	[32.9, 81.6]	[30.8, 78.5]
LIC ≥7 mg Fe/g dw	n=12	n=26	n=38	n=46
Success rate (n (%))	4 (33.3)	12 (46.2)	16 (42.1)	16 (34.8)
95% CI	[6.7, 60.0]	[27.0, 65.3]	[26.4, 57.8]	[21.0, 48.5]

Source: Sponsor submission page 75

In the overall ITT population the success rate was 50.5% (95% CI 43.3, 57.8). The success rate was 59.3% (95% CI 50.2, 68.4) in the subgroup of patients who had an LIC ≥7 mg Fe/g dw by biopsy. This was also true for the same subgroup in the PP-1 population (success rate, 64.4% [CI 55.2, 73.6]). The success rate was somewhat greater in patients with β-thalassemia than with rare anemias. There were no statistically significant differences in success rates among patients with myelodysplastic syndrome, Diamond-Blackfan syndrome or other miscellaneous anemias, perhaps because the number of patients enrolled in each category was too small to demonstrate a difference. Patients who had large transfusion requirements tended to fare poorly, while those whose transfusion requirements were small responded more favorably to the administration of Exjade.

Secondary endpoints included the following:

- Liver iron concentration. The mean liver iron concentrations at baseline in patients who had LIC determination by biopsy (101/147 patients in the PP-2 population) was 21.9 ± 10.29 mg Fe/g dw as compared to a mean LIC of 9.5 ± 5.35 mg Fe/g dw in patients whose LIC was determined by SQUID (46/147 patients in the PP-2 population).. This difference at baseline approximates the now known 2:1 ratio between LIC measured by biopsy versus SQUID. Proportionally more children and older patients with myelodysplasia had LIC by SQUID than other age groups and these patients were protocol-assigned to lower doses of Exjade. Patients assigned to low doses (5-10 mg/kg/d) of Exjade had an increase in LIC over the period of the study. Those assigned to a dose of 20 mg/kg/d had an equal or slightly lower LIC at study's end, while those assigned to 30 mg/kg/d had a mean decrease in LIC between 5-10 mg Fe/g dw depending in part on the underlying cause of the anemia. In patients with biopsy demonstrated LIC of ≥ 7 mg Fe/g dw at baseline, there was a decrease of 6.5 ± 7.98 mg Fe/g dw at the end of the study (p<0.001). There was a statistically similar decrease in LIC in patients whose LIC was ≥ 7 mg Fe/g dw as determined by SQUID but the decrease was less marked (mean, 2.4 ± 3.49 mg Fe/g dw).
- Iron balance. The average iron intake was 0.35 ± 0.12 mg/kg/d for patients with β-thalassemia, 0.28 ± 0.14 mg/kg/d for patients with myelodysplastic anemia, 0.4 ± 0.11 mg/kg/d for patients with Diamond-Blackfan syndrome and 0.31 ± 0.19 mg/kg/d for patients with miscellaneous anemias. The mean ratio of Fe excretion/Fe intake was 1.45 ± 0.948 for all patients. It was generally lower for patients with Diamond-Blackfan syndrome than it was for myelodysplastic syndrome and miscellaneous anemias, primarily because of the greater intake of iron in patients with Diamond-Blackfan syndrome.
- Serum ferritin. Serum ferritin, although varying markedly throughout the trial in all populations, did appear to track the changes in LIC. In patients receiving Exjade at a dose of 5-10 mg/kg/d, serum ferritin tended to rise over the year of the trial. In patients receiving Exjade at a dose of 20 mg/kg/d, serum ferritin was stable or fell somewhat. In patients receiving Exjade at a dose of 30 mg/kg/d, serum ferritin decreased (mean decrease 854.3 ± 1728.4 µg/L) in all groups studied but by different amounts depending on the underlying cause of anemia.
- Serum iron, serum transferrin and transferrin saturation. These markers were of no value in following the course of treatment with Exjade.
- Liver pathology. No statistically significant changes in scored liver pathology were present in patients treated with Exjade.

Reviewer's Comments. The methodology of this trial is similar to that of 0107. The differences included:

- *No comparator arm was included.*
- *Patients with hemosiderosis due to blood transfusions for both β-thalassemia and other chronic anemias (MDS, BDS, miscellaneous) were included.*

The efficacy results are similar. Patients who received low doses of Exjade seemed not to benefit. Higher doses of the drug were associated with what appeared to be a significant reduction in LIC during therapy for one year in patients whose liver iron measured by biopsy was ≥7 mg Fe/g dw. This study adds support to the idea that Exjade, at least at higher doses, is able to decrease LIC in patients with transfusion related hemosiderosis even as they continue to receive transfusions, even though the decrease is limited by the number of transfusions that are administered during the interval. The study of iron balance is suspect because the formula for its calculation requires an accurate measure of LIC and that is not possible with SQUID.

5.1.4   Efficacy Findings

Reviewer's Summary of Efficacy

The sponsor failed to achieve the primary efficacy objective in its pivotal trial, Study 0107. The efficacy objective was to demonstrate non-inferiority of the proportion of patients with β-thalassemia and transfusion induced hemosiderosis "successfully treated" (i,e., who met specified values for LIC after 48 weeks of treatment) with Exjade compared to a similar group of patients who were treated with DFO. The success rate in the PP-1 population was 146/276 (52.9%, CI, 47.0, 58.8) of patients treated with Exjade compared to 184/277 (66.4%, CI 60.9, 72.0) of patients treated with DFO. The difference in success rates between the two arms was -13.5%. The confidence interval of the point estimate (-21.6, -5.4) exceeded the prespecified non-inferiority margin of -15%. This would normally be interpreted as not providing support for approval of an indication. However, there are several other aspects of the data that should be examined in order to better evaluate the efficacy of the agent.

First, it appears that the main cause for failure for the overall population in the trial was an insufficient dose of Exjade in many of the patients. Insufficient dosing appears to have been an error of the sponsor's own doing. It is peculiar that the sponsor would even have considered using Exjade in doses of 5-10 mg/kg/d in any of its trials since in an earlier twelve day pharmacodynamic study (0104) in 23 patients with transfusion dependent β-thalassemia, the mean iron excretion rate in patients receiving Exjade at a dose of 10 mg/kg/d was only 0.119 ± 0.06 mg/kg/d. For a 50 kg patient, iron excretion would have amounted to approximately 6 mg daily (180 mg monthly). This degree of iron excretion is clearly insufficient to keep pace with iron intake from continuing transfusion requirements of several units of packed red cell transfusions monthly. One could view Study 0107 as a dose-comparison concurrent control study with several doses of Exjade compared to DFO and conclude that high dose Exjade demonstrates a clinically meaningful iron excretion compared to DFO. The same conclusion could be reached for the other studies performed by the sponsor. Such an interpretation, however, would have to consider both the lack of randomization (since Exjade dose was based on LIC) and blinding.

Second, the sponsor did not use the data from the phase II dose/response studies (0105 and 0106) properly in the design of the pivotal trial (0107). As preliminarily suggested from Study 0104, the sponsor showed in these two studies that Exjade at a dose of 10 mg/kg/d was incapable of reducing either LIC (as measured by SQUID) or serum ferritin in transfused β-thalassemia pediatric or adult patients. While underdosing was in part related to the use of SQUID measurement of LIC, of additional concern to the sponsor was the prospect of overchelation of iron and the possibility that this would lead to an increase in adverse events, particularly renal, that had been suggested in preclinical studies. Nonetheless, it seems in retrospect that the primary endpoint would have been achieved had the sponsor employed doses in the pivotal trial that would have been suggested by the results from the earlier trials. Part of the problem is due to the fact that the trials often overlapped.

Third, although subgroup analysis is frowned upon to support an indication, it should be noted that the sponsor did pre-specify in the pivotal trial that there would be an efficacy analysis of the subgroup of patients whose LIC was ≥7 mg Fe/g dw. This is an important subgroup of patients as it is probable that patients with higher LICs are at greater risk of iron organ damage than patients whose LICs are lower. In the group of patients with LIC ≥7 mg Fe/g dw as measured by either biopsy or SQUID, non-inferiority to DFO was achieved. Additionally, in this same group the secondary endpoints of a decrease in mean LIC from baseline to end of study and a decrease in serum ferritin over the same time frame were also achieved. This is important because an argument can be made that a significant reduction in LIC is the most desirable outcome in patients as it seems to correlate with total body iron burden.

Fourth, the non-inferiority margin selected should be based on the known efficacy of the comparator. Although there is a body of information on the improvement of survival and morbidity in patients with β-thalassemia treated with DFO, there is a paucity of data on the quantitative changes in liver biopsy determined LIC. In one prospective study of 16 children with β-thalassemia (9), LIC fell from a baseline value of approximately 3.3 to 2.6 μg Fe/g dw after one year of therapy with DFO. No control population was studied. The selection of the non-inferiority margin of -15% for the analysis of comparison to DFO was arbitrarily chosen. Whether or not that non-inferiority margin was correct from a clinical point of view is uncertain because of the lack of information from previous studies of the effect of DFO on biopsy-determined LIC. In Study 0107, the 95% confidence interval for the point estimate of -13.5% in the difference in success rate between Exjade and DFO for the entire PP-1 population (553 patients) was [-21.6, -5.4].

Fifth, Study 0108 lends support to the findings in the pivotal trial, since the results in the patients with β-thalassemia mirror the results in Study 0107. In patients with other transfusion dependent anemias, the data are less convincing and must be interpreted in light of the differences in the natural histories of the diseases that were included in that population.

Study 0107 suggests that Exjade is effective in reducing iron overload in pediatric patients with LICs ≥7 mg Fe/g dw since a large fraction of the patients in the trial were in the pediatric age group and their response to therapy was the same as adult patients. Similarly, there does not

appear to be any difference in response related to gender. Most of the patients receiving therapy with Exjade were Caucasians because of the ethnic distribution of the disease of interest. The sponsor is currently conducting an efficacy study in patients with sickle cell disease and transfusional hemosiderosis that will provide data on a largely Black population.

Judgments about the clinical effectiveness of an agent must be made in comparison with available therapy. The only approved drug for the indication is DFO. DFO suffers primarily from its required method of administration. While it appears to be effective in those who can adhere to an onerous schedule, those physicians and patients who contend with the problems of its long term use to gain its benefits are in the minority. Many of the patients who could likely benefit from an iron offloading agent are therefore never treated.

5.1.5   Clinical Microbiology

Not applicable.

5.1.6   Efficacy Conclusions

6   INTEGRATED REVIEW OF SAFETY

6.1   Methods and Findings

The review of safety was based on the data submitted by the sponsor from all the clinical trials performed to date. The data included adverse events, laboratory assessments, various examinations (particularly ocular and auditory) and other evaluations.

6.1.1   Deaths

No deaths occurred during Studies 0105 or 0106.

There were 4 deaths in Study 0107, 1 in an Exjade treated patient and 3 in DFO treated patients. The causes of death are shown in the following table.

Causes of death by system organ class and preferred term

Primary system organ class Preferred Term	ICL670 N=296 n (%)	DFO N=290 n (%)	All patients N=586 n (%)
Any primary system organ class	1 (0.3)	3 (1.0)	4 (0.7)
Cardiac disorders	-	1 (0.3)	1 (0.2)
Intracardiac thrombus	-	1 (0.3)	1 (0.2)
General disorders	1 (0.3)	-	1 (0.2)
Sudden death	1 (0.3)	-	1 (0.2)
Infections and infestations	-	1 (0.3)	1 (0.2)
Septic shock	-	1 (0.3)	1 (0.2)
Nervous system disorders	-	1 (0.3)	1 (0.2)
Convulsion	-	1 (0.3)	1 (0.2)

Source: Sponsor submission page 102

Descriptions of the deaths are as follows:

One patient died while receiving Exjade.
- Patient 1902/00049 was a 3 year old Tunisian male who was diagnosed with β-thalassemia major in   . He lived 400 km from the study center. He had been splenectomized on   to reduce transfusion requirements, had been immunized and was taking prophylactic penicillin. He had been receiving DFO for 2 months prior to entry on the study. His LIC by biopsy at study entry was 16.0 mg Fe/g dw. He commenced Exjade therapy at a dose of 31.2 mg/kg/d on   . He had received his last blood transfusion on   . His last laboratory studies were performed on   . These were generally normal except for the following: ferritin, 1209 µg/L; LDH, 315 U/L; β-2 microglobulin, 2350 µg/L; C-reactive protein, 8.6 mg/L; and transferrin saturation, 108%.   He died on   which was the 84th day of Exjade administration. The clinical description was that the child had been well on the day of death but awakened from sleep sobbing and appeared to be very ill. There was no obvious fever. He then died suddenly before any medical evaluation could be performed. Because of the distance from his home to the medical facility and the rapidity of his demise, he was not seen by any health related individual at the time of death. No autopsy was performed. No specific cause of death was established.

Reviewer's Comments. This case is troubling but the lack of any evaluation of the episode does not permit speculation on the cause of death and what, if any, relationship there was to Exjade.

Three patients died while receiving DFO.
- Patient 0418/00013 was a 40 year old male with β-thalassemia intermedia who was splenectomized at age 12. On study Day 328, the patient experienced severe diarrhea, fever, vomiting and headaches, and was hospitalized the next day. He presented with dehydration, altered consciousness, mental and physical agitation, and convulsions. CT scan of the brain was normal but laboratory results were compatible with infection.

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Shortly after the CT scan, the patient had a convulsion and died. The final diagnosis was viral encephalitis. No autopsy was performed.

- Patient 1101/00009 was a 20 year old female with β-thalassemia major. On Day 96, she reported concentration problems which persisted and was prescribed essitalopram for ten days. The patient saw her doctor on Day 178 of the study with complaints of vomiting, sore throat and somnolence. Due to severe vomiting and dehydration, the patient was hospitalized that same day. The patient was rehydrated and also received a blood transfusion. Her general condition was considered satisfactory but she was kept in the hospital for observation. That evening, severe vomiting recurred together with hemoptysis and cyanosis. She was transferred to the intensive care unit where she was intubated, experienced further convulsions and developed acidosis. The patient was given nitrazepam. The following day, an X-ray revealed severe acute respiratory distress syndrome. The patient developed fever and was started on vancomycin and penicillin. She subsequently received ceftriaxone and ciprofloxacin due to septic shock and possible Yersinia infection. She developed hypotension and hyperglycemia and died the next day. No autopsy was performed. Septic shock was thought to be the cause of death, although the results of blood, throat and tracheal aspirate cultures were negative. The exact cause of death was unclear.
- Patient 1903/00005 was a 10 year old girl with β-thalassemia major who had had a splenectomy. On Day 366 of the study, an intraventricular thrombus and heart failure were diagnosed and she was hospitalized. Symptoms and treatment were not specified. Study drug was discontinued on Day 378. The patient died five days later.

Reviewer's Comments. The causes of death in patients in the DFO arm of the trial are similarly uncertain.

The four deaths out of less than 600 subjects in a period of one year, particularly in patients in this age group, are disconcerting. Patients entered into the trial had to have reasonable organ function at the time of entry, so none of them could have been considered "end-stage". Three of the deaths occurred in the comparator arm of the trial.

In Study 0108, all patients received Exjade as there was no control arm. There were 6 deaths in Study 0108 and all were in the "rare anemia" group (99 patients were in the rare anemia group and 85 patients had β-thalassemia with a total study size of 184 patients). Five of the deaths occurred in patients with myelodysplastic syndrome and one occurred in a patient with Diamond-Blackfan syndrome. No deaths occurred among the patients with β-thalassemia (85 patients). The deaths are described as follows:

- Patient 0410-00001 was a 76-year-old Caucasian man diagnosed with MDS two years prior to study entry. His main medical conditions included left ventricular hypertrophy, reduced diastolic function, and chronic obstructive bronchitis. On study Day 20 of the study, the patient was hospitalized due to severe dehydration. Study drug was discontinued. Following appropriate treatment including rehydration, his condition improved. On Day 27, while still hospitalized, he experienced dyspnea, tachycardia, mental confusion, and died due to cardiorespiratory arrest. No autopsy was performed.

- Patient 0503-00009 was a 71-year-old Caucasian woman in whom MDS was diagnosed ten years prior to study entry. Ongoing medical problems included coronary artery disease and hypothyroidism. At study entry, the absolute neutrophil count (ANC) was 0.85 x 10^9/L. On Day 291 of the study, the patient experienced back pain and decreased energy and presented to her general practitioner two days later. She was admitted to the hospital the same day with sepsis and pneumonia which rapidly progressed to acute respiratory distress syndrome. Neutropenia (ANC 0.68 x 10^9/L) was present and ascribed to 5-azacytidine which had been taken as treatment for MDS since Day 272. The patient began antibiotics but died that night. No autopsy was performed.

- Patient 0504-00006 was a 49-year-old Caucasian woman diagnosed with MDS two years prior to study entry. She had undergone a partial right lung lobectomy due to a pulmonary embolism six weeks prior to study entry. She was taking warfarin and acetylsalicylic acid in an effort to prevent recurrence. On Day 20, while at the doctor's office, she experienced inability to breathe, cough and hemoptysis, and cardiac arrest. Attempts at resuscitation were unsuccessful. At autopsy, the cause of death was recorded as asphyxia due to hemoaspiration due to a pulmonary infarction.

- Patient 0904-00002 was a 54-year-old Caucasian man who was diagnosed with MDS six years prior to study entry. The disease course was complicated by severe neutropenia and episodes of septic fever. At study entry, the absolute neutrophil count (ANC) was 0.63 x 10^9/L. On Day 24 of the study, the patient experienced neutropenic sepsis and was admitted to the hospital where he died three days later. The ANC on Day 27 was 0.06 x 10^9/L.

- Patient 1202-00003 was a 71-year-old Caucasian woman who was diagnosed with MDS five years prior to study entry. Medical conditions at study entry included angina pectoris, hypertension, polyarthrosis, osteoporosis, gastritis, intestinal dysfunction and anxiety. On Day 348 of the study, as per protocol, the patient underwent an end-of-study liver biopsy to evaluate liver iron content. Three days later, she developed severe abdominal pain and was hospitalized the same day. Peritoneal bleeding due to liver lacerations sustained during the liver biopsy was diagnosed. Hypovolemic shock, disseminated intravascular coagulation and renal failure followed and the patient was admitted to intensive care. She underwent a laparotomy for liver suture and was treated with multiple transfusions, artificial ventilation and antibiotics. On Day 355, she developed ileus and an abdominal infection. She was treated with antibiotics, rectal catheters, gastric catheters and parenteral alimentation. Study drug was discontinued on Day 370. Six days later, she developed *Enterococcus* and *Staphylococcus* septicemia and died 18 days later. The cause of death was septic complications following a laparotomy to repair liver lacerations. An autopsy was not performed.

- Patient 0801-00018 was a 42-year-old Caucasian female with Diamond-Blackfan syndrome who had medical problems at study entry that included bone marrow failure, hypothyroidism and depression. At entry into the study, her absolute neutrophil count (ANC) was 0.36 x 10^9/L. On Day 159, she was admitted to the hospital with fever, thought to be due to a hematoma. She was started on intravenous antibiotics and discharged the next day but attended the hospital daily for treatment. She was re-hospitalized on Day 167 with fever and hypotension. The ANC was 0.11 x 10^9/L. Study

drug was discontinued. She developed gram-negative sepsis and her condition deteriorated despite medical intervention. She died four days later.

Reviewer's Comments. Two of the six deaths were cardiorespiratory in nature, one related to pulmonary embolism (with a pre-existing embolic event) and one possibly embolic or due to myocardial infarction. Three of the six deaths were probably attributable to sepsis associated with neutropenia. Although all three were neutropenic prior to institution of Exjade, it is possible that Exjade contributed to the worsening of the neutropenia. One patient died of post-operative complications after surgery to repair a biopsy induced hepatic laceration.

6.1.2 Other Serious Adverse Events

Serious adverse events (SAE) observed in Study 0105 are shown in the following table.

Table 10-3 Numbers (%) of patients with SAEs (safety population)

Primary system organ class Preferred term	ICL670 10 mg/kg N=24 n (%)	ICL670 20 mg/kg N=24 n (%)	DFO 40 mg/kg N=23 n (%)	All treatments N=71 n (%)
Any primary system organ class	4 (16.7)	3 (12.5)	5 (21.7)	12 (16.9)
Cardiac disorders	0 (0.0)	1 (4.2)	2 (8.7)	3 (4.2)
Arrhythmia NOS	0 (0.0)	1 (4.2)	1 (4.3)	2 (2.8)
Atrial fibrillation	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
Cardiac failure NOS	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
Gastrointestinal disorders	1 (4.2)	0 (0.0)	2 (8.7)	3 (4.2)
Abdominal pain NOS	1 (4.2)*	0 (0.0)	2 (8.7)	3 (4.2)
Infections and infestations	1 (4.2)	1 (4.2)	1 (4.3)	3 (4.2)
Bacterial infection NOS	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.4)
Pyelonephritis NOS	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
General disorders	1 (4.2)	0 (0.0)	1 (4.3)	2 (2.8)
Edema peripheral	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.4)
Pyrexia	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
Renal and urinary disorders	1 (4.2)	1 (4.2)	0 (0.0)	2 (2.8)
Renal colic	1 (4.2)	1 (4.2)	0 (0.0)	2 (2.8)
Hepatobiliary disorders	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Cholecystitis NOS	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Injury etc.	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Femur fracture	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Injury NOS	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Radius fracture	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Investigations	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
Urinary endoscopy	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
Vascular disorders	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.4)
Thrombophlebitis	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.4)

Source: Sponsor submission page 57

Reviewer's Comments. All patients in this study had β-thalassemia. The frequency of SAEs was similar in patients receiving either dose level of Exjade or DFO. One patient receiving Exjade at a dose of 10 mg/kg/d and one patient receiving Exjade at a dose of 20 mg/kg/d had an episode of renal colic. One cardiac SAEs (arrhythmia, CHF) occurred in a patient receiving Exjade at a dose of 20 mg/kg/d. SAEs led to drug discontinuation in 2 cases: trauma from an automobile accident led to discontinuation in one patient receiving Exjade; arrhythmia with CHF led to discontinuation in one patient receiving DFO.

Serious adverse events observed in Study 0106 are shown in the following table.

Table 10-3   Number (%) of patients with SAEs

Primary system organ class Preferred term	Children <12 yrs N=20 n (%)	Children ≥12 yrs N=20 n (%)	All patients N=40 n (%)
Any primary system organ class	1 (5.0)	3 (5.0)	4 (10.0)
Gastrointestinal disorders	0 (0.0)	1 (5.0)	1 (2.5)
Pancreatitis	0 (0.0)	1 (5.0)	1 (2.5)
Hepatobiliary disorders	0 (0.0)	1 (5.0)	1 (2.5)
Cholelithiasis	0 (0.0)	1 (5.0)	1 (2.5)
Infections and infestations	0 (0.0)	1 (5.0)	1 (2.5)
Gastroenteritis	0 (0.0)	1 (5.0)	1 (2.5)
Injury etc	1 (5.0)	1 (5.0)	2 (5.0)
Head injury	1 (5.0)	0 (0.0)	1 (2.5)
Transfusion reaction	0 (0.0)	1 (5.0)	1 (2.5)
Surgical and medical procedures	0 (0.0)	2 (10.0)	2 (5.0)
Cholecystectomy	0 (0.0)	1 (5.0)	1 (2.5)
Tonsillectomy	0 (0.0)	1 (5.0)	1 (2.5)

Source: Sponsor submission page 59

Reviewer's Comments. All of the patients in this study were children with β-thalassemia. The episode of cholelithiasis with pancreatitis leading to cholecystectomy is probably due to hemolysis. The SAEs do not appear to be drug related and none of the SAEs led to drug discontinuation.

Serious adverse events observed in Study 0107 are shown in the following table.

Table 10-5 Number (%) of patients with SAEs by primary system organ class a preferred term

Primary system organ class Preferred term	ICL670 N=296 n (%)	DFO N=290 n (%)	All patients N=586 n (%)
Any primary system organ class*	27 (9.1)	25 (8.6)	52 (8.9)
Infections and infestations	7 (2.4)	9 (3.1)	16 (2.7)
Septic shock**	-	1 (0.3)	1 (0.2)
Gastrointestinal disorders	4 (1.4)	5 (1.7)	9 (1.5)
Abdominal pain	1 (0.3)	1 (0.3)	2 (0.3)
Diarrhoea	-	1 (0.3)	1 (0.2)
Dyspepsia	1 (0.3)	-	1 (0.2)
Gastric ulcer	1 (0.3)	-	1 (0.2)
Gastritis	-	1 (0.3)	1 (0.2)
Hiatus hernia	-	1(0.3)	1 (0.2)
Peritoneal haemorrhage	1 (0.3)	-	1 (0.2)
Vomiting	-	2 (0.7)	2 (0.3)
General disorders	5 (1.7)	2 (0.7)	7 (1.2)
Chest pain	1 (0.3)	-	1 (0.2)
Sudden death**	1 (0.3)	-	1 (0.2)
Pyrexia	3 (1.0)	2 (0.7)	5 (0.9)
Injury etc.	5 (1.7)	1 (0.3)	6 (1.0)
Cardiac disorders	2 (0.7)	3 (1.0)	5 (0.9)
Arrhythmia	1 (0.3)	-	1 (0.2)
Cardiac arrest	-	1 (0.3)	1 (0.2)
Intracardiac thrombus**	-	1 (0.3)	1 (0.2)
Palpitations	-	1 (0.3)	1 (0.2)
Ventricular tachycardia	1 (0.3)	-	1 (0.2)
Nervous system disorders	3 (1.0)	2 (0.7)	5 (0.9)
Brain oedema	-	1 (0.3)	1 (0.2)
Convulsion*	-	2 (0.7)	2 (0.3)
Encephalopathy	-	1 (0.3)	1 (0.2)
Loss of consciousness	1 (0.3)	-	1 (0.2)
Psychomotor hyperactivity	1 (0.3)		1 (0.2)
Somnolence		1 (0.3)	1 (0.2)
Syncope	1 (0.3)	-	1 (0.2)
Blood and lymphatic system disorders	2 (0.7)	2 (0.7)	4 (0.7)
Anaemia	-	1 (0.3)	1 (0.2)
Hypersplenism acquired	-	1 (0.3)	1 (0.2)
Lymphadenopathy	1 (0.3)	-	1 (0.2)

Neutropenia	1 (0.3)	-	1 (0.2)
Musculoskeletal disorders	2 (0.7)	2 (0.7)	4 (0.7)
Arthralgia	1 (0.3)	0 (0.0)	1 (0.2)
Back pain	-	2 (0.7)	2 (0.3)
Osteoporotic fracture	1 (0.3)	-	1 (0.2)
Surgical and medical procedures	2 (0.7)	2 (0.7)	4 (0.7)
Splenectomy	2 (0.7)	2 (0.7)	4 (0.7)
Hepatobiliary disorders	2 (0.7)	-	2 (0.3)
Hepatitis	2 (0.7)	-	2 (0.3)
Metabolic and nutritional disorders	-	2 (0.7)	2 (0.3)
Dehydration	-	1 (0.3)	1 (0.2)
Diabetes mellitus	-	1 (0.3)	1 (0.2)
Renal and urinary disorders	-	2 (0.7)	2 (0.3)
Calculus urinary	-	1 (0.3)	1 (0.2)
Vesicoureteric reflux	-	1 (0.3)	1 (0.2)
Skin disorders	2 (0.7)	-	2 (0.3)
Dermatitis allergic	1 (0.3)	-	1 (0.2)
Rash	1 (0.3)	-	1 (0.2)
Reproductive disorders	-	2 0.7)	2 (0.3)
Pregnancy	-	1 (0.3)	1 (0.2)
Pregnancy	-	1 (0.3)	1 (0.2)
Psychiatric disorders	1 (0.3)	-	1 (0.2)
Insomnia	1 (0.3)	-	1 (0.2)
Ear and labyrinth disorders	1 (0.3)	-	1 (0.2)
Vertigo	1 (0.3)	-	1 (0.2)
Eye disorders	1 (0.3)	-	1 (0.2)
Cataract	1 (0.3)	-	1 (0.2)
Respiratory disorders	-	1 (0.3)	1 (0.2)

Source: Sponsor submission page 103-4

Two patients developed hepatitis, one with accompanying neutropenia, while receiving Exjade. These cases are further described as follows:

Patient 0801-00003.

This 14-year-old Caucasian girl with β-thalassemia major was taking conjugated estrogens as hormone replacement therapy when randomized in the study to ICL670. Transaminase levels at study entry were normal and hepatitis serology was negative.

After 20 days of treatment with ICL670, she complained of abdominal pain which led to a one-day interruption of study drug. The abdominal pain resolved spontaneously eight days later. This event was graded as mild, and in the investigator's opinion, was suspected to be related to study drug.

The investigator noted a gradual, moderate increase in liver transaminases, starting on Day 83, when SGOT/AST and SGPT/ALT were 44 and 58 U/L (ULN 30 U/L), respectively. On Day 224, the patient again experienced abdominal pain. Initially mild and infrequent, her symptoms increased in severity. On Day 228, SGOT/AST and SGPT/ALT were 124 and 259 U/L, respectively. Study drug and hormone replacement therapy were permanently discontinued on Day 236 due to persistently elevated transaminases.

Patient 1105-00020

This 18-year-old Caucasian woman with β-thalassemia major had a medical history which included hepatitis B and C, recorded as inactive when the patient entered the study, though the patient was positive for hepatitis B surface antigen. Absolute neutrophil count (ANC) and liver transaminases were normal at study entry.

On Day 122, the patient experienced severe dyspepsia, mild heartburn and epigastric pain. The symptoms improved after treatment with omeprazole but recurred on Day 142. On Day 140, ANC was 1.73×10^9/L, and SGOT/AST and SGPT/ALT were 233 and 475 U/L, respectively. Study drug was interrupted on Day 147 and dyspepsia resolved three days later. The patient was hospitalized on Day 153 for further investigation. ALT levels had increased to 967 U/L and gamma-GT was slightly increased, but alkaline phosphatase, bilirubin, amylase and lipase were normal. Ultrasound showed hepatomegaly and tests for hepatitis B and C were positive. Serology tests for cytomegalovirus IgG were also positive. The patient was discharged after four days with a diagnosis of hepatocellular damage, possibly viral or drug-induced. The patient's condition improved after normalization of the transaminase levels and study drug was reintroduced on Day 172 at 20 mg/kg.

On Day 199, the patient experienced fever and recurrence of severe dyspepsia which led to hospitalization. The fever was found to be due to a dental problem which resolved 13 days later following the administration of cefuroxime. Study drug was temporarily interrupted due to dyspepsia but the patient' symptoms persisted despite treatment with ranitidine and omeprazole. The patient underwent several tests including blood cultures, agglutination tests for salmonella/brucella, urine microscopy and chest X-ray, all of which were negative. A gastroscopy was performed on Day 209 showed mild esophagitis and reflux. Biopsy showed duodenal congestion, antral edema and mild esophagitis. In the investigator's opinion, the esophagitis and gastroesophageal reflux were suspected to be related to study drug.

On Day 261, the dose of ICL670 was increased to 30 mg/kg. Nineteen days later, the patient again reported severe dyspepsia and nausea. When examined three days later, her gastric symptoms had resolved. However, on Day 287, laboratory tests showed a new increase of SGPT/ALT to 2121 U/L and of SGOT/AST to 875 U/L. Mild neutropenia was also present with an ANC of 1.37×10^9/L. A liver biopsy was compatible with drug-induced hepatotoxicity. There was also a mild reactivation of viral hepatitis as shown by low copy numbers of HBV-DNA on PCR. Study drug was permanently discontinued on Day 283. Serum ferritin had decreased from 2533 to 842 µg/L.

The investigator considered that the event was related to study drug.

Reviewer's Comments. All patients in Study 0107 had β-thalassemia. The frequency of SAEs was similar between the Exjade and the DFO treated patients. Infections and fever were the most common SAEs. Injuries were more common in patients receiving Exjade. Two patients developed drug induced hepatitis, one with accompanying neutropenia, while receiving Exjade

as noted in the above narratives. SAEs in Exjade treated patients included syncope, loss of consciousness, hyperactivity, skin rash (2), vertigo and the development of a cataract.

SAEs believed by the investigator to be related to Exjade included a severe skin rash (30 mg/k/d), cataract (30 mg/kg/d), atrial fibrillation (30 mg/kg/d), hyperactivity/insomnia (20 mg/kg/d), hematemesis (30 mg/kg/d), dermatitis (20 mg/kg/d) and increased transaminases (10 mg/kg/d and 30 mg/kg/d). SAEs led to drug discontinuation in 5 patients.

SAEs believed by the investigator to be related to DFO included a single patient who developed Yersinia enterocolitis on day 10 leading to drug discontinuation.

Serious adverse events observed in Study 0108 are shown in the following table.

Table 10-8 Numbers (%) of patients with SAEs by primary system organ class and preferred term

Primary system organ class	β-thalassemia N=85	Rare anemias N=99	All patients N=184
Preferred term	n (%)	n (%)	n (%)
Any primary system organ class*	11 (12.9)	27 (27.3)	38 (20.7)
Infections and infestations	2 (2.4)	15 (15.2)	17 (9.2)
Neutropenic sepsis**	-	1 (1.0)	1 (0.5)
Sepsis** (fatal in 1 patient)	-	3 (3.0)	3 (1.6)
Blood disorders	1 (1.2)	7 (7.1)	8 (4.3)
Anemia	-	2 (2.0)	2 (1.1)
Disseminated intravascular coagulation	-	1 (1.0)	1 (0.5)
Extramedullary hemopoiesis	1 (1.2)	-	1 (0.5)
Febrile neutropenia**	-	1 (1.0)	1 (0.5)
Neutropenia	-	2 (2.0)	2 (1.1)
Pancytopenia	-	1 (1.0)	1 (0.5)
General disorders	-	7 (7.1)	7 (3.8)
Chills	-	1 (1.0)	1 (0.5)
Malaise	-	1 (1.0)	1 (0.5)
Pyrexia	-	7 (7.1)	7 (3.8)
Gastrointestinal disorders	3 (3.5)	3 (3.0)	6 (3.3)
Abdominal pain	2 (2.4)	1 (1.0)	3 (1.6)
Constipation	-	1 (1.0)	1 (0.5)
Gastrointestinal hemorrhage	-	2 (2.0)	2 (1.1)
Ileus	-	1 (1.0)	1 (0.5)
Nausea	1 (1.2)	-	1 (0.5)
Varices esophageal	-	1 (1.0)	1 (0.5)
Vomiting	2 (2.4)	-	2 (1.1)
Cardiac disorders	2 (2.4)	3 (3.0)	5 (2.7)
Atrial fibrillation	1 (1.2)	1 (1.0)	2 (1.1)
Cardiac disorder	-	1 (1.0)	1 (0.5)
Cardio-respiratory arrest**	-	1 (1.0)	1 (0.5)
Mitral valve incompetence	-	1 (1.0)	1 (0.5)
Palpitations	1 (1.2)	-	1 (0.5)
Nervous system disorders	2 (2.4)	3 (3.0)	5 (2.7)
Cerebral hemorrhage	-	1 (1.0)	1 (0.5)
Dizziness	1 (1.2)	-	1 (0.5)
Headache	1 (1.2)	-	1 (0.5)

Loss of consciousness	-	1 (1.0)	1 (0.5)
Migraine	-	1 (1.0)	1 (0.5)
Metabolic and nutritional disorders	1 (1.2)	3 (3.0)	4 (2.2)
Anorexia	-	2 (2.0)	2 (1.1)
Dehydration	-	1 (1.0)	1 (0.5)
Hypocalcaemia	1 (1.2)	-	1 (0.5)
Respiratory disorders	-	4 (4.0)	4 (2.2)
Pulmonary hemorrhage**	-	1 (1.0)	1 (0.5)
Investigations	1 (1.2)	2 (2.0)	3 (1.6)
Blood phosphorus increased	-	1 (1.0)	1 (0.5)
Electrocardiogram abnormal	-	1 (1.0)	1 (0.5)
Heart rate irregular	1 (1.2)	-	1 (0.5)
Psychiatric disorders	2 (2.4)	1 (1.0)	3 (1.6)
Anxiety	2 (2.4)	-	2 (1.1)
Depression	-	1 (1.0)	1 (0.5)
Illusion	1 (1.2)	-	1 (0.5)
Vascular disorders	1 (1.2)	2 (2.0)	3 (1.6)
Hepatobiliary disorders	1 (1.2)	1 (1.0)	2 (1.1)
Cholelithiasis	1 (1.2)	-	1 (0.5)
Hepatic hemorrhage	-	1 (1.0)	1 (0.5)
Injury etc.	-	2 (2.0)	2 (1.1)
Renal and urinary disorders	2 (2.4)	-	2 (1.1)
Renal colic	1 (1.2)	-	1 (0.5)
Renal mass	1 (1.2)	-	1 (0.5)
Ear and labyrinth disorders	-	1 (1.0)	1 (0.5)
Sudden hearing loss	-	1 (1.0)	1 (0.5)
Musculoskeletal disorders	-	1 (1.0)	1 (0.5)
Arthralgia	-	1 (1.0)	1 (0.5)
Neoplasms	-	1 (1.0)	1 (0.5)
Acute leukemia	-	1 (1.0)	1 (0.5)
Skin and subcutaneous tissue disorders	1 (1.2)	-	1 (0.5)
Rash	1 (1.2)	-	1 (0.5)
Surgical and medical procedures	-	1 (1.0)	1 (0.5)
Toe amputation	-	1 (1.0)	1 (0.5)

Source: Sponsor submission page 108-9

Reviewer's Comments. This study included patients with β-thalassemia and other rare anemias. SAEs were more common in patients with rare anemias (27.3%) than in patients with β-thalassemia (12.9%). The most common SAEs were infections and fever. Of note, one patient with β-thalassemia developed renal colic. The SAEs described may have been related to the fact that patients with MDS were older and had concomitant medical conditions.

SAEs believed by the investigator to be related to Exjade in patients with β-thalassemia included anxiety, headache and illusions (Exjade, 30 mg/kg/d), drug rash (30 mg/kg/d), abdominal pain of uncertain etiology (30 mg/kg/d) and dizziness, vomiting, hypotension and arrhythmia (5 mg/kg/d). None of these SAEs led to drug discontinuation.

SAEs believed by the investigator to be related to Exjade in patients with rare anemias included high frequency hearing loss in a 78 year old male with MDS receiving Exjade at a dose of 5 mg/kg/d and loss of consciousness in a 67 year old male with MDS receiving 30 mg/kg/g who also had pneumonia. Neither of these SAEs led to drug discontinuation.

6.1.3   Dropouts and Other Significant Adverse Event

6.1.3.1   Overall profile of dropouts

The following table shows the reasons for, and the number of, dropouts in each of the studies.

Study Number	Exjade Dose	DFO dose	AEs	Drug Ineffective	Withdrawn consent
0105	20 mg/kg		1	1	
		40 mg/kg	2		
0106	10 mg/kg		1		
0107	5-40 mg/kg		7		7
		20->50 mg/kg	1		6
0108	5-30 mg/kg		13		10

In Study 0107, adverse events were responsible for 2 dropouts in the 10 mg/kg/d dose group, 2 dropouts in the 20 mg/kg/d dose group and 3 dropouts in the 30 mg/kg/d dose group. Withdrawal of consent was responsible for 1 dropout in the 5 mg/kg/d dose group and 5 dropouts in the 30 mg/kg/d dose group.

In Study 0108, adverse events were responsible for 2 dropouts in the 5 mg/kg/d dose group, 2 dropouts in the 20 mg/kg/d dose group and 9 dropouts in the 30 mg/kg/d dose group. Withdrawal of consent was responsible for 6 dropouts in the 20 mg/kg/d dose group and 4 dropouts in the 30 mg/kg/d dose group.

6.1.3.2   Adverse events associated with dropouts

In Study 0105, there were 2 dropouts in the Exjade arm. One patient (1/05) receiving 20 mg/kg/d had a traffic accident and discontinued therapy. One patient (3/08) receiving 20 mg/kg/d had 1st degree AVB on day 73 at which point the dose was decreased to 10 mg/kg/d. The LIC increased and it was believed that the higher dose should be resumed. However, by that time he had had a slight prolongation of the QT interval, and he was restarted on DFO.

There were 2 dropouts in the DFO arm. One patient (3/13) developed fever, headache and arthralgia believed related to the drug. One patient (2/10) developed arrhythmia and cardiac failure and the drug was discontinued.

In Study 0105, AEs that led to dose adjustment or temporary interruption are listed in the following table.

Table 10-4   Numbers (%) of patients experiencing non-serious AEs which led to dose adjustment or temporary interruption of therapy

Primary system organ class Preferred term	ICL670 10 mg/kg N=24 n (%)	ICL670 20 mg/kg N=24 n (%)	DFO 40 mg/kg N=23 n (%)	All treatments N=71 n (%)
-Any primary system organ class	6 (25.0)	13 (54.2)	6 (26.1)	25 (35.2)
Infections and infestations	**2 (8.3)**	**3 (12.5)**	**3 (13.0)**	**8 (11.3)**
Bacterial infections NOS	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.4)
Influenza	0 (0.0)	1 (4.2)	1 (4.3)	2 (2.8)
Pyelonephritis NOS	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Tonsillitis	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
Upper respiratory tract infection NOS	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
Urinary tract infection NOS	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.4)
Varicella	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Investigations	**2 (8.3)**	**5 (20.8)**	**0 (0.0)**	**7 (9.9)**
ALT increased	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.4)
β-2 microglobulin increased ##	0 (0.0)	4 (16.7)#	0 (0.0)	4 (16.7)#
Blood creatinine increased	0 (0.0)	1 (4.2)#	0 (0.0)	1 (1.4)#
Creatinine renal clearance decreased	0 (0.0)	1 (4.2)#	0 (0.0)	1 (1.4)#
QTc prolonged	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.4)
Gastrointestinal disorders	**2 (8.3)**	**3 (12.5)**	**2 (8.7)**	**7 (9.9)**
Abdominal pain NOS	1 (4.2)	0 (0)	2 (8.7)	3 (4.2)
Abdominal pain upper	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.4)
Diarrhea NOS	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Nausea	1 (4.2)	2 (8.3)	0 (0.0)	3 (4.2)
Vomiting NOS	0 (0.0)	2 (8.3)	0 (0.0)	2 (2.8)
General disorders	**0 (0.0)**	**2 (8.3)**	**3 (13.0)**	**5 (7.0)**
Local reaction	0 (0.0)	0 (0.0)	1 (4.3)#	1 (1.4)#
Pyrexia	0 (0.0)	2 (8.3)	2 (8.7)	4 (5.6)
Blood and lymphatic system disorders	**0 (0.0)**	**0 (0.0)**	**1 (4.3)**	**1 (1.4)**
Neutropenia	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
Cardiac disorders	**0 (0.0)**	**1 (4.2)**	**0 (0.0)**	**1 (1.4)**
First degree AV block	0 (0.0)	1 (4.2)#	0 (0.0)	1 (1.4)#
Hepatobiliary disorders	**0 (0.0)**	**1 (4.2)**	**0 (0.0)**	**1 (1.4)**
Cholecystitis NOS	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Injury etc.	**0 (0.0)**	**1 (4.2)**	**0 (0.0)**	**1 (1.4)**
Over chelation	0 (0.0)	1 (4.2)#	0 (0.0)	1 (1.4)#
Metabolic and nutritional disorders	**0 (0.0)**	**1 (4.2)**	**0 (0.0)**	**1 (1.4)**
Food intolerance NOS	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)
Renal and urinary disorders	**0 (0.0)**	**1 (4.2)**	**0 (0.0)**	**1 (1.4)**
Renal colic	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.4)

Source: Post-text Table 10.2-4
AEs suspected to be drug-related (one case of nausea and vomiting in a patient treated with ICL670 20 mg/kg was also suspected to be drug-related)
includes the terms β-2 microglobulin increased and β-2 microglobulin urine increased

Reviewer's Comments. Dose reductions occurred more frequently in patients receiving the higher dose of Exjade than those receiving the lower dose or receiving DFO. Renal abnormalities were the most common cause for alterations in dose with Exjade, particularly at a dose of 20 mg/kg/d. One patient receiving Exjade had renal colic, and one had an elevation in serum transaminase. Nausea, vomiting and diarrhea were seen only in the Exjade treated patients. AEs believed by the investigator to be related to Exjade included renal abnormalities, 1st degree AVB and overchelation.

In Study 0106, a single patient (0102-00010) was prematurely removed form the study on the 11th day because of a moderately severe pruritic rash that was believed related to Exjade.

In Study 0106, adverse events that led to drug interruption or drug reduction are listed in the following table.

Table 10-4   **Number (%) of patients with AEs requiring dose reduction or interruption**

Primary system organ class Preferred term	Children <12 yrs N=20 n (%)	Adolescents ≥12 yrs N=20 n (%)	All patients N=40 n (%)
Any primary system organ class	9 (45.0)	5 (25.0)	14 (35.0)
Gastrointestinal disorders	1 (5.0)	4 (20.0)	5 (12.5)
Diarrhea	0 (0.0)	1 (5.0)	1 (2.5)
Enteritis	1 (5.0)	0 (0.0)	1 (2.5)
Odynophagia	0 (0.0)	1 (5.0)	1 (2.5)
Pancreatitis	0 (0.0)	1 (5.0)	1 (2.5)
Vomiting	0 (0.0)	1 (5.0)	1 (2.5)
General disorders	2 (10.0)	0 (0.0)	2 (5.0)
Pyrexia	2 (10.0)	0 (0.0)	2 (5.0)
Hepatobiliary disorders	0 (0.0)	1 (5.0)	1 (2.5)
Cholelithiasis	0 (0.0)	1 (5.0)	1 (2.5)
Infections and infestations	2 (10.0)	1 (5.0)	3 (7.5)
Gastroenteritis	0 (0.0)	1 (5.0)	1 (2.5)
Influenza	1 (5.0)	0 (0.0)	1 (2.5)
Pharyngitis	1 (5.0)	0 (0.0)	1 (2.5)
Investigations	5 (25.0)	1 (5.0)	6 (15.0)
QTc prolonged	1 (5.0)	0 (0.0)	1 (2.5)
Transaminase increased	4 (20.0)	1 (5.0)	5 (12.5)
Renal and urinary disorders	0 (0.0)	1 (5.0)	1 (2.5)
Renal colic	0 (0.0)	1 (5.0)	1 (2.5)
Skin disorders	1 (5.0)	0 (0.0)	1 (2.5)
Rash pruritic	1 (5.0)	0 (0.0)	1 (2.5)
Surgical and medical procedures	0 (0.0)	1 (5.0)	1 (2.5)
Cholecystectomy	0 (0.0)	1 (5.0)	1 (2.5)

Source: Sponsor submission page 60

Reviewer's Comments. The most important AE that led to a dose change was a rise in transaminase levels. These were more commonly seen in patients age <12 years. However, these did not lead to drug discontinuation in any patient. Gastrointestinal disorders occurred in 5 patients. One patient had a skin rash. One episode of renal colic occurred.

In Study 0107 (pivotal), adverse events leading to discontinuation of study drug are listed in the following table.

Table 10-7 Number (%) of patients with AEs leading to discontinuation of study drug by primary system organ class and preferred term

Primary system organ class Preferred term	ICL670 N=296 n (%)	DFO N=290 n (%)	All patients N=586 n (%)
Any primary system organ class*	8 (2.7)	4 (1.4)	12 (2.0)
General disorders	2 (0.7)	1 (0.3)	3 (0.5)
Sudden death*	1 (0.3)	-	1 (0.2)
Pyrexia	1 (0.3)	1 (0.3)	2 (0.3)
Cardiac disorders	.	1 (0.3)	1 (0.2)
Intracardiac thrombus**	-	1 (0.3)	1 (0.2)
Investigations	3 (1.0)	-	3 (0.5)
ALT increased	2 (0.7)	-	2 (0.3)
AST increased	1 (0.3)	-	1 (0.2)
Transaminases increased	1 (0.3)	-	1 (0.2)
Nervous system disorders	1 (0.3)	2 (0.7)	3 (0.5)
Brain oedema	-	1 (0.3)	1 (0.2)
Convulsions ** (fatal in 1 patient)	-	2 (0.7)	2 (0.3)
Encephalopathy	-	1 (0.3)	1 (0.2)
Psychomotor hyperactivity	1 (0.3)	-	1 (0.2)
Somnolence	-	1 (0.3)	1 (0.2)
Eye disorders	1 (0.3)	-	1 (0.2)
Cataract	1 (0.3)	-	1 (0.2)
Gastrointestinal disorders	-	1 (0.3)	1 (0.2)
Diarrhoea	-	1 (0.3)	1 (0.2)

Primary system organ class	ICL670	DFO	All patients
Preferred term	N=296	N=290	N=586
	n (%)	n (%)	n (%)
Vomiting	-	1 (0.3)	1 (0.2)
Hepatobiliary disorders	1 (0.3)	-	1 (0.2)
Hepatitis	1 (0.3)	-	1 (0.2)
Infections and infestations	-	1 (0.3)	1 (0.2)
Septic shock**	-	1 (0.3)	1 (0.2)
Yersinia infection	-	1 (0.3)	1 (0.2)
Metabolic disorders	-	1 (0.3)	1 (0.2)
Dehydration		1 (0.3)	1 (0.2)
Pregnancy	-	1 (0.3)	1 (0.2)
Pregnancy	-	1 (0.3)	1 (0.2)
Psychiatric disorders	1 (0.3)	-	1 (0.2)
Insomnia	1 (0.3)	-	1 (0.2)
Respiratory disorders	-	1 (0.3)	1 (0.2)
Acute respiratory distress syndrome	-	1 (0.3)	1 (0.2)
Skin disorders	1 (0.3)	-	1 (0.2)
Rash maculo-papular	1 (0.3)	-	1 (0.2)
Rash pruritic	1 (0.3)	-	1 (0.2)

Source: Sponsor submission page 108-9

Reviewer's Comments. Seven patients receiving Exjade were discontinued from study drug because of AEs. These included fever and skin rash (1), increase in transaminases/hepatitis (4), cataract formation (1) and hyperactivity/insomnia (1). One patient receiving DFO was discontinued from study drug because of pregnancy. Discontinuation from the study because of death occurred in one patient in the Exjade arm and 3 patients in the DFO arm.

In Study 0107 (pivotal), dose reduction and interruption due to AEs are shown in the following table.

Table 10-6 Number (%) of patients with AEs requiring dose reduction or interruption by primary system organ class

Primary system organ class	ICL670 N=296 n (%)	DFO N=290 n (%)	All patients N=586 n (%)
Any primary system organ class	92 (31.1)	54 (18.6)	146 (25.0)
Infections and infestations	20 (6.8)	26 (8.9)	46 (7.8)
Investigations	37 (12.5)	-	37 (6.3)
General disorders	12 (4.0)	20 (6.9)	32 (5.5)
Gastrointestinal disorders	15 (5.1)	10 (3.4)	25 (4.2)
Skin disorders	15 (5.1)	1 (0.3)	16 (2.7)
Respiratory disorders	5 (1.7)	5 (1.7)	10 (1.7)
Nervous system disorders	5 (1.6)	2 (0.7)	7 (1.3)
Injury etc.	4 (1.4)	2 (0.7)	6 (0.9)
Musculoskeletal disorders	3 (1.0)	3 (1.0)	6 (1.1)
Cardiac disorders	5 (1.7)	-	5 (0.8)
Ear and labyrinth disorders	-	3 (1.0)	3 (0.5)
Renal and urinary disorders	2 (0.6)	1 (0.3)	3 (0.6)
Reproductive disorders	-	2 (0.6)	2 (0.4)
Blood disorders	-	1 (0.3)	1 (0.2)
Congenital disorders	-	1 (0.3)	1 (0.2)
Eye disorders	1 (0.3)	-	1 (0.2)
Hepatobiliary disorders	1 (0.3)	-	1 (0.2)
Psychiatric disorders	1 (0.3)	-	1 (0.2)
Surgical/medical procedures	-	1 (0.3)	1 (0.2)

Source: Sponsor submission page 106

Reviewer's Comments. More Exjade treated patients (31.1%) had a dose reduction or interruption because of AEs compared to patients receiving DFO (18.6%). The most common AEs among patients receiving Exjade which led to dose change were mild increases in serum creatinine, infections, and GI and skin disorders. There appeared to be a dose effect for serum creatinine with 2.6%, 8.3% and 20.2% of Exjade treated patients requiring dose adjustments at dose levels of 10, 20 and 30 mg/kg/d, respectively. Most of these dose adjustments occurred in the 16-50 year age group.   In most patients, dose adjustment led to a return of the serum creatinine to baseline. A rise in transaminase levels caused a temporary interruption in 2 children, ages 8 and 9, before treatment was resumed at the same dose without recrudescence of the laboratory abnormality.

In Study 0108, the following table shows the number of patients in whom Exjade was discontinued.

Table 10-11 Number (%) of patients with AEs leading to discontinuation of study drug by primary system organ class and preferred term

Primary system organ class Preferred term	β-thalassemia N=85 n (%)	Rare anemias N=99 n (%)	All patients N=184 n (%)
Any system organ class	4 (4.7)	14 (14.1)	18 (9.8)
Investigations	2 (2.4)	3 (3.0)	5 (2.7)
Albumin urine present	1 (1.2)	-	1 (0.5)
Blood creatinine increased	-	2 (2.0)	2 (1.1)
Heart rate irregular	1 (1.2)	-	1 (0.5)
Liver function test abnormal	-	1 (1.0)	1 (0.5)
Cardiac disorders	1 (1.2)	2 (2.0)	3 (1.6)
Atrial fibrillation	1 (1.2)	-	1 (0.5)
Cardio-respiratory arrest**	-	1 (1.0)	1 (0.5)
Mitral valve incompetence	-	1 (1.0)	1 (0.5)
Neoplasms	-	3 (3.0)	3 (1.6)
Acute leukemia	-	2 (2.0)	2 (1.1)
Acute myeloid leukemia	-	1 (1.0)	1 (0.5)
Blood and lymphatic system disorders	-	2 (2.0)	2 (1.1)
Disseminated intravascular coagulation	-	1 (1.0)	1 (0.5)
Febrile neutropenia**	-	1 (1.0)	1 (0.5)
Gastrointestinal disorders	-	2 (2.0)	2 (1.1)
Diarrhea	-	1 (1.0)	1 (0.5)
Vomiting	-	1 (1.0)	1 (0.5)
Infections and infestations	-	2 (2.0)	2 (1.1)
Neutropenic sepsis**	-	1 (1.0)	1 (0.5)
Sepsis**	-	1 (1.0)	1 (0.5)
Nervous system disorders	-	1 (1.0)	1 (0.5)
Cerebral hemorrhage	-	1 (1.0)	1 (0.5)
Renal and urinary disorders	-	1 (1.0)	1 (0.5)
Renal failure	-	1 (1.0)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	-	1 (1.0)	1 (0.5)
Pulmonary hemorrhage**	-	1 (1.0)	1 (0.5)
Skin disorders	1 (1.2)	-	1 (0.5)
Rash pruritic	1 (1.2)	-	1 (0.5)

Source: Post-text table 10.2-3
* Subjects with multiple adverse events within a primary system organ class are counted only once in the total row   ** fatal

Reviewer's Comments. More patients in the rare anemia group discontinued Exjade than did those in the β-thalassemia group. The main reasons for discontinuation were renal dysfunction, rash and hematological disorders. One patient in the rare anemia group discontinued Exjade because of an increase in serum transaminase.

In Study 0108, dose reductions or interruptions are shown in the following table.

Table 10-9 Number (%) of patients with AEs leading to dose reduction or interruption by primary system organ class

Primary system organ class	β-thalassemia N=85 n (%)	Rare anemias N=99 n (%)	All patients N=184 n (%)
Any primary system organ class	39 (45.9)	53 (53.5)	92 (50.0)
Investigations	14 (16.5)	18 (18.2)	32 (17.4)
Gastrointestinal disorders	11 (12.9)	14 (14.1)	25 (13.6)
Infections and infestations	11 (12.9)	13 (13.1)	24 (13.0)
Skin and subcutaneous tissue disorders	7 (8.2)	2 (2.0)	9 (4.9)
General disorders	3 (3.5)	6 (6.1)	9 (4.9)
Hepatobiliary disorder	-	1 (1.0)	1 (0.5)
Renal and urinary disorders	3 (3.5)	5 (5.1)	8 (4.3)
Blood and lymphatic system disorders	1 (1.2)	5 (5.1)	6 (3.3)
Nervous system disorders	3 (3.5)	2 (2.0)	5 (2.7)
Musculoskeletal disorders	2 (2.4)	2 (2.0)	4 (2.2)
Cardiac disorders	1 (1.2)	2 (2.0)	3 (1.6)
Respiratory disorders	1 (1.2)	2 (2.0)	3 (1.6)
Metabolic and nutritional disorders	-	3 (3.0)	3 (1.6)
Vascular disorders	1 (1.2)	2 (2.0)	3 (1.6)
Ear and labyrinth disorders	-	2 (2.0)	2 (1.1)
Eye disorders	2 (2.4)	-	2 (1.1)
Surgical and medical procedures	-	2 (2.0)	2 (1.1)
Injury etc.	1 (1.2)	1 (1.0)	2 (1.1)
Psychiatric disorders	1 (1.2)	-	1 (0.5)
Social circumstances	-	1 (1.0)	1 (0.5)

Source: Sponsor submission page 111

Reviewer's Comments. Half of the patients had dose reductions or interruptions and these were more frequent in patients with rare anemias than in patients with β-thalassemia. A dose-response effect was noted only for increases in serum creatinine. Dose changes for increases in serum creatinine were more common in adults than in children. Patients with MDS were twice as likely to have dose changes as patients with Blackfan-Diamond syndrome.

A rise in serum creatinine was responsible for 17.4% of all dose changes, a frequency that was similar between patients with β-thalassemia and rare anemias. In 13/32 patients with dose changes, the creatinine rose but did not exceed 2x ULN. In the remainder, the creatinine rose but remained WNL. Dose reduction or interruption was most often associated with a return of the serum creatinine to normal. Eleven patients experienced a rise in urinary protein/creatinine ratio which led to a reduction in dose in 3 patients. All 3 eventually discontinued study drug but in only one was the discontinuation determined on the basis of the renal findings. Of the other two patients, one withdrew consent and one no longer required study drug.

Gastrointestinal symptoms led to change in drug dose in 6 patients.

Skin rash led to change in drug dose in 9 patients, but most were able to return to the original dose of the drug.

Neutropenia led to change in drug dose in 2 patients, one with myelofibrosis and one with Blackfan-Diamond syndrome. Both were receiving Exjade at a dose of 30 mg/kg/d. Interruption of the drug did not lead to improvement in the neutropenia. One patient was restarted on the drug, the other was not.

Thrombocytopenia led to drug interruption in a 56 year old patient with MDS treated with Exjade at a dose of 5 mg/kg/d, but the drug was reintroduced at a dose of 15 mg/kg/d.

Hearing loss was documented in 2 patients and a cataract developed in another patient that led to drug interruption. The drug was later resumed in all three.

6.1.3.3   Other significant adverse events

The following other significant adverse events occurred in Study 0105.
- Five patients treated with Exjade at a dose of 20 mg/kg/d had dose reductions to 10 mg/kg/d for AEs. These included two with an increase in β-2 microglobulin but without an increase in serum creatinine; one patient with a slightly elevated serum creatinine; one with an AV block; and one for uncertain reasons.
- Treatment with DFO (40 mg/kg/d) was discontinued because of suspected drug-related fever, headache and arthralgia in one patient.
- Two patients treated with DFO had dose reductions because of marked reductions in LIC.

The following other significant adverse events occurred in Study 0106.
- There was an increase in transaminase in 5/40 patients (4 patients <age 12 years and 1 patient ≥age 12 years).

The following other significant adverse events occurred in Study 0107.
- There was a mild non-progressive increase in serum creatinine in 33/296 (11.1%) of patients receiving Exjade compared to 0/290 in patients receiving DFO. There appeared to be a dose-response relationship to Exjade.
- Three patients had an increase in transaminase while receiving Exjade. A relation to dose could not be made.

The following other significant adverse events occurred in Study 0108.
- A non-progressive increase in serum creatinine that led to drug interruption or dose decrease occurred in 8/184 patients (4.3%). Three patients had β-thalassemia, 4 patients had MDS and 1 patient had another rare anemia. In addition, 31/85 patients with ß-thalassemia and 23/99 patients with rare anemias had a rise in creatinine >33% of baseline. Of these, the serum creatinine had risen to > ULN in 3 patients with ß-thalassemia and 16 with other rare anemias.
- Neutropenia developed in 2 patients receiving Exjade, one with myelodysplastic syndrome and one with Blackfan Diamond syndrome. Both patients were receiving a dose of 30 mg/kg/d. The white blood cell count did not improve after Exjade was discontinued.
- Thrombocytopenia developed in one patient with MDS receiving Exjade at a dose of 5 mg/kg/d.
- Serum transaminase rose to 5x ULN in 14/184 (7.6%) patients (8 with β-thalassemia, 6 with rare anemia). Thirteen of these patients entered the study with a raised transaminase, but there was a further rise while receiving Exjade. The increases did not appear to be dose dependent.
- There was an increase in urinary protein/creatinine ratio of ≥1.0 mg/mg in 11 patients, 3 of whom already had a ratio ≥1.0 mg/mg at baseline. Three patients discontinued study drug because of this increase in urinary protein/creatinine ratio. There was no significant change in any of the types of urinary proteins measured.

- Fourteen (14%) percent and 57% of patients developed low levels of serum copper and zinc, respectively, at some time during the trial, but they were variable and were deemed clinically insignificant. As a rule, serum copper declined for the first 4 weeks of the trial and then rose to normal for the remainder of the time. In contrast, serum zinc fell by the 4th week of the trial and remained at that level for the remainder of the study.

Reviewer's Comments. Adverse events that are associated with the administration of Exjade include renal and hepatic dysfunction. There is a possible association with the development of neutropenia and thrombocytopenia. There is some reduction in the blood levels of zinc and copper.

6.1.4 Other Search Strategies

Not applicable.

6.1.5 Common Adverse Events

6.1.5.1 Eliciting adverse events data in the development program

AEs were summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having an AE in each primary system organ class and having each individual AE. A summary and listing of clinically relevant toxic events, i.e., AEs that were serious or were considered related to study drug, AEs or laboratory tests that led to a change of dose or discontinuation from study drug were provided.

In addition, AEs essentially describing the same phenomenon (abdominal pain, diarrhea, gastroenteritis and rash) have been 'grouped' to give an estimate of the true incidence of these events unbiased by the use of different preferred terms.

AEs were elicited at each visit which was at least monthly in all of the trials.

6.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were reported by system organ class and preferred term. This method was acceptable in reporting adverse events in the population studied.

6.1.5.3   Incidence of common adverse events

In Study 0105, common adverse events are listed in the following table.

Table 10-1   Number (%) of patients with the most frequently reported AEs overall and by body system (≥ 4 patients in any group)

Primary system organ class Preferred term	ICL670 10 mg/kg N=24 n (%)	ICL670 20 mg/kg N=24 n (%)	DFO 40 mg/kg N=23 n (%)	All treatments N=71 n (%)
-Any primary system organ class	24 (100.0)	23 (95.8)	21 (91.3)	68 (95.8)
Respiratory disorders	**21 (87.5)**	**15 (62.5)**	**13 (56.5)**	**49 (69.0)**
Pharyngitis	10 (41.7)	7 (29.2)	8 (34.8)	25 (35.2)
Rhinitis NOS	7 (29.2)	9 (37.5)	6 (26.1)	22 (31.0)
Pharyngolaryngeal pain	5 (20.8)	6 (25.0)	6 (26.1)	17 (23.9)
Bronchitis NOS	5 (20.8)	0 (0.0)	1 (4.3)	6 (8.5)
Cough	5 (20.8)	10 (41.7)	4 (17.4	19 (26.8)
Gastrointestinal disorders	**17 (70.8)**	**14 (58.3)**	**11 (47.8)**	**42 (59.2)**
Nausea	2 (8.3)	8 (33.3)	2 (8.7)	12 (16.9)
Vomiting NOS	0 (0.0)	8 (33.3)	2 (8.7)	10 (14.1)
Abdominal pain NOS	11 (45.8)	6 (25.0)	4 (17.4)	21 (29.6)
Diarrhea NOS	7 (29.2)	6 (25.0)	6 (26.1)	19 (26.8)
Abdominal pain upper	7 (29.2)	4 (16.7)	5 (21.7)	16 (22.5)
Dyspepsia	1 (4.2)	4 (16.7)	2 (8.7)	7 (9.9)
General disorders	**13 (54.2)**	**14 (58.3)**	**11 (47.8)**	**38 (53.5)**
Pyrexia	7 (29.2)	10 (41.7)	6 (26.1)	23 (32.4)
Asthenia	3 (12.5)	7 (29.2)	4 (17.4)	14 (19.7)
Influenza like illness	7 (29.2)	3 (12.5)	4 (17.4)	14 (19.7)
Musculoskeletal/connective tissue disorders	**12 (50.0)**	**12 (50.0)**	**12 (52.2)**	**36 (50.7)**
Back pain	8 (33.3)	10 (41.7)	8 (34.8)	26 (36.6)
Arthralgia	4 (16.7)	2 (8.3)	3 (13.0)	9 (12.7)
Infections and infestations	**18 (75)**	**11 (45.8)**	**12 (52.2)**	**41 (57.7)**
Urinary tract infection NOS	4 (16.7)	1 (4.2)	1 (4.3)	6 (8.5)
Influenza	1 (4.2)	5 (20.8)	5 (21.7)	11 (15.5)
Nervous system disorders	**9 (37.5)**	**9 (37.5)**	**6 (26.1)**	**24 (33.8)**
Headache	9 (37.5)	7 (29.2)	4 (17.4)	20 (28.2)
Investigations	**3 (12.5)**	**6 (25.0)**	**2 (8.7)**	**11 (15.5)**
Skin/subcutaneous disorders	**5 (20.8)**	**5 (20.8)**	**5 (21.7)**	**15 (21.1)**
Injury etc.	**3 (12.5)**	**5 (20.8)**	**1 (4.3)**	**9 (12.7)**
Cardiac disorders	**0 (0.0)**	**3 (12.5)**	**4 (17.4)**	**7 (9.9)**
Ear and labyrinth disorders	**6 (25.0)**	**3 (12.5)**	**4 (17.4)**	**13 (18.3)**
Vertigo	5 (20.8)	2 (8.3)	3 (13.0)	10 (14.1)
Renal and urinary disorders	**6 (25.0)**	**2 (8.3)**	**4 (17.4)**	**12 (16.9)**
Eye disorders	**2 (8.3)**	**4 (16.7)**	**0 (0.0)**	**6 (8.5)**
Conjunctivitis allergic	0 (0.0)	4 (16.7)	0 (0.0)	4 (5.6)

Source: Sponsor submission page 54-55

Reviewer's Comments. Most patients experienced at least one AE and these were usually of mild or moderate intensity. Most AEs were related to the respiratory or gastrointestinal tract. Gastrointestinal symptoms were more common with Exjade than with DFO. With Exjade, nausea, vomiting and dyspepsia appeared to be dose related, but were often transient and did not lead to any permanent discontinuations. Skin rash occurred in 7 patients receiving Exjade and 1 patient receiving DFO. Most rashes appeared after about 3 months of therapy. There were no drug interruptions or discontinuation for skin rash. Headache and injury were more common in patients receiving Exjade than in patients receiving DFO.

In Study 0106, the most frequent AEs are listed in the following table.

Table 10-1   Number (%) of patients with AEs overall and by body system an preferred term (greater than 5 percent of the safety population)

Primary system organ class Preferred term	Children < 12 yrs N=20 n (%)	Adolescents ≥12 yrs N=20 n (%)	All patients N=40 n (%)
Any primary system organ class	20 (100.0)	20 (100.0)	40 (100.0)
Infections and infestations	17 (85.0)	17 (85.0)	34 (85.0)
Rhinitis	12 (60.0)	6 (30.0)	18 (45.0)
Pharyngitis	4 (20.0)	10 (50.0)	14 (35.0)
Influenza	4 (20.0)	2 (10.0)	6 (15.0)
Ear infection	5 (25.0)	0 (0.0)	5 (12.5)
Tonsillitis	3 (15.0)	2 (10.0)	5 (12.5)
Bronchitis	2 (10.0)	2 (10.0)	4 (10.0)
Gastroenteritis	0 (0.0)	3 (15.0)	3 (7.5)
Nasopharyngitis	2 (10.0)	1 (5.0)	3 (7.5)
Varicella	2 (10.0)	1 (5.0)	3 (7.5)
Gastrointestinal disorders	14 (70.0)	11 (55.0)	25 (62.5)
Vomiting	9 (45.0)	3 (15.0)	12 (30.0)
Diarrhea	6 (30.0)	4 (20.0)	10 (25.0)
Abdominal pain	4 (20.0)	4(20.0)	8 (20.0)
Constipation	1 (5.0)	3 (15.0)	4 (10.0)
Enteritis	2 (10.0)	2 (10.0)	4 (10.0)
Nausea	2 (10.0)	2 (10.0)	4 (10.0)
General disorders	14 (70.0)	11 (55.0)	25 (62.5)
Pyrexia	14 (70.0)	9 (45.0)	23 (57.5)
Asthenia	2 (10.0)	1 (5.0)	3 (7.5)
Respiratory disorders	10 (50.0)	10 (50.0)	20 (50.0)
Cough	9 (45.0)	10 (50.0)	19 (47.5)
Nervous system disorders	4 (20.0)	8 (40.0)	12 (30.0)
Headache	4 (20.0)	7 (35.0)	11 (27.5)
Skin disorders	6 (30.0)	5 (25.0)	11 (27.5)
Injury etc.	5 (25.0)	4 (20.0)	9 (22.5)
Investigations	5 (25.0)	2 (10.0)	7 (17.5)
Transaminases increased	4 (20.0)	1 (5.0)	5 (12.5)
Musculoskeletal disorders	4 (20.0)	3 (15.0)	7 (17.5)
Back pain	1 (5.0)	2 (10.0)	3 (7.5)
Eye disorders	2 (10.0)	2 (10.0)	4 (10.0)
Conjunctivitis	2 (10.0)	1 (5.0)	3 (7.5)

Source: Sponsor submission page 57

Reviewer's Comments. All patients experienced at least 1 AE during the course of the trial. Most were related to upper respiratory infections and gastrointestinal complaints. Most were of mild or moderate intensity. There was little difference in AEs between children and adolescents.

In Study 0107 (pivotal), common adverse events in Exjade treated and DFO treated patients are shown by system organ class in the following table.

Table 10-1 Number (%) of patients with AEs overall and by primary system organ class

Primary system organ class	ICL670 N=296 n (%)	DFO N=290 n (%)	All patients N=586 n (%)
Any primary system organ class	254 (85.8)	246 (84.8)	500 (85.3)
Infections and infestations	182 (61.5)	182 (62.8)	364 (62.1)
Gastrointestinal disorders	126 (42.6)	91 (31.4)	217 (37.0)
General disorders	88 (29.7)	119 (41.0)	207 (35.3)
Respiratory, thoracic and mediastinal disorders	80 (27.0)	102 (35.2)	182 (31.1)
Musculoskeletal disorders	55 (18.6)	69 (23.8)	124 (21.2)
Nervous system disorders	55 (18.6)	67 (23.1)	122 (20.8)
Skin and subcutaneous tissue disorders	65 (22.0)	45 (15.5)	110 (18.8)
Injury, poisining and procedural complications	39 (13.2)	40 (13.8)	79 (13.5)
Investigations	57 (19.3)	16 (5.5)	73 (12.5)
Ear and labyrinth disorders	21 (7.1)	27 (9.3)	48 (8.2)
Eye disorders	21 (7.1)	24 (8.3)	45 (7.7)
Cardiac disorders	15 (5.1)	20 (6.9)	35 (6.0)
Blood system disorders	12 (4.1)	14 (4.8)	26 (4.4)
Psychiatric disorders	14 (4.7)	10 (3.4)	24 (4.1)
Reproductive system and breast disorders	8 (2.7)	15 (5.2)	23 (3.9)
Metabolic and nutritional disorders	11 (3.7)	10 (3.4)	21 (3.6)
Renal and urinary disorders	9 (3.0)	10 (3.4)	19 (3.2)
Hepatobiliary disorders	14 (4.7)	5 (1.7)	19 (3.2)
Vascular disorders	7 (2.4)	5 (1.7)	12 (2.0)
Surgical and medical procedures	5 (1.7)	6 (2.1)	11 (1.9)
Immune system disorders	4 (1.4)	7 (2.4)	11 (1.9)
Endocrine disorders	4 (1.4)	4 (1.4)	8 (1.4)
Neoplasms	0 (0.0)	4 (1.4)	4 (0.7)
Congenital disorders	0 (0.0)	1 (0.3)	1 (0.2)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	1 (0.3)	1 (0.2)
Social circumstances	1 (0.3)	0 (0.0)	1 (0.2)

Source: Sponsor submission page 98

In Study 0107 (pivotal), common adverse events in Exjade treated and DFO treated patients are shown by preferred term in the following table.

Table 10-2 Most frequently reported AEs (>7 patients in any treatment group)

Preferred Term	ICL670 N=296		DFO N=290		All patients N=586	
	Total n (%)	Moderate /severe n (%)	Total n (%)	Moderate /severe n (%)	Total n (%)	Moderate /severe n (%)
Pyrexia	56 (18.9)	12 (4.1)	69 (23.8)	13 (4.5)	125 (21.3)	25 (4.3)
Headache	47 (15.9)	10 (3.4)	59 (20.3)	8 (2.8)	106 (18.1)	18 (3.1)
Abdominal pain	41 (13.9)	8 (2.7)	28 (9.7)	7 (2.4)	69 (11.8)	15 (2.6)
Cough	41 (13.9)	9 (3.0)	55 (19.0)	11 (3.8)	96 (16.4)	20 (3.4)
Nasopharyngitis	39 (13.2)	2 (0.7)	42 (14.5)	5 (1.7)	81 (13.8)	7 (1.2)
Diarrhoea	35 (11.8)	5 (1.7)	21 (7.2)	6 (2.1)	56 (9.6)	11 (1.9)
Influenza	32 (10.8)	6 (2.0)	29 (10.0)	9 (3.1)	61 (10.4)	15 (2.6)
Nausea	31 (10.5)	3 (1.0)	14 (4.8)	1 (0.3)	45 (7.7)	4 (0.7)
Pharyngolaryngeal pain	31 (10.5)	5 (1.7)	43 (14.8)	4 (1.4)	74 (12.6)	9 (1.5)
Creatinine increased*	33 (11.1)	6 (2.0)	0	0	33 (5.6)	6 (1.0)
Vomiting	30 (10.1)	2 (0.7)	28 (9.7)	8 (2.8)	58 (9.9)	10 (1.7)
Resp. tract infection	28 (9.5)	9 (3.0)	23 (7.9)	4 (1.4)	51 (8.7)	13 (2.2)
Bronchitis	27 (9.1)	2 (0.7)	32 (11.0)	1 (0.3)	59 (10.1)	3 (0.5)
Rash	25 (8.4)	8 (2.7)	9 (3.1)	1 (0.3)	34 (5.8)	9 (1.5)
Abdominal pain upper	23 (7.8)	5 (1.7)	15 (5.2)	2 (0.7)	38 (6.5)	7 (1.2)
Pharyngitis	23 (7.8)	8 (2.7)	30 (10.3)	9 (3.1)	53 (9.0)	17 (2.9)
Arthralgia	22 (7.4)	4 (1.4)	14 (4.8)	1 (0.3)	36 (6.1)	5 (0.9)
Acute tonsillitis	19 (6.4)	6 (2.0)	15 (5.2)	4 (1.4)	34 (5.8)	10 (1.7)
Fatigue	18 (6.1)	1 (0.3)	14 (4.8)	3 (1.0)	32 (5.5)	4 (0.7)
Rhinitis	18 (6.1)	2 (0.7)	22 (7.6)	1 (0.3)	40 (6.8)	3 (0.5)
Back pain	17 (5.7)	4 (1.4)	32 (11.0)	7 (2.4)	49 (8.4)	11 (1.9)
Ear infection	16 (5.4)	3 (1.0)	7 (2.4)	2 (0.7)	23 (3.9)	5 (0.9)
Tonsillitis	12 (4.1)	4 (1.4)	13 (4.5)	2 (0.7)	25 (4.3)	6 (1.0)
Urticaria	11 (3.7)	2 (0.7)	17 (5.9)	0	28 (4.8)	2 (0.3)
Gastroenteritis	10 (3.4)	1 (0.3)	9 (3.1)	0	19 (3.2)	1 (0.2)
Dyspepsia	9 (3.0)	3 (1.0)	5 (1.7)	0	14 (2.4)	3 (0.5)
Post procedural pain	9 (3.0)	3 (1.0)	7 (2.4)	3 (1.0)	16 (2.7)	6 (1.0)
Sinusitis	9 (3.0)	1 (0.3)	6 (2.1)	0	15 (2.6)	1 (0.2)
Constipation	8 (2.7)	3 (1.0)	7 (2.4)	1 (0.3)	15 (2.6)	4 (0.7)
Ear pain	8 (2.7)	1 (0.3)	4 (1.4)	2 (0.7)	12 (2.0)	3 (0.5)
Otitis media	8 (2.7)	1 (0.3)	7 (2.4)	2 (0.7)	15 (2.6)	3 (0.5)
Rhinorrhoea	8 (2.7)	1 (0.3)	8 (2.8)	1 (0.3)	16 (2.7)	2 (0.3)
Asthenia	7 (2.4)	1 (0.3)	11 (3.8)	3 (1.0)	18 (3.1)	4 (0.7)
Transfusion reaction	7 (2.4)	3 (1.0)	14 (4.8)	1 (0.3)	21 (3.6)	4 (0.7)
Bone pain	6 (2.0)	1 (0.3)	8 (2.8)	2 (0.7)	14 (2.4)	3 (0.5)
Pain in extremity	6 (2.0)	0	8 (2.8)	2 (0.7)	14 (2.4)	2 (0.3)
Conjunctivitis	5 (1.7)	0	8 (2.8)	0	13 (2.2)	0
Epistaxis	4 (1.4)	0	8 (2.8)	1 (0.3)	12 (2.0)	1 (0.2)
Influenca like illness	3 (1.0)	0	8 (2.8)	2 (0.7)	11 (1.9)	2 (0.3)
Viral infection	3 (1.0)	0	8 (2.8)	2 (0.7)	11 (1.9)	2 (0.3)

Source: Post-text Table 10.1-3   (* = includes 'Blood creatinine increased' and 'Blood creatinine abnormal')

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Reviewer's Comments. Most patients had at least one AE during the course of the trial. Most of the AEs were related to infections, gastrointestinal, general, respiratory or musculoskeletal disorders. There were no differences between patients receiving Exjade compared to DFO except for a greater frequency of infusion site reactions in patients receiving DFO, and a greater frequency of skin rash, gastrointestinal symptoms, increases in serum creatinine and arthralgia in patients receiving Exjade. There appeared to be a dose-response effect for the increase in serum creatinine and gastrointestinal symptoms with Exjade. Most AEs were mild to moderate in intensity. Events judged to be severe in intensity occurred in 8.1% of patients receiving Exjade and 4.8% of patients receiving DFO.

Hearing loss occurred in 8 patients receiving Exjade and in 7 patients receiving DFO. Cataracts developed in 2 patients receiving Exjade and in 5 patients receiving DFO. One patient receiving Exjade had prolongation of the QT interval. Arthralgia developed in 22 patients receiving Exjade and in 14 patients receiving DFO. Neutropenia developed in one patient who also developed elevated transaminases while receiving Exjade.

In Study 0108, the number of AEs is listed in the following table.

Table 10-1 Number (%) of patients with AEs overall and by primary system organ class

Primary system organ class	β-thalassemia N=85 n (%)	Rare anemias N=99 n (%)	All patients N=184 n (%)
Any system organ class	84 (98.8)	97 (98.0)	181 (98.4)
Gastrointestinal disorders	61 (71.8)	72 (72.7)	133 (72.3)
Infections and infestations	60 (70.6)	65 (65.7)	125 (67.9)
General and admin. site disorders	41 (48.2)	48 (48.5)	89 (48.4)
Respiratory disorders	37 (43.5)	39 (39.4)	76 (41.3)
Nervous system disorders	34 (40.0)	34 (34.3)	68 (37.0)
Musculoskeletal disorders	32 (37.6)	35 (35.4)	67 (36.4)
Investigations	28 (32.9)	31 (31.3)	59 (32.1)
Skin disorders	34 (40.0)	23 (23.2)	57 (31.0)
Injury etc.	23 (27.1)	14 (14.1)	37 (20.1)
Cardiac disorders	14 (16.5)	16 (16.2)	30 (16.3)
Renal/urinary disorders	10 (11.8)	19 (19.2)	29 (15.8)
Metabolism and nutrition disorders	4 (4.7)	18 (18.2)	22 (12.0)
Eye disorders	12 (14.1)	7 (7.1)	19 (10.3)
Psychiatric disorders	8 (9.4)	10 (10.1)	18 (9.8)
Vascular disorders	6 (7.1)	12 (12.1)	18 (9.8)
Ear and labyrinth disorders	10 (11.8)	7 (7.1)	17 (9.2)
Blood disorders	4 (4.7)	10 (10.1)	14 (7.6)
Surgical and medical procedures	2 (2.4)	10 (10.1)	12 (6.5)
Reproductive disorders	6 (7.1)	5 (5.1)	11 (6.0)
Hepatobiliary disorders	5 (5.9)	5 (5.1)	10 (5.4)
Immunes system disorders	6 (7.1)	4 (4.0)	10 (5.4)
Neoplasms	-	6 (6.1)	6 (3.3)
Endocrine disorders	3 (3.5)	2 (2.0)	5 (2.7)
Social circumstances	-	1 (1.0)	1 (0.5)

Source: Sponsor submission page 99

Reviewer's Comments. Most AEs were related to the gastrointestinal system or to infections. AEs were generally mild or moderate in intensity, but 22.8% were severe in intensity. AEs related to the skin, injury and eyes were more common in patients with β-thalassemia whereas AEs related to renal/urinary disorders, metabolic/nutritional, blood, surgical/medical procedures and neoplasms were more common in patients with rare anemias. A possible dose-response relationship was apparent only for diarrhea, and was more common in those >65 and <6 years of age. Nausea was uncommon below the age of 12 years.

Seven patients with rare anemias developed renal impairment, but none of these events was considered serious. Four of these patients, ages 67-80 years, all with MDS receiving Exjade at a dose of 20-30 mg/kg/d had mild elevations in serum creatinine but were continued on study drug. Three other patients, ages 65-76 years, all with MDS receiving Exjade at a dose of 20-30 mg/kg/d developed greater increases in serum creatinine, one in association with sepsis, one in

association with hypovolemic shock due to post-liver biopsy hemorrhage and one who had had pre-existing renal insufficiency. All 3 patients were discontinued from study drug although not necessarily because of the AE.

Hearing loss developed in 5 patients. Three of these patients had MDS, were aged 63-78 years, were receiving Exjade at a dose of 5, 30 and 30 mg/kg/d and had received the drug from 62-292 days. Two patients with β-thalassemia developed hearing loss while on Exjade at doses of 5-10 mg/kg/d.

Two patients developed cataracts, one age 77 years with MDS receiving Exjade at a dose of 30 mg/kg/d for 369 days and another with β-thalassemia, age 31 years receiving Exjade at a dose of 30 mg/kg/d for 52 days. The latter patient withdrew consent to continue in the study.

One patient with β-thalassemia, age 21 years, developed mild prolongation of the QT interval after receiving Exjade at a dose of 30 mg/kg/d for 228 days.

In Study 0108, common adverse events in Exjade treated patients in various subsets of rare anemias are shown by system organ class in the following table.

Table 10-2 Number (%) of patients with AEs overall and by primary system organ class – Rare anemias

Primary system organ class	MDS N=47 n (%)	DBA N=30 n (%)	Other anemias N=22 n (%)	All rare anemias N=99 n (%)
Any system organ class	45 (95.7)	30 (100.0)	22 (100.0)	97 (98.0)
Gastrointestinal disorders	33 (70.2)	24 (80.0)	15 (68.2)	72 (72.7)
Infections and infestations	23 (48.9)	26 (86.7)	16 (72.7)	65 (65.7)
General and admin. site disorders	25 (53.2)	12 (40.0)	11 (50.0)	48 (48.5)
Respiratory disorders	14 (29.8)	13 (43.3)	12 (54.5)	39 (39.4)
Nervous system disorders	12 (25.5)	14 (46.7)	8 (36.4)	34 (34.3)
Musculoskeletal disorders	20 (42.6)	9 (30.0)	6 (27.3)	35 (35.4)
Investigations	12 (25.5)	10 (33.3)	9 (40.9)	31 (31.3)
Skin and sc tissue disorders	9 (19.1)	7 (23.3)	7 (31.8)	23 (23.2)
Injury etc.	6 (12.8)	4 (13.3)	4 (18.2)	14 (14.1)
Cardiac disorders	11 (23.4)	2 (6.7)	3 (13.6)	16 (16.2)
Renal/urinary disorders	13 (27.7)	1 (3.3)	5 (22.7)	19 (19.2)
Metabolism and nutrition disorders	8 (17.0)	6 (20.0)	4 (18.2)	18 (18.2)
Eye disorders	3 (6.4)	3 (10.0)	1 (4.5)	7 (7.1)
Psychiatric disorders	8 (17.0)	2 (6.7)	0	10 (10.1)
Vascular disorders	5 (10.6)	4 (13.3)	3 (13.6)	12 (12.1)
Ear and labyrinth disorders	6 (12.8)	1 (3.3)	0	7 (7.1)
Blood disorders	5 (10.6)	3 (10.0)	2 (9.1)	10 (10.1)
Surgical and medical procedures	2 (4.3)	4 (13.3)	4 (18.2)	10 (10.1)
Reproductive disorders	1 (2.1)	2 (6.7)	2 (9.1)	5 (5.1)
Hepatobiliary disorders	2 (4.3)	3 (10.0)	0	5 (5.1)
Immunes system disorders	0	3 (10.0)	1 (4.5)	4 (4.0)
Neoplasms	6 (12.8)	0	0	6 (6.1)
Endocrine disorders	1 (2.1)	1 (3.3)	0	2 (2.0)
Social circumstances	0	1 (3.3)	0	1 (1.0)

Source: Appendix 8.1 Table 10.1-1

In Study 0108, common adverse events in Exjade treated patients in various subsets of rare anemias are shown by preferred term in the following table.

Table 10-4 Most frequently reported AEs – Rare anemias (≥5%, all patients)

Preferred term	MDS N=47 Total n (%)	MDS N=47 Moderate/ severe n (%)	Diamond-Blackfan N=30 Total n (%)	Diamond-Blackfan N=30 Moderate/ severe n (%)	Other anemias N=22 Total n (%)	Other anemias N=22 Moderate/ severe n (%)	All patients N=99 Total n (%)
Diarrhea	19 (40.4)	5 (10.6)	13 (43.3)	3 (10.0)	8 (36.4)	2 (9.1)	40 (40.4)
Vomiting	12 (25.5)	2 (4.3)	13 (43.3)	1 (3.3)	4 (18.2)	-	29 (29.3)
Nausea	14 (29.8)	3 (6.4)	9 (30.0)	-	4 (18.2)	-	27 (27.3)
Headache	6 (12.8)	1 (2.1)	12 (40.0)	1 (3.3)	6 (27.3)	1 (4.5)	24 (24.2)
Abdominal pain	10 (21.3)	3 (6.4)	10 (33.3)	2 (6.7)	2 (9.1)	2 (9.1)	22 (22.2)
Pyrexia	10 (21.3)	6 (12.8)	8 (26.7)	4 (13.3)	4 (18.2)	1 (4.5)	22 (22.2)
Cough	6 (12.8)	-	7 (23.3)	1 (3.3)	7 (31.8)	-	20 (20.2)
Nasopharyngits	6 (12.8)	1 (2.1)	8 (26.7)	1 (3.3)	5 (22.7)	1 (4.5)	19 (19.2)
Creatinine increased	5 (10.6)	4 (8.5)	2 (6.7)	-	8 (36.4)	2 (9.1)	15 (15.2)
URTI*	-	-	7 (23.3)	2 (6.7)	6 (27.3)	-	13 (13.1)
Back pain	8 (17.0)	3 (6.4)	2 (6.7)	-	2 (9.1)	-	12 (12.1)
Asthenia	8 (17.0)	3 (6.4)	-	-	2 (9.1)	1 (4.5)	10 (10.1)
Fatigue	7 (14.9)	1 (2.1)	3 (10.0)	2 (6.7)	-	-	10 (10.1)
Constipation	6 (12.8)	2 (4.3)	3 (10.0)	-	-	-	9 (9.1)
Bone pain	5 (10.6)	1 (2.1)	1 (3.3)	-	2 (9.1)	-	8 (8.1)
Bronchitis	2 (4.3)	1 (2.1)	4 (13.3)	3 (10.0)	2 (9.1)	-	8 (8.1)
Oedema peripheral	4 (8.5)	2 (4.3)	-	-	4 (18.2)	1 (4.5)	8 (8.1)
Rash	2 (4.3)	-	3 (10.0)	2 (6.7)	3 (13.6)	-	8 (8.1)
Transfusion reaction	2 (4.3)	1 (2.1)	2 (6.7)	1 (3.3)	4 (18.2)	1 (4.5)	8 (8.1)
Abdominal pain upper	1 (2.1)	-	4 (13.3)	1 (3.3)	2 (9.1)	2 (9.1)	7 (7.1)
Epistaxis	-	-	3 (10.0)	-	4 (18.2)	1 (4.5)	7 (7.1)
Pharyngeal pain	2 (4.3)	1 (2.1)	2 (6.7)	-	3 (13.6)	1 (4.5)	7 (7.1)
Rhinitis	3 (6.4)	0	2 (6.7)	-	2 (9.1)	-	7 (7.1)
Anorexia	3 (6.4)	2 (4.3)	2 (6.7)	-	1 (4.5)	-	6 (6.1)
Arthralgia	1 (2.1)	1 (2.1)	4 (13.3)	1 (3.3)	1 (4.5)	-	6 (6.1)
Depression	5 (10.6)	2 (4.3)	1 (3.3)	1 (3.3)	-	-	6 (6.1)
Dyspnoea	2 (4.3)	1 (2.1)	3 (10.0)	2 (6.7)	1 (4.5)	1 (4.5)	6 (6.1)
Influenza	3 (6.4)	-	2 (6.7)	1 (3.3)	1 (4.5)	-	6 (6.1)
Chest pain	2 (4.3)	1 (2.1)	1 (3.3)	1 (3.3)	2 (9.1)	1 (4.5)	5 (5.1)
Dizziness	3 (6.4)	-	2 (6.7)	-	-	-	5 (5.1)
Dyspepsia	4 (8.5)	-	-	-	1 (4.5)	-	5 (5.1)
Gastritis	4 (8.5)	2 (4.3)	-	-	1 (4.5)	1 (4.5)	5 (5.1)
Gastroenteritis	1 (2.1)	-	4 (13.3)	2 (6.7)	-	-	5 (5.1)
Muscle cramp	3 (6.4)	-	1 (3.3)	-	1 (4.5)	-	5 (5.1)
Oedema	4 (8.5)	2 (4.3)	-	-	1 (4.5)	1 (4.5)	5 (5.1)

Source: Appendix 8.1 Table 10.1-3
* URTI Upper respiratory tract infection

Reviewer's Comments. Most AEs were related to the gastrointestinal system or to infections. AEs were generally mild or moderate in intensity, but 22.8% were severe in intensity. AEs related to the skin, injury and eyes were more common in patients with β-thalassemia whereas AEs related to renal/urinary disorders, metabolic/nutritional, blood, surgical/medical procedures and neoplasms were more common in patients with rare anemias. A possible dose-response relationship was apparent only for diarrhea, and was more common in those >65 and <6 years of age. Nausea was uncommon below the age of 12 years.

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One patient with β-thalassemia, age 21 years, developed mild prolongation of the QT interval after receiving Exjade at a dose of 30 mg/kg/d for 228 days.

In Study 0108, common adverse events in Exjade treated patients in various subsets of rare anemias are shown by system organ class in the following table.

Table 10-2 Number (%) of patients with AEs overall and by primary system organ class – Rare anemias

Primary system organ class	MDS N=47 n (%)	DBA N=30 n (%)	Other anemias N=22 n (%)	All rare anemias N=99 n (%)
Any system organ class	45 (95.7)	30 (100.0)	22 (100.0)	97 (98.0)
Gastrointestinal disorders	33 (70.2)	24 (80.0)	15 (68.2)	72 (72.7)
Infections and infestations	23 (48.9)	26 (86.7)	16 (72.7)	65 (65.7)
General and admin. site disorders	25 (53.2)	12 (40.0)	11 (50.0)	48 (48.5)
Respiratory disorders	14 (29.8)	13 (43.3)	12 (54.5)	39 (39.4)
Nervous system disorders	12 (25.5)	14 (46.7)	8 (36.4)	34 (34.3)
Musculoskeletal disorders	20 (42.6)	9 (30.0)	6 (27.3)	35 (35.4)
Investigations	12 (25.5)	10 (33.3)	9 (40.9)	31 (31.3)
Skin and sc tissue disorders	9 (19.1)	7 (23.3)	7 (31.8)	23 (23.2)
Injury etc.	6 (12.8)	4 (13.3)	4 (18.2)	14 (14.1)
Cardiac disorders	11 (23.4)	2 (6.7)	3 (13.6)	16 (16.2)
Renal/urinary disorders	13 (27.7)	1 (3.3)	5 (22.7)	19 (19.2)
Metabolism and nutrition disorders	8 (17.0)	6 (20.0)	4 (18.2)	18 (18.2)
Eye disorders	3 (6.4)	3 (10.0)	1 (4.5)	7 (7.1)
Psychiatric disorders	8 (17.0)	2 (6.7)	0	10 (10.1)
Vascular disorders	5 (10.6)	4 (13.3)	3 (13.6)	12 (12.1)
Ear and labyrinth disorders	6 (12.8)	1 (3.3)	0	7 (7.1)
Blood disorders	5 (10.6)	3 (10.0)	2 (9.1)	10 (10.1)
Surgical and medical procedures	2 (4.3)	4 (13.3)	4 (18.2)	10 (10.1)
Reproductive disorders	1 (2.1)	2 (6.7)	2 (9.1)	5 (5.1)
Hepatobiliary disorders	2 (4.3)	3 (10.0)	0	5 (5.1)
Immunes system disorders	0	3 (10.0)	1 (4.5)	4 (4.0)
Neoplasms	6 (12.8)	0	0	6 (6.1)
Endocrine disorders	1 (2.1)	1 (3.3)	0	2 (2.0)
Social circumstances	0	1 (3.3)	0	1 (1.0)

In Study 0108, common adverse events in Exjade treated patients in various subsets of rare anemias are shown by preferred term in the following table.

Table 10-4 Most frequently reported AEs – Rare anemias (≥5%, all patients)

Preferred term	MDS N=47 Total n (%)	MDS N=47 Moderate/ severe n (%)	Diamond-Blackfan N=30 Total n (%)	Diamond-Blackfan N=30 Moderate/ severe n (%)	Other anemias N=22 Total n (%)	Other anemias N=22 Moderate/ severe n (%)	All patients N=99 Total n (%)
Diarrhea	19 (40.4)	5 (10.6)	13 (43.3)	3 (10.0)	8 (36.4)	2 (9.1)	40 (40.4)
Vomiting	12 (25.5)	2 (4.3)	13 (43.3)	1 (3.3)	4 (18.2)	-	29 (29.3)
Nausea	14 (29.8)	3 (6.4)	9 (30.0)	-	4 (18.2)	-	27 (27.3)
Headache	6 (12.8)	1 (2.1)	12 (40.0)	1 (3.3)	6 (27.3)	1 (4.5)	24 (24.2)
Abdominal pain	10 (21.3)	3 (6.4)	10 (33.3)	2 (6.7)	2 (9.1)	2 (9.1)	22 (22.2)
Pyrexia	10 (21.3)	6 (12.8)	8 (26.7)	4 (13.3)	4 (18.2)	1 (4.5)	22 (22.2)
Cough	6 (12.8)	-	7 (23.3)	1 (3.3)	7 (31.8)	-	20 (20.2)
Nasopharyngits	6 (12.8)	1 (2.1)	8 (26.7)	1 (3.3)	5 (22.7)	1 (4.5)	19 (19.2)
Creatinine increased	5 (10.6)	4 (8.5)	2 (6.7)	-	8 (36.4)	2 (9.1)	15 (15.2)
URTI*	-	-	7 (23.3)	2 (6.7)	6 (27.3)	-	13 (13.1)
Back pain	8 (17.0)	3 (6.4)	2 (6.7)	-	2 (9.1)	-	12 (12.1)
Asthenia	8 (17.0)	3 (6.4)	-	-	2 (9.1)	1 (4.5)	10 (10.1)
Fatigue	7 (14.9)	1 (2.1)	3(10.0)	2 (6.7)	-	-	10 (10.1)
Constipation	6 (12.8)	2 (4.3)	3 (10.0)	-	-	-	9 (9.1)
Bone pain	5 (10.6)	1 (2.1)	1 (3.3)	-	2 (9.1)	-	8 (8.1)
Bronchitis	2 (4.3)	1 (2.1)	4 (13.3)	3 (10.0)	2 (9.1)	-	8 (8.1)
Oedema peripheral	4 (8.5)	2 (4.3)	-	-	4 (18.2)	1 (4.5)	8 (8.1)
Rash	2 (4.3)	-	3 (10.0)	2 (6.7)	3 (13.6)	-	8 (8.1)
Transfusion reaction	2 (4.3)	1 (2.1)	2 (6.7)	1 (3.3)	4 (18.2)	1 (4.5)	8 (8.1)
Abdominal pain upper	1 (2.1)	-	4 (13.3)	1 (3.3)	2 (9.1)	2 (9.1)	7 (7.1)
Epistaxis	-	-	3 (10.0)	-	4 (18.2)	1 (4.5)	7 (7.1)
Pharyngeal pain	2 (4.3)	1 (2.1)	2 (6.7)	-	3 (13.6)	1 (4.5)	7 (7.1)
Rhinitis	3 (6.4)	0	2 (6.7)	-	2 (9.1)	-	7 (7.1)
Anorexia	3 (6.4)	2 (4.3)	2 (6.7)	-	1 (4.5)	-	6 (6.1)
Arthralgia	1 (2.1)	1 (2.1)	4 (13.3)	1 (3.3)	1 (4.5)	-	6 (6.1)
Depression	5 (10.6)	2 (4.3)	1 (3.3)	1 (3.3)	-	-	6 (6.1)
Dyspnoea	2 (4.3)	1 (2.1)	3 (10.0)	2 (6.7)	1 (4.5)	1 (4.5)	6 (6.1)
Influenza	3 (6.4)	-	2 (6.7)	1 (3.3)	1 (4.5)	-	6 (6.1)
Chest pain	2 (4.3)	1 (2.1)	1 (3.3)	1 (3.3)	2 (9.1)	1 (4.5)	5 (5.1)
Dizziness	3 (6.4)	-	2 (6.7)	-	-	-	5 (5.1)
Dyspepsia	4 (8.5)	-	-	-	1 (4.5)	-	5 (5.1)
Gastritis	4 (8.5)	2 (4.3)	-	-	1 (4.5)	1 (4.5)	5 (5.1)
Gastroenteritis	1 (2.1)	-	4 (13.3)	2 (6.7)	-	-	5 (5.1)
Muscle cramp	3 (6.4)	-	1 (3.3)	-	1 (4.5)	-	5 (5.1)
Oedema	4 (8.5)	2 (4.3)	-	-	1 (4.5)	1 (4.5)	5 (5.1)

Reviewer's Comments. Virtually all of the patients had AEs during the course of the trial. More than half the patients had AEs related to the gastrointestinal tract and infections, but many other organs systems were also affected. Most often, the AEs were mild in severity. In comparing frequencies of AEs among groups, it appeared that in MDS there was a greater frequency of psychiatric, otological and neoplastic AEs and a lesser frequency of surgical/medical procedures than in the other two groups. In patients with BDS, there appeared to be a greater frequency of infection with a lesser frequency of cardiac and renal/urinary AEs compared to the other two groups. Patients with other anemias had more respiratory AEs than did patients in the other two groups. Interpretation of the data, however, is limited by the small numbers of patients in the subgroups.

6.1.5.4   Common adverse event tables

See above.

6.1.5.5   Identifying common and drug-related adverse events

There were no placebo treated control groups in any of the submitted trials.

In Study 0105, no SAEs or AEs were identified that were believed related to Exjade. One patient receiving DFO developed arthralgia, fever and headache which were believed related to the drug.

In Study 0106, AEs believed related to study drug are shown in the following table.

```
                          Adverse events related to study drug
                by primary system organ class, preferred term, maximum severity and age group
                                   Safety population

                                    Children          Adolescents         All patients
    Primary system organ class       < 12 yrs            >= 12 yrs
        Preferred term                N=20                N=20               N=40
           Severity                  n   (%)            n    (%)            n   (%)
    ---------------------------------------------------------------------------------------

    -Any primary system organ class
       -Total
          Mild                       0( 0.0)            2(10.0)            2( 5.0)
          Moderate                   4(20.0)            1( 5.0)            5(12.5)
          Severe                     1( 5.0)            0( 0.0)            1( 2.5)

    Gastrointestinal disorders
       -Totals
          Mild                       0( 0.0)            2(10.0)            2( 5.0)

        Nausea
          Mild                       0( 0.0)            2(10.0)            2( 5.0)

    Investigations
       -Totals
          Mild                       0( 0.0)            1( 5.0)            1( 2.5)
          Moderate                   2(10.0)            1( 5.0)            3( 7.5)
          Severe                     1( 5.0)            0( 0.0)            1( 2.5)

        Beta 2 microglobulin urine increased
          Mild                       0( 0.0)            1( 5.0)            1( 2.5)


    Investigations
        Transaminases increased
          Moderate                   2(10.0)            1( 5.0)            3( 7.5)
          Severe                     1( 5.0)            0( 0.0)            1( 2.5)

    Skin and subcutaneous tissue disorders
       -Totals
          Moderate                   2(10.0)            0( 0.0)            2( 5.0)

        Rash pruritic
          Moderate                   2(10.0)            0( 0.0)            2( 5.0)
```

Source: Sponsor submission page 481-2

In Study 0107, AEs that occurred in more than 2% of patients treated with Exjade or DFO and believed related to study drug are shown in the following table.

Adverse Events considered to be drug related and occurring in more than 2% of Patients (Study 0107)

Primary system organ class and preferred term	Exjade N=296 n (%)	DFO N=290 n (%)	All Patients N=586 n (%)
Total	108 (36.5)	55 (19.0)	163 (27.9)
Gastrointestinal	45 (15.2)	2 (0.7)	47 (8.0)
Abdominal pain	11 (3.6%)	0 (0.0)	11 (1.9)
Diarrhea	7 (2.4)	1 (0.3)	8 (1.4)
Nausea	16 (5.3)	0 (0.0)	7 (1.2)
Vomiting	7 (2.4)	0 (0.0)	7 (1.2)
Administrative site conditions	5 (2.0)	31 (10.6)	37 (6.3)
Infections	1 (0.3)	7 (2.4)	8 (1.4)
Investigations	43 (14.5)	1 (0.3)	44 (7.5)
Serum creatinine increased	29 (9.8)	0 (0.0)	29 (4.9)

| Skin rash | 30 (10.1) | 7 (2.4) | 37 (6.4) |

Source: Reviewer revision from Sponsor submission page 989

Reviewer's Comments. Patients receiving Exjade had more drug related gastrointestinal AEs, increased serum creatinine and skin rash than did patients treated with DFO. Patients receiving DFO had more infusion site reactions and infections than did patients receiving Exjade.

In Study 0108, AEs that occurred in more than 2% of patients treated with Exjade and believed related to study drug are shown in the following table.

Adverse Events considered to be related to Exjade and occurring in more than 2% of Patients (Study 0108)

Primary system organ class and preferred term	B-thalassemia N=85 n (%)	Rare Anemias N=99 n (%)	All Patients N=184 n (%)
Total	53 (62.4)	64 (64.6)	117 (63.5)
Cardiac	3 (3.6)	1 (1.0)	4 (2.1)
Ear/Labyrinth	0 (0.0)	3 (3.0)	3 (1.6)
Eye Disorders	3 (3.6)	1 (1.0)	4 (2.1)
Gastrointestinal	37 (43.6)	47 (47.4)	84 (45.7)
Abdominal pain	10 (11.8%)	8 (8.1)	18 (9.8)
Diarrhea	12 (14.1)	24 (24.3)	36 (19.5)
Nausea	9 (10.6)	19 (19.2)	28 (15.3)
Vomiting	4 (4.8)	11 (11.2)	15 (8.1)
General Disorders	2 (2.4)	6 (6.1)	8 (4.3)
Nervous System	7 (8.3)	6 (6.1)	13 (7.0)
Investigations	20 (23.6)	14 (14.2)	34 (18.6)
Serum creatinine increased	16 (18.6)	12 (12.1)	28 (15.3)
Proteinuria	4 (4.8)	2 (2.0)	6 (3.2)
Skin rash	12 (14.1)	7 (7.0)	19 (10.3)

Source: Reviewer revision from Sponsor submission page 105

Reviewer's Comments. Although the nature of AEs seen patients with β-thalassemia in Study 0108 were similar in those in Study 0107, the frequency of the AEs were about twice as great in patients with β-thalassemia in Study 0108 as in Study 0107. This may be related to the generally higher dose of Exjade received by patients with β-thalassemia in Study 0108 (20 mg/kg/d, 20.8%; 30 mg/kg/d, 73.6%) compared to Study 0107 (20 mg/kg/d, 28.4%; 30 mg/kg/d, 40.2%). Nausea, vomiting and diarrhea were more common, and skin rash and an increase in serum creatinine were less common, in patients with rare anemias compared to patients with β-thalassemia.

6.1.5.6 Additional analyses and explorations

The following do not appear to be predictive of the propensity to develop AEs.
- Sex
- Age
- Race (although the number of non-Caucasians in most of the studies was too low for analysis)
- Duration of therapy

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- Concomitant therapy

The following appear to be predictive of the propensity to develop AEs.
- Dose and renal dysfunction
- Dose and gastrointestinal symptoms
- Myelodysplastic syndrome as the admitting diagnosis

The following may mitigate AEs.
- Steroid treatment of drug related skin rash may allow the continuation of drug

6.1.6 Less Common Adverse Events

The number of patients treated in the trials was insufficient to provide an estimate of the causality of the drug upon the development of uncommon AEs. However, there appear to be possible or probable effects in small numbers of patients on the following clinical problems:
- Hearing loss
- Cataract formation
- Drug induced hepatitis
- QT prolongation (This finding may be related to the disease process since the sponsor conducted a formal QT study in normal volunteers that indicated that Exjade did not cause QT prolongation in that population).

6.1.7 Laboratory Findings

6.1.7.1 Overview of laboratory testing in the development program

Blood and urine samples were collected on all patients at baseline and every 28 days during the trials for analysis of hematology and chemistry values and for urinalysis. For some of the studies, additional analysis (serum magnesium, copper, zinc), creatinine clearance, urinary N-acetyl-β-glucosaminidase (NAG) and β-2-microglobulin were also performed. Because of the difficulties in collecting 24 hour urine, in Studies 0106, 0107 and 0108, creatinine clearance was estimated using the Cockcroft-Gault formula.

6.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Studies 0106 and 0108 were uncontrolled single arm trials. In Studies 0105 and 0107, the control group was treated with DFO.

6.1.7.3   Standard analyses and explorations of laboratory data

Laboratory studies in Study 0105 revealed the following:
- Hematology. 2/22 patients receiving Exjade, 10 mg/kg/d developed neutropenia, and 2/22 developed thrombocytopenia. No patients receiving Exjade, 20 mg/kg/d developed either neutropenia or thrombocytopenia. In patients receiving DFO, 2/22 developed neutropenia and 1/22 developed thrombocytopenia.
- Hepatic function. 22/48 patients with normal baseline ALT/AST had an increase to >ULN while receiving Exjade at a dose of 10-20 mg/kg/d. There was no relation to dose. 5/23 patients with normal baseline ALT/AST had an increase to >ULN while receiving DFO. 18/48 (37.5%) of patients receiving Exjade and 11/23 (47.8%) of patients receiving DFO, all of whom had a normal bilirubin level at baseline, developed some degree of hyperbilirubinemia during the course of the trial. The transaminases were variable during the trial.
- Serum copper, magnesium and zinc levels fell from normal in approximately 50%, 13% and 22%, respectively, of all patients in the study regardless of drug (Exjade or DFO) or dose of drug. These values often became normal despite continuation of therapy. No patient was discontinued because of the laboratory finding.

Laboratory studies in Study 0106 revealed the following.
- Hematology. 1/20 children <12 years and 3/20 adolescents ≥12 years developed a neutrophil count <1,500/ml while receiving Exjade at dose of 10 mg/kg/d. No change in medication regimen was made and the counts reverted to normal despite continuation of the drug. No patient developed thrombocytopenia.
- Hepatic function. 4/29 patients with normal ALT at baseline developed ALT >5x ULN and 1/33 patients with normal AST at baseline developed AST >5x ULN during the course of the trial. Two patients had values of AST or ALT >10x ULN. These increases were seen between day 44 and 322. Five patients had Exjade dose changes in response to the increased transaminase levels and resumption of Exjade was not associated with recrudescence of increased levels of transaminase.
- Renal function. One patient had an increase in serum creatinine to above ULN on 2 consecutive visits but this value normalized without any change in the dose of Exjade. Slightly more than 50% of patients developed an increase in the urinary protein/creatinine ratio compared to baseline, but these were usually of a mild degree and many were transient.
- Serum copper and zinc fell slightly in some patients but the fall was usually non-progressive or transient.

Laboratory studies in Study 0107 revealed the following.
- Hematology. Two and four tenths percent (2.4%) of patients receiving Exjade and 4.5% of patients receiving DFO developed a neutrophile count of <1,500/ml and 1 patient had a single value of <500/ml. These were not dose related and all resolved even though there was no alteration in drug dose.   One and four tenths percent (1.4%) of patients receiving Exjade developed a platelet count of <100,000/ml but rose spontaneously to

normal without a change in drug dose, except for one patient whose platelet count fell to 42,000/ml which led to a reduction in the dose of Exjade from 10 to 5 mg/kg/d with resolution of the thrombocytopenia.

- Hepatic function. Abnormalities in transaminases are shown in the following table.

Table 10-9 Number (%) of patients with transaminases greater than 5 x ULN

Laboratory parameter	ICL670 N=296 n (%)	DFO N=290 n (%)	All patients N=586 n (%)
SGOT/AST			
No. patients with SGOT/AST >5 x ULN at ≥2 post-baseline visits	1 (0.3)	-	1 (0.2)
No. patients with SGOT/AST >5 x ULN at ≥2 consecutive post-baseline visits	1 (0.3)	1 (0.3)	2 (0.3)
SGPT/ALT			
No. patients with SGPT/ALT >5 x ULN at ≥2 post-baseline visits	8 (2.7)	2 (0.7)	10 (1.7)
No. patients with SGPT/ALT >5 x ULN at ≥2 consecutive post-baseline visits	17 (5.7)	5 (1.7)	22 (3.8)

Source: Sponsor submission page 113

A single patient in each treatment group had SGOT/AST levels >5 x ULN at consecutive visits during the study and no patient had levels >10 x ULN.

Seventeen (5.7%) patients on Exjade and five (1.7%) on DFO had SGPT/ALT levels >5 x ULN at consecutive visits during the study. Of the 17 patients on Exjade, nine (7.6%), two (2.4%), five (6.4%) and one (6.7%) were treated at 30, 20, 10 and 5 mg/kg, respectively. Overall, 13 of the 17 patients had elevated transaminases at baseline (two >5-fold elevated and the remainder <5-fold), including eight of the nine patients on 30 mg/kg, and all but one continued therapy without dose reduction and with no deterioration in transaminase levels. A single patient with elevated levels at baseline (0403/00017, 18 years, 10 mg/kg) discontinued Exjade on Day 137. In retrospect, there were no obvious differences in the pattern of transaminase elevations between this patient and those who continued therapy. The remaining four patients treated at 10, 10, 20 and 30 mg/kg, respectively, developed de novo elevations on Days 55, 148, 29 and 22. Study drug was continued in two patients and temporarily withheld in one but was restarted at the same dose when the transaminase levels did not normalize. The fourth patient (0801/00003, 14 years, 10 mg/kg) discontinued Exjade on Day 238. A single patient treated with Exjade and none on DFO experienced transaminase levels >10 x ULN at consecutive visits. This patient (1105/00020, 18 years, 30 mg/kg) discontinued Exjade when the levels increased to >2000 U/L following re-challenge.

Two patients who had normal baseline ALT had a single ALT of >10x ULN, while a single patient with an elevated ALT <5x ULN had 2 consecutive ALT >10x ULN.

In patients with a normal baseline bilirubin, 38.5% receiving Exjade and 32.1% receiving DFO had an increase in bilirubin at some time during the trial.

- Renal function. The number of patients with an increase in serum creatinine is shown in the following table.

Table 10-10 Number (%) of patients with increases in serum creatinine

Laboratory parameter	ICL670 N=296 n (%)	DFO N=290 n (%)	All patients N=586 n (%)
Serum creatinine			
No. patients with creatinine> 33% at ≥2 consecutive post-baseline visits	106 (35.8)	40 (13.8)	146 (24.9)
No. patients with creatinine increase > 33% and >ULN at ≥2 consecutive post-baseline visits	7 (2.4)	1 (0.3)	8 (1.4)

Patients are counted only once in each post-baseline category
Source: Sponsor submission page 113

In patients treated with Exjade and DFO, respectively, 106 (35.8%) and 40 (13.8%) had post-baseline increases in serum creatinine >33% at two or more consecutive visits. An additional seven (2.4%) patients in the Exjade treatment group had 33% increases from baseline at consecutive visits that were also above the ULN compared with a single DFO-treated patient (0.3%). Thus, 113/296 (38.2%) of patients treated with Exjade developed mild creatinine increases at some point during the study. There was a dose response effect with creatinine increases in 6.7%, 19.2%, 39.3% and 53.8% in patients treated at 5, 10, 20 and 30 mg/kg, respectively. Importantly, no patient had progressive increases in creatinine and no patient developed a serum creatinine level that was ≥2-fold above the ULN. In fact only a single patient (1103/00001, 9 years, 30 mg/kg) had a creatinine >1.5-fold above the ULN. This occurred at a single visit. However, of the 113 patients with 33% increases in serum creatinine, about 25% required dose reduction under the provisions of Amendment 2. The main reasons for this discrepancy are as follows. Firstly, in many patients, serum creatinine values fell spontaneously at subsequent visits before dose reductions could be implemented and in such patients, no action was taken. Secondly, Amendment 2 required dose reduction in pediatric patients <15 years of age only if the 33% increases resulted in serum creatinine values that were also >ULN. Serum creatinine values >ULN was a rare finding in pediatric patients and therefore dose reduction in patients aged < 15 was unusual. The number of patients with post-baseline creatinine increases was considerably lower when the extended range criteria are applied (post-baseline increases in serum creatinine of >50% compared to the average of the baseline values, confirmed by a second assessment at least seven days later). Thus, in patients treated with Exjade, 31/296 (10.5%) had two consecutive values that were >50% of baseline and an additional 5/296 (1.7%) had consecutive 50% increases that were also >ULN. The corresponding numbers for the DFO group were 9/290 (3.1%) and 1/290 (0.3%).

A box-plot of serum creatinine shows an increase from baseline of approximately 10 µmol/L in patients treated with Exjade which is apparent by Week 4 and which remains stable for the first six months. This is shown in the following figure.

Figure 10-1 Changes in serum creatinine from baseline (Safety population)
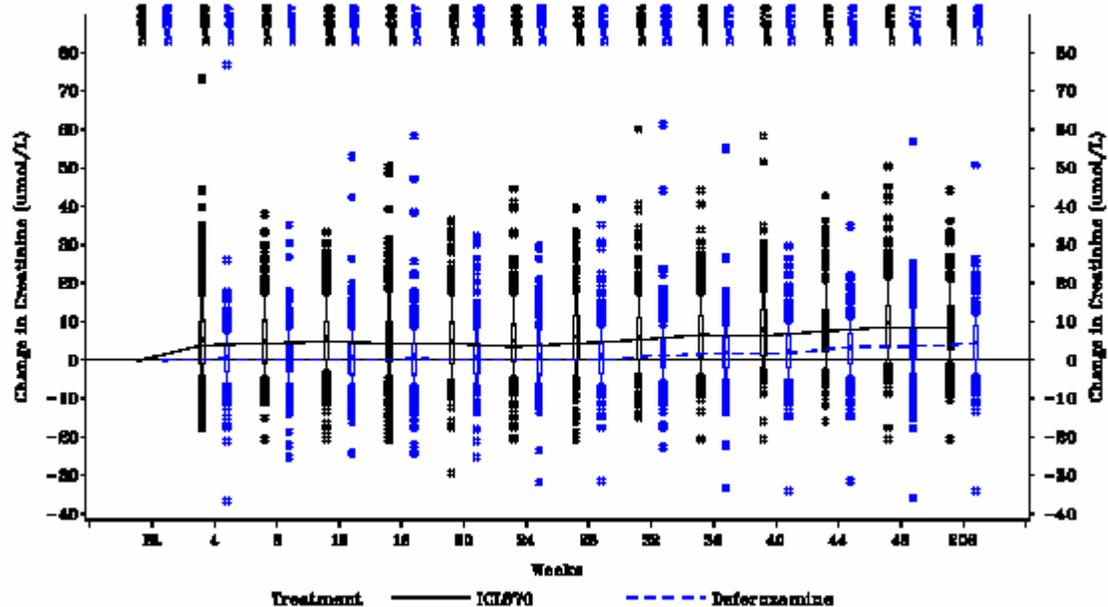
Source: Sponsor submission page 116

Starting at weeks 28 to 32 there is an additional slight upward trend in the mean serum creatinine values which is similar in both treatment groups. By EOS, the mean creatinine level in patients treated with DFO is also higher than at baseline though the increases in patients treated with Exjade are higher by a factor of approximately 10 µmol/L. A similar pattern is discernible in all age groups and at all dose levels apart from 5 mg/kg where the number of patients treated is small.

The following table depicts patients with increases in urinary protein/creatinine ratio since this is considered to be the most informative of the urinary parameters. The ULN for this parameter is 0.2 mg/mg.

Table 10-11 Number (%) of patients with increases in total urinary protein/creatinine ratio

Laboratory parameter	ICL670 N = 296 n (%)	DFO N = 290 n (%)	All patients N = 586 n (%)
Urinary protein/creatinine ratio (UPCR)			
No. patients with UPCR 0.2 - <0.4 mg/mg post-baseline	126 (42.6)	169 (58.3)	295 (50.3)
No. patients with UPCR 0.4 - <0.6 mg/mg post-baseline	56 (18.9)	42 (14.5)	98 (16.7)
No. patients with UPCR >=0.6 mg/mg post-baseline	55 (18.6)	21 (7.2)	76 (13.0)

Patients are counted only once in each post-baseline category
Source: Sponsor submission page 117

Approximately 60% of patients had a urinary protein/creatinine ratio that was within the normal range at baseline. Most patients showed transient increases at some point during the study to levels that were generally less than twice the ULN. No patient developed progressive proteinuria. Four patients experienced an increase in the protein/creatinine ratio to >1.0 mg/mg. Of these, a 49 year old patient receiving Exjade, 30 mg/kg/d, had a dose reduction because of mild proteinuria and an increase in serum creatinine.

Levels of other urinary proteins were elevated in many patients at baseline and became somewhat more elevated during treatment with a relation to dose, but no patient had a dose decrease or interruption because of these changes.

Laboratory studies in Study 0108 revealed the following.
- Hematology. Two patients with β-thalassemia developed a neutrophil count of <1,500/ml on 2 consecutive occasions and none had a platelet count of <100,000/ml during the trial. The frequency of neutropenia and thrombocytopenia for patients with rare anemias is shown in the following table.

Table 10-13 Number (%) of patients with neutropenia or thrombocytopenia – Rare anemias

	MDS N=47 n (%)	DBA N=30 n (%)	Other anemias N=22 n (%)	All rare anemias N=99 n (%)
Absolute neutrophil count				
No. patients with ANC <1.50 x 10^9/L at ≥2 post-baseline visits	1 (2.1)	3 (10.0)	1 (4.5)	5 (5.1)
No. patients with ANC <1.50 x 10^9/L at ≥2 consecutive post-baseline visits	15 (31.9)	13 (43.3)	7 (31.8)	35 (35.4)
Platelets				
No. patients with platelets <100 x 10^9/L at ≥2 post-baseline visits	-	-	-	-
No. patients with platelets <100 x 10^9/L at ≥2 consecutive post-baseline visits	11 (23.4)	5 (16.7)	7 (31.8)	23 (23.2)

Patients are counted only once in each post-baseline category for each parameter

Source: Sponsor submission page 118

- Hepatic function. No patient had an elevated AST on 2 consecutive visits, but 1 patient with β-thalassemia had an AST >5x ULN on more than 2 non-consecutive visits. ALT was raised in patients with both β-thalassemia and rare anemias as indicated in the following table.

Table 10-14 Number (%) of patients with transaminases greater than 5 x ULN

Laboratory parameter	β-thalassemia N=85 n (%)	Rare anemias N=99 n (%)	All patients N=184 n (%)
SGOT/AST			
No. patients with SGOT/AST >5 x ULN at ≥2 post-baseline visits	1 (1.2)	-	1 (0.5)
No. patients with SGOT/AST >5 x ULN at ≥2 consecutive post-baseline visits	-	-	-
SGPT/ALT			
No. patients with SGPT/ALT >5 x ULN at ≥2 post-baseline visits	5 (5.9)	1 (1.0)	6 (3.3)
No. patients with SGPT/ALT >5 x ULN at ≥2 consecutive post-baseline visits	8 (9.4)	6 (6.1)	14 (7.6)

Patients are counted only once in each post-baseline category for each parameter
Source: Sponsor submission page 119

A baseline transaminase was raised in all of the patients with β-thalassemia and 5/6 of the patients with rare anemias who subsequently had an elevation in ALT. The changes in transaminase did not appear to be dose related.

- Renal function. In the patients with β-thalassemia, increases in serum creatinine and urinary protein/creatinine ratio were similar to those seen in Study 0107. In one patient receiving Exjade at a dose of 30 mg/kg/d, an increase in urinary protein led to discontinuation of the drug.

    In patients with rare anemias, the changes in serum creatinine are shown in the following table.

Table 10-17 Number (%) of patients with increases in serum creatinine – Rare anemias

Laboratory parameter	MDS N=47 n (%)	DBA N=30 n (%)	Other anemias N=22 n (%)	All rare anemias N=99 n (%)
Serum creatinine				
No. patients with creatinine> 33% at ≥2 consecutive post-baseline visits	8 (17.0)	8 (26.7)	7 (31.8)	23 (23.2)
No. patients with creatinine increase > 33% and >ULN at ≥2 consecutive post-baseline visits	9 (9.1)	2 (6.7)	5 (22.7)	16 (16.2)

Patients are counted only once in each post-baseline category
Source: Sponsor submission page 121

Creatinine increases of >33% were more common in patients with rare anemias (16.2%) compared to β-thalassemia (3.5%). The increase in creatinine appeared to be dose related. No patient had a progressive increase in serum creatinine or an increase to >2x ULN and only about half of the patients had a dose reduction in response to the rise in serum creatinine.

In patients with rare anemias, the number of patients with an increased urinary protein/creatinine ratio is shown in the following table.

Table 10-19 Number (%) of patients with increases in total urinary protein/creatinine ratio – Rare anemias

Laboratory parameter	MDS N=47 n (%)	DBA N=30 n (%)	Other anemias N=22 n (%)	All rare anemias N=99 n (%)
Urinary protein/creatinine ratio (UPCR)				
No. pts with UPCR 0.2 - <0.4 mg/mg post-baseline	8 (17.0)	14 (46.7)	10 (45.5)	32 (32.3)
No. pts with UPCR 0.4 - <0.6 mg/mg post-baseline	14 (29.8)	1 (3.3)	3 (13.6)	18 (18.2)
No. pts with UPCR >=0.6 mg/mg post-baseline	11 (23.4)	3 (10.0)	4 (18.2)	18 (18.2)

Patients are counted only once in each post-baseline category
Source: Sponsor submission page 123

The frequency of the increase in urinary protein/creatinine ratio is similar to that seen in β-thalassemia. There was no increase in urinary protein over time and the increase in urinary protein was not dose related. Eleven patients had an increase in urinary protein/creatinine of ≥1.0 mg/mg but 3 of these had an elevated ratio at baseline. Most of the elevations in urinary protein were associated with episodes of sepsis. Three patients discontinued Exjade because of an increase in urinary protein. There was a minimal increase in other urinary proteins in patients receiving Exjade at a dose of 20-30 mg/kg/d.

- Approximately 14% and 57% of patients developed low levels of serum copper and zinc, respectively, at some time during the trial. The levels were not progressive and often fluctuated during the trial.

6.1.7.3.1 Analyses focused on measures of central tendency

Not applicable.

6.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

6.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Previously discussed.

6.1.7.4   Additional analyses and explorations

Not applicable.

6.1.7.5   Special assessments

The primary laboratory assessment of interest related to treatment with Exjade is renal function. Preclinical studies suggested that renal abnormalities might be induced in laboratory animals by the administration of Exjade. This seemed to be particularly true when the drug was administered to non-iron overloaded animals in contrast to a lower frequency of renal effects in iron overloaded animals. This has led to the theory that the renal effects may in some way be mediated by iron deficiency in the kidney.

All patients in all clinical trials of Exjade were required to have close follow up of serum creatinine and there was a dose adjustment (different for children and adults) when the serum creatinine rose even within the normal range.

Periodic serum ferritin measurements were included in all clinical protocols as it was the intention of the sponsor to determine the correlation between serum ferritin and LIC. The sponsor believes that it has established a correlation between the two that can be used as one indicator of the need for commencing Exjade therapy and following its therapeutic effects.

Because of the evidence that Exjade could cause cataract formation and impaired hearing, periodic assessments of these functions were performed.

6.1.8   Vital Signs

6.1.8.1   Overview of vital signs testing in the development program

Vital signs were measured in all studies during screening and then every 4 weeks at scheduled visits. Pulse rate and systolic and diastolic pressures were measured after the patient was in the sitting position for at least 3 minutes. Blood pressure was performed on the same arm at every visit. Treatment with Exjade produced no consistent or clinically relevant effect on vital signs.

6.1.8.2   Selection of studies and analyses for overall drug-control comparisons

See above.

6.1.8.3   Standard analyses and explorations of vital signs data

See above.

6.1.8.3.1   Analyses focused on measures of central tendencies

Not applicable.

6.1.8.3.2   Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

6.1.8.3.3   Marked outliers and dropouts for vital sign abnormalities

Not applicable.

6.1.8.4   Additional analyses and explorations

See above.

6.1.9   Electrocardiograms (ECGs)

6.1.9.1   Overview of ECG testing in the development program, including brief review of preclinical results

In all clinical studies, standard ECGs were obtained at baseline and at 4 week intervals during the trial. The interpretation of the ECG was to be performed at each study center using the same physician, but it was not stipulated who that physician would be. The tracings were performed after the patient had been in the supine position for at least 10 minutes and had to show at least 5 R-R intervals to allow the proper calculation of the QTc.

For Study 0107, Amendment 3 added central ECG and quantitative QT/QTc analysis in order to comply with ICH draft guideline E14. This was the only study in which central analysis was performed. (See 7.1.9.3 below for discussion of results).

6.1.9.2   Selection of studies and analyses for overall drug-control comparisons

See above.

6.1.9.3   Standard analyses and explorations of ECG data

In Study 0105, 2 patients receiving Exjade at a dose of 10 or 20 mg/kg/d had prolongation of QT compared to baseline (0.39 to 0.45 sec; 0.42 to 0.52 sec). Neither was believed related to study drug. One patient continued on Exjade. The other was begun on treatment with DFO.

In Study 0106, 1 patient receiving Exjade at a dose of 20 mg/kg/d had an increase in QT from 0.39 to 0.49. After a brief interruption, Exjade was restarted at the same dose and no further ECG abnormalities occurred.

In Study 0107, seven patients treated with Exjade and three randomized to DFO developed new or worsening ECG abnormalities during the study. Most of these episodes were not reported as AEs. The events included prolongation of the QTc interval in one patient on Exjade (0301/00007, 35 years, 20 mg/kg) which was assessed as study drug-related and resulted in a brief hold of therapy before restarting at the same dose, and in two on DFO (0601/00005, 30 years, 50 mg/kg; 0504/ 00003, 34 years, 30 mg/kg), neither of which was reported as an AE.

The total of 503 patients (86% of the safety population) had ECGs reviewed centrally according to Amendment 3. A similar mean QTcB change from baseline was observed for both treatment groups, although the mean QTcF change from baseline was slightly higher in the Exjade group (4.2 ms) compared to the DFO group (0.6 ms). No dose relationship relating to the QT/QTc interval was observed with either Exjade or DFO. A similar percentage of patients receiving Exjade and DFO were found to have a ≥30 ms increase in QTcB or QTcF. Other cardiac intervals were similar between the two groups. There was no evidence of consistent relevant effects on any of the other cardiac safety parameters measured.

In Study 0108, eight patients, two with β-thalassemia and six with rare anemias, developed new or worsening ECG abnormalities considered clinically significant by the investigator. These included atrial fibrillation in two patients; Grade 1 AV block (1); t-wave abnormalities (not otherwise specified) (1); left ventricular hypertrophy (1); and early repolarization (1), prominent u-waves (1) and non specific S-T abnormalities (1). None of these changes was reported as an AE and study drug was continued at the same dose in all patients.

6.1.9.3.1 Analyses focused on measures of central tendency

Not applicable.

6.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

See above.

6.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

See above.

6.1.9.4 Additional analyses and explorations

See above.

6.1.10 Immunogenicity

Not applicable.

6.1.11 Human Carcinogenicity

There were no instances of the development of cancers in any studies in any patients with β-thalassemia treated with Exjade. However, in Study 0108, in patients with rare anemias, 6/99 patients developed neoplasms. All patients who developed neoplasms had an underlying diagnosis of MDS at entry into the trial. Neoplasms developing in these patients included acute leukemia (2), acute myeloid leukemia (1), lipoma (1), rectal cancer (1) and thyroid cancer (1).

In Study 0107, 4/290 patients receiving DFO developed neoplasms.

6.1.12 Special Safety Studies

Special attention was paid to the development of ophthalmological, otological and structural hepatic abnormalities during the trials. Methods included visual acuity, eye examination, audiometry and liver echography.

In Study 0105, 1 patient (Exjade, 10 mg/kg/d) had deterioration of pre-existing myopia from day 233. Two patients (Exjade, 20 mg/kg/d) experienced mild hearing loss. There were no structural changes in the liver on echography.

In Study 0106, there were no changes in the eye or ear evaluation. One patient was noted to have inspissated bile on echography of the liver on day 382.

In Study 0107, 3 patients receiving Exjade (10, 30, 30 mg/kg/d) and 5 patients receiving DFO (26-40 mg/kg/d) developed lenticular opacities from day 84-365. Exjade was discontinued in only 1 of the patients receiving the drug. Eleven patients receiving Exjade (10-30 mg/kg/d) and 10 patients receiving DFO developed new or worsening hearing abnormalities during the trial from day 62-338. Liver echography showed new or worsening abnormalities in 5 patients receiving Exjade (gallstones or biliary sludge in 3) and in 3 patients receiving DFO.

In Study 0108, cataracts developed in 3 patients with β-thalassemia. One patient with β-thalassemia developed a retinal hole. One patient with Diamond-Blackman syndrome developed amblyopia/strabismus and another developed hypermetropia/astigmatism. All patients were receiving Exjade in a dose of 20-30 mg/kg/d and the events occurred between day 52-271. Audiometry revealed clinically significant abnormalities in 19 patients, 14 of whom had abnormalities at baseline. New findings occurred in 5 patients receiving Exjade at a dose of 5-30

mg/kg/d by study's end. New liver echography findings developed in 5 patients (3 gallstones, 1 fatty liver, 1 portal hypertension).

6.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no evidence of withdrawal phenomena or abuse potential with the use of Exjade. Patients had discontinuations, dose changes and interruptions without developing withdrawal symptoms.

6.1.14 Human Reproduction and Pregnancy Data

Two patients receiving Exjade in Study 0109 became pregnant. One patient had a therapeutic abortion and there is no information regarding the abortus. There was no information provided regarding the second pregnancy

6.1.15 Assessment of Effect on Growth

There was a strong focus on the evaluation of growth and development in pediatric patients enrolled in the trials and there were assessments of specific anthropometric measures and sexual development in Studies 0106, 0107 and 0108. Measurements of height, weight, sitting height and body mass index showed the expected growth over the year of the trial. In Study 0107, pediatric patients receiving Exjade had small but consistently superior measurements compared to patients receiving DFO. The differences were most marked in the age range of 12-<16 years of age group.

Chronological and bone ages of the patients increased on the average of one year over the course of the trial. One patient in Study 0106 and 2 patients in Study 0107 receiving Exjade developed pathological metaphyseal findings in the wrist compared to 4 patients receiving DFO who developed similar abnormalities.

Sexual development as measured by breast development, pubic hair and testicular stage were normal over the course of the trials. The same was true for patients treated with DFO in Study 0107.

6.1.16 Overdose Experience

There were no apparent overdoses in any patients in the trials.

6.1.17 Postmarketing Experience

The drug has not been marketed in any country in the world.

6.2 Adequacy of Patient Exposure and Safety Assessments

6.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The data sources used to evaluate safety are described above. They include all of the phase I, II and III studies that the sponsor has submitted with the application. The key studies supporting the safety claim include data obtained in 835 patients with transfusional hemosiderosis in various diseases (β-thalassemia, rare anemias) who were recruited in the four main safety and efficacy studies in the Exjade clinical development program (studies 0105, 0106, 0107 and 0108). Of these patients, 520 received Exjade and 313 received DFO. Most of these patients were followed for a median of one year. There is additional safety data available from an ongoing study (0109) for a median of six months exposure in SCD patients (132 ICL670, 63 DFO). Of the total of 652 patients receiving Exjade in the five studies, 292 (44.7%) were pediatric patients <16 years of age. In patients receiving Exjade, 52 (8.0%) were less than 6 years, 121 (18.6%) were between 6 and 12 years and 119 (18.3%) were between 12 and 16 years of age. An additional 22 (3.4%) patients were aged 50-<65 and 30 (4.6%) were aged ≥65 years In addition, long-term safety data with exposure to Exjade of up to 35 months were obtained in a study in 51 adult patients with β-thalassemia (study 0105E2). The safety data from Studies 0109 and 0105E2 are included in Appendix 1.

6.2.1.1 Study type and design/patient enumeration

See Section 3.2, page 11 (Tables of Clinical Studies) and tables below.

6.2.1.2 Demographics

The following table shows the demographic characteristics of the patients who received Exjade in phase II and III studies. Patients with inherited anemias and Blackfan-Diamond syndrome were young, whereas patients with MDS were old. There were many more females in the treated SCD population. There were virtually no Black patients in any of the disease categories except in SCD where they formed the overwhelming majority.

Table 5-1   Demographics features of patient populations receiving ICL670

Variable / statistic	Pooled β-thalassemia N=421	MDS N=47	DBA N=30	Other anemia N=22	Sickle cell disease N=132
Age (years)					
Mean ± SD	17.9 ± 10.02	65.1 ± 12.45	16.1 ± 10.28	35.8 ± 22.86	19.1 ± 10.7
Median	16	66	15	32	15
Min - Max	2 - 59	20 – 81	3 - 42	4 - 80	3 – 54
Age category (years)					
< 6	39 (9.3%)	-	7 (23.3%)	2 (9.1%)	4 (3.0%)
6 - <12	85 (20.2%)	-	5 (16.7%)	1 (4.5%)	30 (22.7%)
12 - <16	81 (19.2%)	-	3 (10.0%)	2 (9.1%)	33 (25.0%)
16 - <50	215 (51.0%)	5 (10.6%)	15 (50.0%)	10 (45.5%)	63 (47.7%)
50 - <65	1 (0.3%)	15 (31.9%)	-	4 (18.2%)	2 (1.5%)
≥ 65		27 (57.4%)	-	3 (13.6%)	-
Gender					
Male	199 (47.3%)	26 (55.3%)	16 (53.3%)	9 (40.9%)	52 (39.4%)
Female	222 (52.7%)	21 (44.7%)	14 (46.7%)	13 (59.1%)	80 (60.6%)
Race					
Caucasian	359 (85.3%)	44 (93.6%)	26 (86.7%)	19 (86.4%)	8 (6.1%)
Black	2 (0.5%)	-	-	-	118 (89.4%)
Oriental	20 (4.8%)	1 (2.1%)	-	3 (13.6%)	-
Other	40 (9.5%)	2 (4.3%)	4 (13.3%)	-	6 (4.5%)
Weight (kg)					
Mean± SD	43.8 ±16.61	70.4 ± 12.45	39.1 ± 18.7	56.1 ± 18.48	51.6 ± 19.39
Median	45.2	70.7	42.9	56.7	52.6
Min - Max	10.4 - 87.9	48.6 – 93	13.4 - 79.6	13 - 80	16 - 105

Source: Sponsor submission page 42

6.2.1.3   Extent of exposure (dose/duration)

The following table shows the overall duration of patient exposure. In most studies, exposure approximated a duration of 1 year. In the extension study (0105E2), patients remained on Exjade for an average of 2 ½ years.

Table 5-2   Summary of overall duration of exposure by study and treatment

	0105E2 ICL670 n=51	0106 ICL670 n=40	0107 ICL670 n=296	0108 ICL670 N=184	0109 ICL670 n=132	0107 DFO n=290	0109 DFO n=63
mean (weeks)	127	49.2	52.1	47.5	28.8	53	28.5
SD	34	8.4	8.1	14.08	10.59	6.72	10.54
median	143	49.9	53	52.6	25.6	52.9	25.7
range	3-152	1.6-56.7	3.7-67.9	0.7-66.9	0.1-60.1	4.7-68.6	3.3-53.4

Source: Sponsor submission page 43

6.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable.

6.2.2.1 Other studies

Not applicable.

6.2.2.2 Postmarketing experience

The drug is not marketed in any country in the world.

6.2.2.3 Literature

Not applicable.

6.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience appears to be adequate to evaluate the safety of the drug for the population of patients with ß-thalassemia, but not for patients with other rare anemias. A significant proportion of patients were in the pediatric age groups, including both children and adolescents. Most of the patients were Caucasian, so safety in non-Caucasian patients is less well known. There do not appear to be any gender specific safety concerns. There is some suggestion that advancing age or concomitant illness may exaggerate the adverse events seen in association with the drug.

The doses that were used by the sponsor, particularly those of 20-30 mg/kg/d appear to be those that are reasonably effective. Doses above 30 mg/kg/d cause gastrointestinal AEs that prevent their use above that level. The duration of exposure was 1 year in all the trials and there has been an extension of Study 0105E2 to as long as 3 years. While the drug is likely to be required for the life of the individual, the length of time in the studies provides a reasonable body of data that permits evaluation for an acceptable period of time.

Exclusion criteria employed in the studies, particularly those that excluded patients with renal, ocular, auditory and hepatic disease, limit the generalization of the data obtained. It will be necessary to perform additional studies before recommendations can be made for these groups of patients.

The only group for which there is adequate data supporting efficacy is the population with β-thalassemia. The reports of neutropenia and thrombocytopenia in patients with "other rare anemias", while possibly attributable to the underlying disease process, cannot be eliminated as having been caused partially or wholly by Exjade.

6.2.4 Adequacy of Special Animal and/or In Vitro Testing

Preclinical studies provided a reasonable basis upon which to perform clinical trials and were useful in producing data that led to a focus on the organ systems in humans to which attention should be paid. Extensive renal studies in normal and iron overloaded animals were performed.

6.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was extensive and adequate.

6.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Refer to Section 5 and the Clinical Pharmacology Review.

6.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor conducted an adequate evaluation for potential adverse events. These included a close monitoring of hepatic and renal dysfunction, a formal QTc study in normal persons and a QTc evaluation in their clinical studies, ophthalmological and auditory examinations, and longitudinal developmental evaluations in all pediatric patients. However, for a drug that is likely to be prescribed for a patient's entire life, the sponsor should continue to gather data on longer term use.

6.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the data to conduct a safety review was acceptable. This opinion is based on the review of the data submitted by the sponsor.

6.2.9 Additional Submissions, Including Safety Update

The sponsor has submitted preliminary safety data from Study 0109, a trial of the use of Exjade in the treatment of transfusion induced hemosiderosis in patients with sickle cell anemia, as well as safety data from Study 0105E2, a 3 year extension of Exjade treatment for patients originally enrolled in Study 0105. The review of this information is in Appendix 1.

6.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Drug related adverse events of importance associated with Exjade include the following:

- Renal dysfunction. Approximately one-third of patients treated with Exjade are noted to have developed an increase in serum creatinine and/or proteinuria. The long term natural history of this adverse event is not clear. Oftentimes, the increase is evanescent even when the drug is continued at the same dose. If the dose of the drug is halted or decreased, the serum creatinine falls to baseline. When drug is then restarted, the serum creatinine often does not rise again. The proteinuria frequently responds to dose modification. The sponsor states that there has been no evidence of progressive renal impairment despite the use of the drug for periods up to three years in duration.

- Increased hepatic transaminases. The serum transaminase and bilirubin were often elevated in patients enrolled in the trial. A number of the patients had hepatitis A and/or B and hemolysis is part of the underlying anemia. Both hepatitis and iron overload are associated with hepatic inflammatory processes. However, several episodes were documented to be clearly related to the administration of Exjade and the drug was discontinued. The long term sequelae of this form of drug hepatitis are not known.

- Cataract formation. This is likely to be a direct consequence of the use of Exjade, but appears to be an infrequent complication, although it may become more common as the drug is used for a longer period of time.

- Diminished hearing. This is likely to be a direct consequence of the use of Exjade, but appears to be an infrequent complication, although it may become more common as the drug is used for a longer period of time.

- Neutropenia/thrombocytopenia. The frequency of these complications was rare and the significance of their appearance is uncertain because of the underlying hematological diseases that patients being treated with Exjade already have.

6.4 General Methodology

6.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

See above.

6.4.1.1 Pooled data vs. individual study data

See above.

6.4.1.2 Combining data

See above.

6.4.2 Explorations for Predictive Factors

See above.

6.4.2.1 Explorations for dose dependency for adverse findings

See above.

6.4.2.2 Explorations for time dependency for adverse findings

See above.

6.4.2.3 Explorations for drug-demographic interactions

See above.

6.4.2.4 Explorations for drug-disease interactions

Not applicable.

6.4.2.5 Explorations for drug-drug interactions

See above.

6.4.3 Causality Determination

See above.

7 ADDITIONAL CLINICAL ISSUES

7.1 Dosing Regimen and Administration

Exjade is recommended to be administered as a once-a-day oral preparation in which tablets are completely dissolved in water and then drunk in its entirety. The sponsor has conducted a study in which bioequivalence with dissolution in orange juice has been established. Based on the data available, this seems to be acceptable.

The sponsor is basing the commencement and dosing of Exjade on evidence of the body iron burden which it defines as a history of the transfusion of 20 units of blood and a level of serum ferritin of >1,000 μg/L. The recommended initial dose of the drug is 20-30 mg/kg/d for most patients with the option of starting with a dose of 5-10 mg/kg/d in patients who are believed to have developed a lesser body iron burden. Maintenance doses of 20 mg/kg/d appear to be able to maintain a stable LIC in chronically transfused people (2-3 units of PRBC/month). In order to diminish LIC in a chronically transfused person, a dose of 30 mg/kg/d seems necessary. Individual tailoring of the dose depends on periodic assessment of body iron burden.

There is little data to indicate a significant dose-toxicity relationship for Exjade other than for renal dysfunction which seems to be dose-related. Gastrointestinal adverse events also appear to be dose-related.

Doses per unit of body weight for children appear to be somewhat greater then for adults because children tend to have a greater transfusion requirement relative to size. Although women seem to have a somewhat higher exposure for a given dose of drug than men, the difference does not lead to a quantifiable difference in dose for women.

In clinical practice, there is little likelihood that physicians will require that an invasive test, such as a liver biopsy, be performed prior to the initiation of Exjade in an appropriate population. Advances in the measurement of total iron body burden using non-invasive methodologies (MRI, blood tests, etc), particularly those which focus on the myocardial iron level (the main cause of mortality), should be evaluated to more precisely determine the need for, and the dose of, Exjade administration.

Although the sponsor has conducted a food study with Exjade that shows no difference in bioavailability of the drug when taken with a high fat meal, the sponsor is recommending that the drug be taken on an empty stomach in the morning. The once a day dosing schedule, the only schedule studied by the sponsor, seems appropriate based on the long half-life of the drug.

7.2 Drug-Drug Interactions

The only drug-drug interaction study performed by the sponsor was with digoxin. That study showed no interaction. (Please refer to the Biopharmaceutics review).

7.3 Special Populations

The initial dose of the drug should be 20-30 mg/kg/d in all patients requiring ongoing transfusion therapy. Although as explained above there are some differences in children (greater iron intake) and women (greater iron off-loading), these factors are small when considering the difficulty in assessing body iron stores and individual response to therapy. Dose adjustments should be made periodically and slowly based on repetitive assessment of iron intake and body stores.

All studies with Exjade excluded patients with any significant renal or hepatic dysfunction, so the efficacy and safety of the use of Exjade in patients with these disorders is not known. Dosing in patients experiencing renal dysfunction should be lowered as this was the manner in which such patients were managed.

Patients who were pregnant or lactating were excluded from the studies and the effect of Exjade on these conditions is unknown.

7.4   Pediatrics

Proportionally, there was a large representation of pediatric patients in virtually all of the clinical studies conducted. PK and PD data are available from some of the studies. The safety and efficacy of Exjade in the pediatric population appears to be similar to that seen in non-pediatric population. Since the pediatric population was more likely to have had an LIC performed by SQUID, a number received doses of Exjade that were apparently sub-therapeutic. In pediatric patients whose LIC was determined by liver biopsy, it appears that the efficacy of Exjade is similar to that for non-pediatric patients.

because of CMC, preclinical and clinical deficiencies (letter to sponsor dated

incomplete clinical data available to the Agency.

7.5   Advisory Committee Meeting

Discussion of Exjade is scheduled for a meeting of the Blood Products Advisory Committee on September 29, 2005.

7.6   Literature Review

See references.

7.7   Postmarketing Risk Management Plan

There is no risk management plan provided by the sponsor other than the recommendation that periodic determination of iron status, renal function, hepatic function, and ophthalmological and audiological examinations be performed.

7.8   Other Relevant Materials

Consultations have been requested, and are currently pending, from the following entities:

- Division of Drug Marketing, Advertising and Communications
- Office of Drug Safety
- Division of Scientific Investigation
- Center for Devices and Radiological Health
- Division of Anti-Infective and Ophthalmological Products

8   OVERALL ASSESSMENT

8.1   Conclusions

Deferoxamine (Desferal), the only currently available treatment for hemosiderosis due to chronic transfusion therapy in β-thalassemia patients, is widely acknowledged by both the patient and physician community to be a problematic drug with which to contend. In fact, because of these problems, a majority of patients who might benefit from its use either refuse to use it or use it in a manner that does not maximize its clinical utility. Yet no replacement for deferoxamine has become available.

Exjade has characteristics that make it attractive as an iron chelator. It is an oral agent with a once-a-day dosing regimen for which there is pharmacodynamic evidence of an iron off-loading capability.

The crucial clinical study(ies), particularly Study 0107, designed to demonstrate efficacy and safety did not meet the pre-specified primary efficacy objective. Nonetheless, there is a fairly large database that can be used to help determine whether or not the drug should be considered for approval.

The efficacy of Exjade is suggested by the following information:

1) There is a dose-response relationship of drug to iron excretion. This was shown in phase 1/2 studies and in the iron balance studies in the Study 0107. The sponsor's trial design appears to have been too conservative in the dosing of Exjade and this led to failure of response in patients who were receiving doses of Exjade of 5-10 mg/kg/d. Patients who had biopsy demonstrated LIC of ≥7mg Fe/g dw and who received doses of Exjade of 20-30 mg/kg/d experienced a success rate that met the requirement of the non-inferiority margin.
2) Exjade produced a statistically significant reduction in LIC (in the population measured by either biopsy alone or in the combined population measured by either biopsy or SQUID) in patients whose baseline LIC was ≥7 mg Fe/g dw. These patients, in fact, are those for whom therapy is likely to be most beneficial.
3) The average decrement in LIC in patients with a baseline LIC of ≥7 mg Fe/g dw was between 5.3-5.6 mg Fe/g dw in a one year period even while continuing transfusion therapy. Presuming a patient were to continue receiving the drug, it seems reasonable to assume there would be an additional decrease in LIC over time.

4) The serum ferritin declined in tandem with the LIC.
5) The supporting studies (0105, 0106 and 0108) add consistency to the results obtained in Study 0107.

There are significant safety concerns associated with the use of Exjade including:
   1) Renal dysfunction. About a third of patients receiving Exjade have an increase in serum creatinine and many have a variable degree of proteinuria. These abnormalities appear to be dose related. The clinical consequences of these laboratory abnormalities are uncertain, but preclinical studies have shown that tubular dysfunction is a toxic effect of Exjade. The sponsor has presented data to show that the renal dysfunction is not progressive in a small group of patients who have received Exjade for up to three years.
   2) Hepatic dysfunction. At least two cases of drug-related hepatitis were evident in the clinical trials. The long term clinical sequelae of these events are unclear.
   3) Neutropenia and thrombocytopenia. Although rare, and possibly related to underlying disease or other drugs, the relation to Exjade is not known.
   4) Cataract development. This is an unusual occurrence.
   5) Hearing loss. This is an unusual occurrence.

9 APPENDICES

9.1 Review of Individual Study Reports

Study 0105E2
Reviewed Primarily for Safety Data and Analysis

Objectives

Primary
- To provide treatment with Exjade
- To evaluate the long term safety and tolerability of Exjade

Secondary
- To determine the effect of Exjade on LIC as measured by SQUID
- To evaluate the role of long term serum ferritin and other surrogate markers on dose titration of Exjade

Design

This was a three year open label, non-comparator controlled extension to Studies 0105 and 0105E1, and was also available to patients from a food effect sub-study named 0105F. In this study, patients who appeared to have benefited from the use of chelator therapy (whether from Exjade or DFO) in Study 0105/0105E/0105F were invited to participate in this extension in which all patients were to be treated with Exjade. The initial dose of Exjade was determined by the LIC at the start of the extension phase of the trial (for patients who had previously been receiving DFO) or was the dose that patients receiving Exjade had already been receiving. The dose of Exjade could be increased or decreased in steps of 5-10 mg/kg/d (within the range of a total dose of 5-40 mg/kg/d) depending on LIC performed every 6 months and safety parameters. Some patients with a history of hepatitis or other liver conditions were offered the option to undergo liver biopsy. Serum ferritin, iron and transferrin were performed monthly as surrogate markers. ECGs, hepatic, renal, visual and auditory evaluations were performed regularly.

The schedule for the study is shown in the table below.

3.5.1 Visit schedule of the extension study

	1st Year — Visits every month (4 weeks)													2nd Year — Visits every month (4 weeks)												3rd Year — Visits every 2 months (8 weeks)					
Week	–	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	104	112	120	128	136	144
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31 EOS
Informed consent	x																														
Physical examination	x																														
Transfusion[1]													AS REQUIRED →																		
SQUID[2]	#						x						x						x						x						x
MRI[3a]	x						x						x						x						x						x
Liver Biopsy[3b]	x						x						x						x						x						x
Pregnancy test[4]	#																														x
Vital signs	#	x		x			x		x		x		x	x		x			x		x		x		x	x	x	x	x	x	x
Body weight/height[5]	#	x	x	x	x	x	x	x	x	x	x	x	x	x		x			x		x		x		x	x	x	x	x	x	x
ECG[6]	#						x						x						x						x						x
Echocardiography[7]	x						x						x						x						x						x
Urinalysis	#	x		x			x		x		x		x	x		x			x		*		*		*	*	*	*	*	*	*
Urinary prot/NAG/A1	#	x	x	x	x	x	x	x	x	x	x	x	x	x		x			x		*b		*b		*b	*b	*b	*b	*b	*b	*b
Serum creat, creat clear (Cockroft)	#	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ocular exams[8]	#						x						x						x						x						x

	1st Year — Visits every month (4 weeks)													2nd Year — Visits every month (4 weeks)												3rd Year — Visits every 2 months (8 weeks)					
Week	–	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	104	112	120	128	136	144
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31 EOS
Audiometry	#												x												x						x
Liver echography	#						x						x						x						x						x
Lab Safety Tests: Hematology, Blood chemistry	#	x		x			x		x		x		x	x		x			x		*		*		*	*	*	*	*	*	*
Serum Ferritin, Serum Iron, Transferrin, Transferrin Saturation	#	x	x	x	x	x	x	x	x	x	x	x	x	x		x			x		*		*		*	*	*	*	*	*	*
Urine for biomarker development[9]	x		x		x		x		x		x		x	x		x			x		x		x		x	x	x	x	x	x	x
Plasma for biomarker development[10]	x		x		x		x		x		x		x	x		x			x		x		x		x	x	x	x	x	x	x
ICL670													██████████																		
ConMed													AS REQUIRED →																		
Comments													AS REQUIRED →																		
Adverse Events	#	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x		x		x		x	x	x	x	x	x	x	x
Drug dispensing[9,11]	#	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Collection of unused med	#	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study completion (prolongation of extension phase)	#																														

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		1st Year Visits every month (4 weeks)												2nd Year Visits every month (4 weeks)												3rd Year Visits every 2 months (8 weeks)					
Week	−	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	104	112	120	128	136	144
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31 EOS
Study completion (extension study)[1012]																															x

[1]To maintain hemoglobin ≥ 9±1 g/dL during study treatment (record on extension CRF).
[2]Each of following evaluations is performed together with every SQUID assessment: Weight, height, body fat, BMI, chi2tissue, thorax radius, Z-liver ± SD, ultrasound liver (source documentation only). After consultation with the Novartis an extra SQUID assessment may be scheduled if a patient's serum ferritin is < 1000 ng/mL at 2 consecutive measurements and a trend (3 consecutive measurements) can be seen towards normal serum ferritin values.
[3a]Optional <u>at one occurrence</u> and based on investigator's judgment, provided a liver biopsy assessment is performed at the same visit/on the same day. Patients are required to sign the consent form addendum which explains this procedure.
[3b]Optional <u>at one occurrence</u> and based on investigator's judgment, provided a MRI assessment is performed at the same visit/on the same day. Patients are required to sign the consent form addendum which explains this procedure.
[4]To be repeated out of schedule if menses are delayed for more than 7 days.
[5]Weight and height will be recorded on the extension CRF only at Visit 1, 7, 13, 25 and 31.
[6]Based on clinical judgment, a 24h-Holter-ECG monitoring may be performed for patients with a history of cardiac arrhythmia.
[7]Only in patients with cardiac diseases.
[8]To be performed by an ophthalmologist.
[9]Collect 3 mL of urine into labeled vial and freeze immediately in a -70°C freezer. The fresh urine sample is aliquoted into three 1 mL aliquots as described in Quintiles Laboratory Investigator Guide. Samples shipped every 2 months to Quintiles Laboratory for analysis. See Appendix 1.
[10]Collect 3 ml of blood into labeled vial. The blood is spun and plasma is aliquoted as described in Quintiles Laboratory Investigator Guide. Then freeze plasma immediately in a -70°C freezer. Samples shipped every 2 months to Quintiles Laboratory for analysis. See Appendix 1.
[#11]First drug to be dispensed at the first extension visit (Visit 1); potential doses adjustments may be performed at every visit or after an extraordinary SQUID assessment.
[#12]An end of study assessment to be performed at extension study completion or upon premature discontinuation.
[a]Do not perform if most recently completed SQUID assessment was performed within 6 weeks of the End of Prolongation of Extension Study visit date.
[b]Only urinary protein analysis to be performed by the local lab. NAG and A1 analysis is no longer required.
#: These assessments are already scheduled at the End of Prolongation of Extension Study visit of the original study and will not be repeated at the first visit of the extension study (Visit 1).
*: Schedule recommendation for these evaluations to be performed by the local lab. Any significant findings, which meet the definition of an AE, must be recorded in the AE summary page of the extension CRF.

Source: Sponsor submission page 23

Patient Population

Patients who had completed Study 0105E or 0105F were eligible for the study. Informed consent and a body weight of at least 35 kg were required. Exclusions were pregnancy or breast feeding women, a history of non-compliance or poor reliability, proteinuria >300 mg/L in a second voided morning specimen and a serum creatinine above the ULN.

Treatments

Exjade tablets were to be dispersed in water by vigorous stirring. The dosing of Exjade was dependent on LIC. Dose reductions were undertaken when the LIC was projected to fall below 2 mg Fe/g dw. Dose escalations and reductions had to be agreed to by the Study Monitoring Committee. The initial dose of Exjade is shown in the following table.

Table 3-1 ICL670 dose assignment based on LIC

Patients with LIC	ICL670 dose assigned
2 – 3 mg Fe/g dw	5 mg/kg/day
>3 – 7 mg Fe/g dw	10 mg/kg/day
>7 - 14 mg Fe/g dw	20 mg/kg/day
>14 mg Fe/g dw	30 mg/kg/day

Source: Sponsor submission page 21

Drug accountability was performed by the field monitor during site visits. Patients returned all unused medication at the end of the trial.

Drug therapy was discontinued or interrupted for any of the following reasons:
- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Unsatisfactory therapeutic results
- Condition no longer required therapy
- Protocol violation
- Withdrawal of consent
- Loss to follow up
- Administrative problems
- Death

Efficacy Assessments

Patients were followed with LIC measured by SQUID, serum ferritin, serum iron and transferrin. Some patients had a liver biopsy and MRI scans of the liver. All SQUID evaluations were done at the Turin University Department of Pediatrics. In addition to the regularly scheduled SQUIDs, patients whose serum ferritin fell below 1000 ng/mL on 2 consecutive measurements had an immediate SQUID. Adverse events were monitored and recorded, and patients had periodic monitoring of hematology, chemistry, urine tests as well as ECGs, echocardiograms and physical examinations. Audiometry, ocular examinations and liver echography were also performed.

Protocol Amendments and Changes

Amendment 1 issued on June 30, 2003 provided for clarification of laboratory procedures that were primarily administrative. In addition, regular meetings of the Safety Monitoring Board were not held as there were no safety issues identified. In an interim analysis, only data from patients who had originally received Exjade in Study 0105 were analyzed.

Statistics

Data from all centers were pooled to provide an adequate number of patients for statistical analysis. The cut-off date for data was June 30, 2004. Data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements.

The populations analyzed included:
- Intent to treat. All patints from Studies 0105/0105E/0105F who had been treated with Exjade and had at least one scheduled post-baseline SQUID assessment.

- Safety. All patients previously receiving Exjade who received at least one dose of drug in Study 0105E2.

Efficacy evaluations included:
- LIC by SQUID
- Iron balance as previously described
- Surrogate markers (serum ferritin, iron and transferrin)

Safety evaluations included:
- AEs
- Laboratory evaluations as shown below

Table 6-1 Definition of notable and extended ranges for selected laboratory parameters

Laboratory parameter	Criteria for notable and extended ranges
Platelet count	$<100 \times 10^9$/L
Absolute neutrophils	$<1.5 \times 10^9$/L
Serum creatinine	>33% increase from baseline (at 2 consecutive measurements) (extended range: >50% increase)
Urinary protein/creatinine ratio	≥1.0 (mg/mg) in a second-void morning urine sample
SGOT/SGPT	>5 x ULN (extended range: >10 x ULN)

Special renal function parameters, expressed as a ratio to urinary creatinine, were summarized as shift tables (baseline vs. highest result during study) using the following ranges:

- Urinary protein / creatinine ratio: <0.2, 0.2 - <0.4, 0.4 - <0.6, ≥0.6 mg/mg
- Urinary α–1 M / creatinine ratio: <1.7, 1.7 - <3.4, 3.4 - <5.1, ≥5.1 mg/mmol
- Urinary NAG / creatinine ratio: <0.46, 0.46 - <0.92, 0.92 - <1.38, ≥1.38 U/mmol

Source: Sponsor submission page 37

- Vital signs, ECGs, ophthalmic, audiometric evaluations and liver echography studies

Patients Studied

The 43 patients analyzed are shown in the following figure.

Figure 7-1 Overview of the various studies and the interim analysis
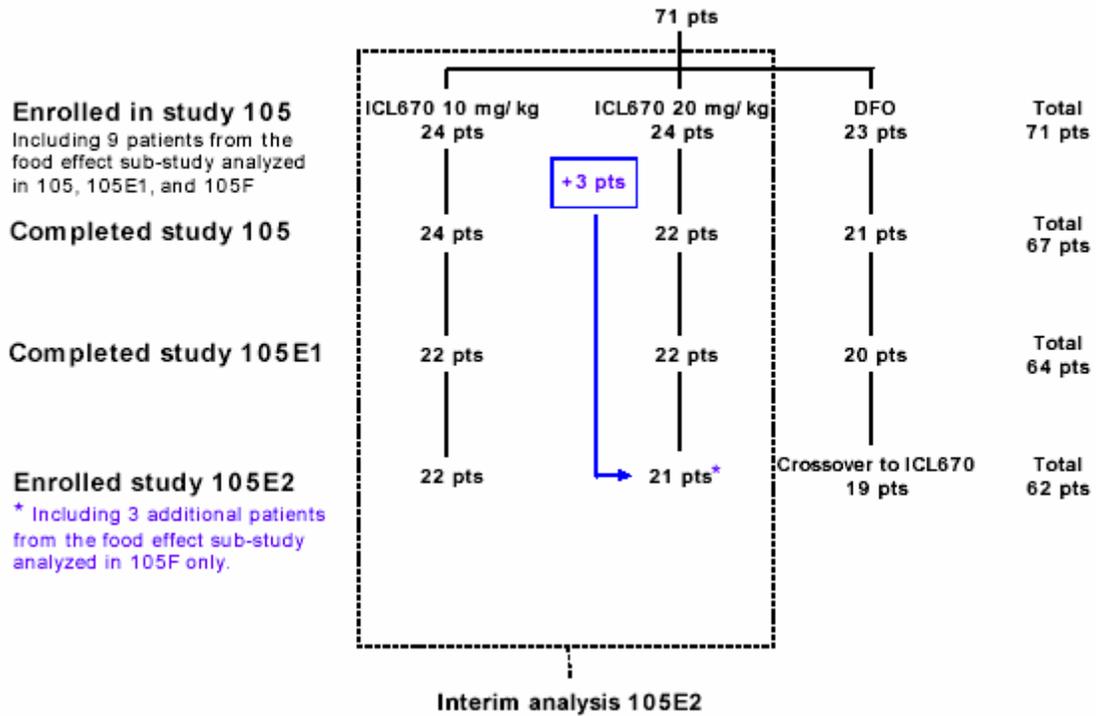
Source: Sponsor submission page 39

The patient disposition for the 43 patients continuing on Study 0105E2 from the previous studies is shown in the following table. The single protocol violation was due to lack of compliance and the patient is included in the analysis populations.

Table 7-1 Patient disposition for each treatment group

Disposition Reason	ICL670 10mg/kg n=24 n (%)	ICL670 20mg/kg n=27 n (%)	All treatments n=51 n (%)
Completed core study (3 months)	24 (100.0)	26 (96.3)#	50 (98.0)
Discontinued	0	1 (3.7)	1 (2.0)
Adverse Events	0	1 (3.7)	1 (2.0)
Continuing into main study (12 months)	24 (100.0)	26 (96.3)#	50 (98.0)
Completed 12 months	24 (100.0)	23 (85.2)	47 (92.2)
Discontinued	0	1 (3.7)	1 (2.0)
Unsatisfactory therapeutic effect	0	1 (3.7)	1 (2.0)
Continuing into prolongation 105E1 (Amd 3)	24 (100.0)	23 (85.2)	47 (92.2)
Completed E1	22 (91.7)	22 (81.5)	44 (86.3)
Discontinued	2 (8.3)	0	2 (3.9)
Adverse Events	2 (8.3)	0*	2 (3.9)*
Continuing into extension study 105E2	22 (91.7)	21 (77.8)#	43 (84.3)#
Discontinued	4 (16.7)	4 (14.8)	8 (15.7)
Adverse Events	0	2 (7.4)	2 (3.9)
Unsatisfactory therapeutic effect	3 (12.5)	1 (3.7)	4 (7.8)
Protocol violation	1 (4.2)	0	1 (2.0)
Subject withdrew consent	0	1 (3.7)	1 (2.0)

Patients initially randomized to ICL670 and analyzed in this interim report are presented only.

#Two patients (1/6 and 1/15) only completed the core study before entering the food effect sub-study and then entered straight into CICL670A0105E2. Patient 3/16 only completed the main study before entering the food effect sub-study and then entered CICL670A0105E2. These 3 patients were not randomized but assigned to 20 mg/kg ICL670 and not included in the analysis of CSR105 and CSR105E1 but in CPR105F.

*Patient 2/18 discontinued treatment with study drug due to an AE but completed the prolongation phase.

Source: Sponsor submission page 40

The number of patients in the analysis populations by treatment group is shown in the following table.

Table 7-2 Number (%) of patients in analysis populations by treatment group

Analysis population	ICL670 10 mg/kg	ICL670 20 mg/kg	All treatments Total
Intent-to-treat population (ITT)	24 (100.0%)	26 (96.3 %)#	50 (98.0%)#
Safety population (SA)	24 (100.0%)	27 (100.0%)	51 (100.0%)

One patient was excluded from ITT analysis due to missing post-baseline SQUID assessment. The patient discontinued due to AE during the first 3 months treatment.

Source: Sponsor submission page 41

The demographic characteristics are listed in Study 0105 and were well balanced in this study except for a preponderance of women in the 10 mg/kg/d group.

Medications

Treatment with Exjade and its interruptions are shown in the following table.

Table 8-1 Therapy interruptions, average daily dose and dose intensi

Study drug administration	ICL670 10 mg/kg N=24	ICL670 20 mg/kg N=27	All treatments N=51
Number of interruptions			
0	9 (37.5%)	10 (37.0%)	19 (37.3%)
1	5 (20.8%)	5 (18.5%)	10 (19.6%)
2	2 (8.3%)	4 (14.8%)	6 (11.8%)
3	5 (20.8%)	4 (14.8%)	9 (17.6%)
>3	3 (12.5%)	4 (14.8%)	7 (13.7%)
Total length of interruptions (days)			
1 interruption			
n	5	5	10
Mean ± SD	12.8 ± 9.76	22.6 ± 31.71	17.7 ± 22.71
Minimum – Maximum	2 - 24	1 - 78	1 – 78
Median	10	15	12.5
2 interruptions			
n	2	4	6
Mean ± SD	24 ± 0	33.8 ± 30.53	30.5 ± 24.18
Minimum – Maximum	24 - 24	4 - 67	4 – 67
Median	24	32	24
3 interruptions			
n	5	4	9
Mean ± SD	26.2 ± 28.96	24.3 ± 14.43	25.3 ± 22.33
Minimum – Maximum	13 - 78	13 - 44	13 – 78
Median	13	20	14
>3 interruptions			
n	3	4	7
Mean ± SD	25 ± 13	34 ± 29.53	30.1 ± 22.7
Minimum – Maximum	17 - 40	16 - 78	16 – 78
Median	18	21	18
Average daily dose (mg/kg/day)			
n	24	27	51
Mean ± SD	17.5 ± 5.03	20 ± 5.91	18.9 ± 5.60
Minimum – Maximum	9.2 - 28.1	10.2 - 30.1	9.2 - 30.1
Median	17.8	20	19.3
Average daily dose group (mg/kg/day)			
7.5 - <15	6 (25.0%)	6 (22.2%)	12 (23.5%)
15 - <25	17 (70.8%)	14 (51.9%)	31 (60.8%)
>=25	1 (4.2%)	7 (25.9%)	8 (15.7%)
Relative dose intensity			
Mean ± SD	1.8 ± 0.5	1 ± 0.3	1.4 ± 0.55
Minimum – Maximum	0.9 - 2.8	0.5 - 1.5	0.5 - 2.8
Median	1.8	1	1.3

Source: Sponsor submission page 42

There was no difference in the percent of patients who underwent dose interruptions in the 2 groups. Most of the patients assigned to the 10 mg/kg/d dose group had their dose increased over the course of the trial because of lack of efficacy, so that their average daily dose was almost equivalent to that of the patients assigned to the 20 mg/kg/d dose group. Almost half of the patients in the 20 mg/kg/d group also had an increase in dose because of lack of efficacy.

Table 8-2 Reasons for dose adjustment

Dose adjustment	ICL670 10mg/kg N=24	ICL670 20mg/kg N=27	All treatments N=51
Dose increase due to lack of efficacy	21 (87.5%)	13 (48.1%)	34 (66.6%)
Time to dose increase (weeks)	17.9-107.1	22.1-144.9	17.9-144.9
Dose decrease due to AEs	0	3	3
Interruptions due to AEs (patients)	10	14	24
Interruptions due to AEs (episodes)	20	22	42

Source: Sponsor submission page 43

The final dose of Exjade administered is shown in the following table.

Table 8-3 Dose adjustments and final dose of study medication

Dose changes	ICL670 10 mg/kg N=24	ICL670 20 mg/kg N=27	All treatments N=51
Any dose adjustment			
No	1 (4.2%)	3 (11.1%)	4 (7.8%)
Yes	23 (95.8%)	24 (88.9%)	47 (92.2%)
Final dose			
Prematurely discontinued	6 (25.0%)	6 (22.2%)	12 (23.5%)
10 mg/kg/day	2 (8.3%)	2 (7.4%)	4 (7.8%)
15 mg/kg/day	1 (4.2%)	0	1 (2.0%)
20 mg/kg/day	8 (33.3%)	9 (33.3%)	17 (33.3%)
25 mg/kg/day	1 (4.2%)	4 (14.8%)	5 (9.8)
30 mg/kg/day	4 (16.7%)	3 (11.1%)	7 (13.7%)
35 mg/kg/day	1 (4.2%)	3 (11.1%)	4 (7.8)
40 mg/kg/day	1 (4.2%)	0	1 (2.0%)

Source: Sponsor submission page 44

The overall exposure to Exjade is shown in the following table.

Table 8-4 Overall exposure to study medication

Duration of exposure (weeks)	ICL670 10mg/kg N=24	ICL670 20mg/kg N=27	All treatments N=51
Exposure			
< 12 weeks	0 (0.0%)	1 (3.7%)	1 (2.0%)
36 - < 48 weeks	0 (0.0%)	1 (3.7%)	1 (2.0%)
48 - < 60 weeks	1 (4.2%)	0 (0.0%)	1 (2.0%)
60 - < 72 weeks	1 (4.2%)	0 (0.0%)	1 (2.0%)
72 - < 84 weeks	1 (4.2%)	2 (7.4%)	3 (5.9%)
84 - < 96 weeks	0 (0.0%)	2 (7.4%)	2 (3.9%)
96 - < 108 weeks	0 (0.0%)	1 (3.7%)	1 (2.0%)
108 - < 120 weeks	0 (0.0%)	3 (11.1%)	3 (5.9%)
120 - < 132 weeks	1 (4.2%)	0 (0.0%)	1 (2.0%)
132 - < 144 weeks	10 (41.7%)	7 (25.9%)	17 (33.3%)
>= 144 weeks	10 (41.7%)	10 (37.0%)	20 (39.2%)
Statistic			
Mean ± SD	133 ± 27	122 ± 38	127 ± 34
Minimum - Maximum	56 - 152	3 - 152	3 – 152
P10	74.7	78.7	78.7
P25	138.3	106.7	109.4
Median	143	143	143
P75	146.0	144.4	145.9
P90	151.1	151.1	151.1

Source: Sponsor submission page 45

Efficacy Results

Liver iron concentration. Over the 3 years of the trial, patients in both arms of the trial had a stable or small reduction in LIC. This may in part be due to the fact that most patients originally assigned to Exjade at a dose of 10 mg/kg/d had an escalation in dose so that after a year or so after initiation of the trial, patients in both arms were receiving comparable doses.   The following figure shows the change in LIC over the 3 year period.

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Figure 9-2 Change in LIC (mg Fe/g dw) during the study (ITT population)
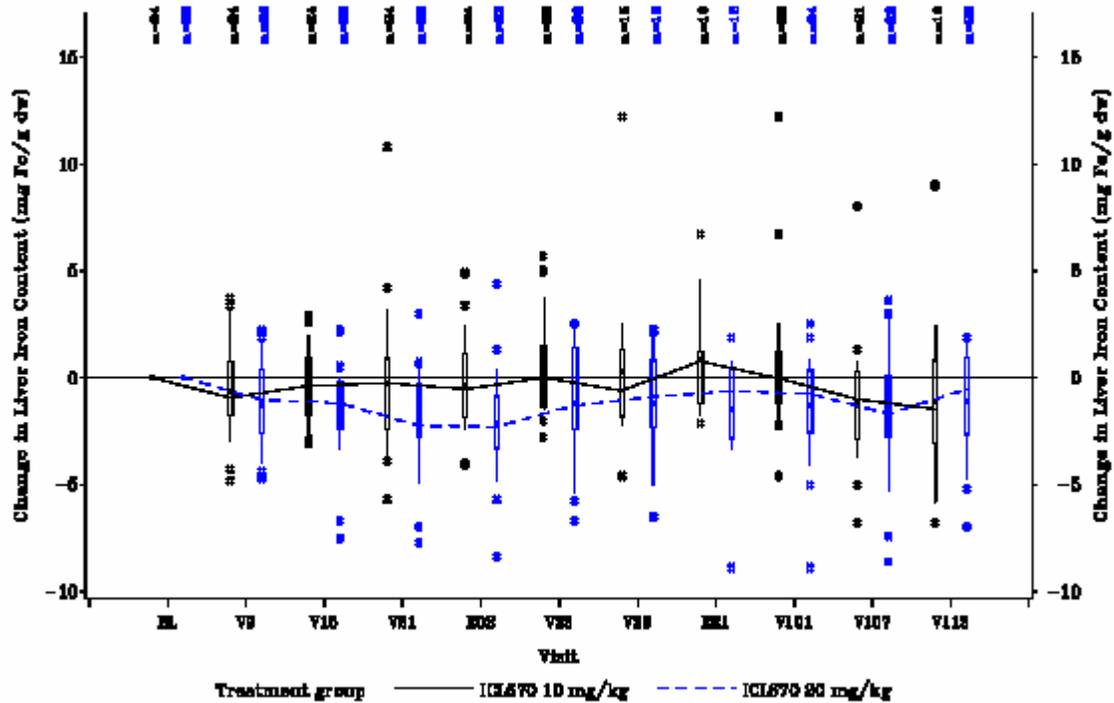
BL: Baseline, EOS: End of study visit of CICL670A0105, EE1: End of prolongation phase under Amendment 3
Visit schedule: every 4 weeks
Source: Sponsor submission page 49

Iron balance. The ratio of Fe excretion/Fe intake was 0.99 and 1.01 in the 10 mg/kg/d and the 20 mg/kg/d dose groups, respectively, indicating a near identity of iron balance in the two groups.

Serum ferritin. Over the time in the trial, the serum ferritin tended to rise from a mean of approximately 2600 ng/mL to 3400 ng/mL in both arms of the trial. Fluctuations in serum ferritin were high throughout the trial. Serum ferritins are shown in the following figure.

Figure 9-3 Serum ferritin levels in patients initially randomized to 10 and 20 mg/kg ICL670 (ITT population)
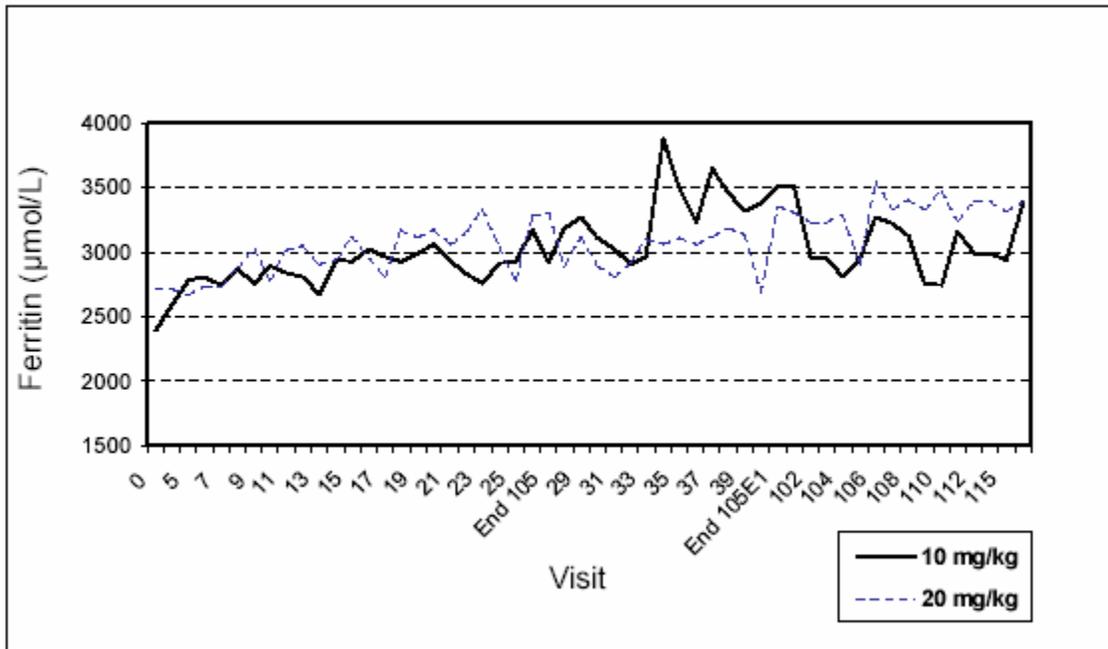
Median serum ferritin levels over time by visit (excluding visit 41 to 44 at the end of the prolongation phase due to small samples sizes).

Source: Sponsor submission page 52

Serum iron and transferrin. There were no consistent changes in the levels of these variables over the course of the trial.

Safety

Adverse Events.
The number of patients with AEs overall by primary organ system and preferred term is shown in the following table. The table includes all AEs occurring during Studies 0105, 0105E1 and 0105E2.

Table 10-1 Number (> 12% in total) of patients with AEs overall by primary system organ class and preferred term

Primary system organ class Preferred term	ICL670 10mg/kg N=24 n (%)	ICL670 20mg/kg N=27 n (%)	All treatments N=51 n (%)
Any primary system organ class	24 (100.0)	27 (100.0)	51 (100.0)
Respiratory disorders	23 (95.8)	23 (85.2)	46 (90.2)
Cough	13 (54.2)	18 (66.7)	31 (60.8)
Nasopharyngitis	5 (20.8)	4 (14.8)	9 (17.6)
Pharyngitis	10 (41.7)	9 (33.3)	19 (37.3)
Pharyngolaryngeal pain	5 (20.8)	10 (37.0)	15 (29.4)
Rhinitis nos	10 (41.7)	9 (33.3)	19 (37.3)
Infections and infestations	23 (95.8)	22 (81.5)	45 (88.2)
Bronchitis	4 (16.7)	3 (11.1)	7 (13.7)
Influenza	9 (37.5)	9 (33.3)	18 (35.3)
Pharyngitis	7 (29.2)	9 (33.3)	16 (31.4)
Rhinitis	6 (25.0)	6 (22.2)	12 (23.5)
Gastrointestinal disorders	19 (79.2)	21 (77.8)	40 (78.4)
Abdominal pain	14 (58.3)	15 (55.6)	29 (56.9)
Diarrhea	7 (29.2)	7 (25.9)	14 (27.5)
Nausea	4 (16.7)	10 (37.0)	14 (27.5)
Vomiting	0 (0.0)	9 (33.3)	9 (17.6)
General disorders	15 (62.5)	21 (77.8)	36 (70.6)
Asthenia	4 (16.7)	11 (40.7)	15 (29.4)
Influenza like illness	7 (29.2)	8 (29.6)	15 (29.4)
Oedema peripheral	3 (12.5)	4 (14.8)	7 (13.7)
Pyrexia	9 (37.5)	14 (51.9)	23 (45.1)
Musculoskeletal disorders	16 (66.7)	17 (63.0)	33 (64.7)
Arthralgia	9 (37.5)	6 (22.2)	15 (29.4)
Back pain	12 (50.0)	13 (48.1)	25 (49.0)
Nervous system disorders	16 (66.7)	14 (51.9)	30 (58.8)
Headache	15 (62.5)	10 (37.0)	25 (49.0)
Skin / subcutaneous tissue disorders	9 (37.5)	9 (33.3)	18 (35.3)
Injury etc.	6 (25.0)	11 (40.7)	17 (33.3)
Investigations	6 (25.0)	10 (37.0)	16 (31.4)
Ear and labyrinth disorders	7 (29.2)	6 (22.2)	13 (25.5)
Vertigo	5 (20.8)	4 (14.8)	9 (17.6)
Renal and urinary disorders	7 (29.2)	6 (22.2)	13 (25.5)
Renal colic	4 (16.7)	3 (11.1)	7 (13.7)
Eye disorders	4 (16.7)	8 (29.6)	12 (23.5)
Cardiac disorders	2 (8.3)	6 (22.2)	8 (15.7)
Reproductive disorders	4 (16.7)	4 (14.8)	8 (15.7)
Vascular disorders	3 (12.5)	4 (14.8)	7 (13.7)

A subject with multiple occurrences of an AE is counted only once in the AE category.
A subject with multiple AEs within a SOC is counted only once in the total row.
Source: Sponsor submission page 54

Although the numbers are small, the patients treated with Exjade at a dose of 20 mg/kg/d appeared to have a greater frequency of nausea, vomiting, asthenia, fever, injury, abnormal

investigations, ocular and cardiac AEs. During the extension phase of Study 0105E2, there were three patients who developed AEs believed by the investigator to have been related to study drug and all involved the gastrointestinal system. One patient (3/04) developed moderate diarrhea and severe skin rash after dose escalation from 10 to 20 mg/kg/d and responded to drug withdrawal. Reinstitution of the drug at low dose followed by escalation in dose to 30 mg/kg/d occurred without recurrence of side effects. The second patient developed mild diarrhea after an increase in dose from 20 to 30 mg/kg/d. The third patient developed moderate nausea that led to the discontinuation of Exjade.

Deaths. No deaths occurred during the trial.

Serious adverse events. Two SAEs were reported during the extension phase (Study 0105E2). A pregnancy occurred in a woman (3/16) receiving Exjade at a dose of 20 mg/kg/d. The pregnancy was terminated, and the drug restarted. She subsequently had a splenectomy and cholecystectomy. The second patient had several hospitalizations for diabetes, venous thrombosis and coxalgia. The patient was discontinued from Exjade for lack of compliance and was recorded as a protocol failure. Neither SAE was believed related to study drug.

Other significant AEs. In Study 0105E2, one patient (3/04) had drug withdrawal and reinstitution because of diarrhea and skin rash (see above). Dose reduction occurred in one patient because of an improvement in iron overload during therapy. In four patients, temporary interruption of drug occurred because of an increase in transaminases (patient 2/22), fever and renal colic (patient 2/11), flu (patient 2/13) and pregnancy (patient 3/16 – see above).

Study drug discontinuation. Two patients discontinued Exjade during Study 0105E2. The first (patient 2/25) who was receiving 30 mg/kg/d developed moderately severe cardiomyopathy. His last LIC was 11.1 mg Fe/g dw and his last serum ferritin was 3768 ng/mL. The second (patient 4/14) discontinued Exjade after developing nausea when the dose was raised from 20 to 30 mg/kg/d.

Laboratory values.
- Bone marrow function. No patient developed 2 consecutive neutrophil counts below 1,500/ml. However, one patient had a neutrophil count of 1,350 and 1,050 on days 321 and 449, respectively. No patient developed thrombocytopenia.
- Hepatic function. Transient increases in AST occurred in 75 and 65% of patients receiving Exjade at doses of 10 and 20 mg/kg/d, respectively. However, no patients developed an increase in ALT >5x ULN on 2 post-baseline visits.

   Transient increases in ALT occurred in virtually all patients receiving Exjade at doses of 10 and 20 mg/kg/d, respectively. One patient (2/22) with an elevated ALT at baseline and receiving Exjade at a dose of 20 mg/kg/d had an elevation in ALT >5x ULN on days 535, 547 (therapy withheld temporarily) and 813. The increases subsided despite continuing therapy. A second patient (4/35) with an elevated ALT at baseline and receiving Exjade at a dose of 10 mg/kg/d had an elevation of ALT .5x ULN on days 333 and 361. After interruption of Exjade, the dose was reinstituted and subsequently raised to 20 mg/kg/d with fluctuating ALT levels.

No patients developed AST or ALT greater than 10x ULN.

- Renal function. During Study 0105E2, one patient (2/06) had a single serum creatinine (141μmol/L) above the ULN on day 1005. The change in creatinine clearance over time and by dose of Exjade is shown in the following figure.

Post-text Figure 10.3-14
Boxplot of change in creatinine clearance (Cockcroft) during study by treatment group
Safety population
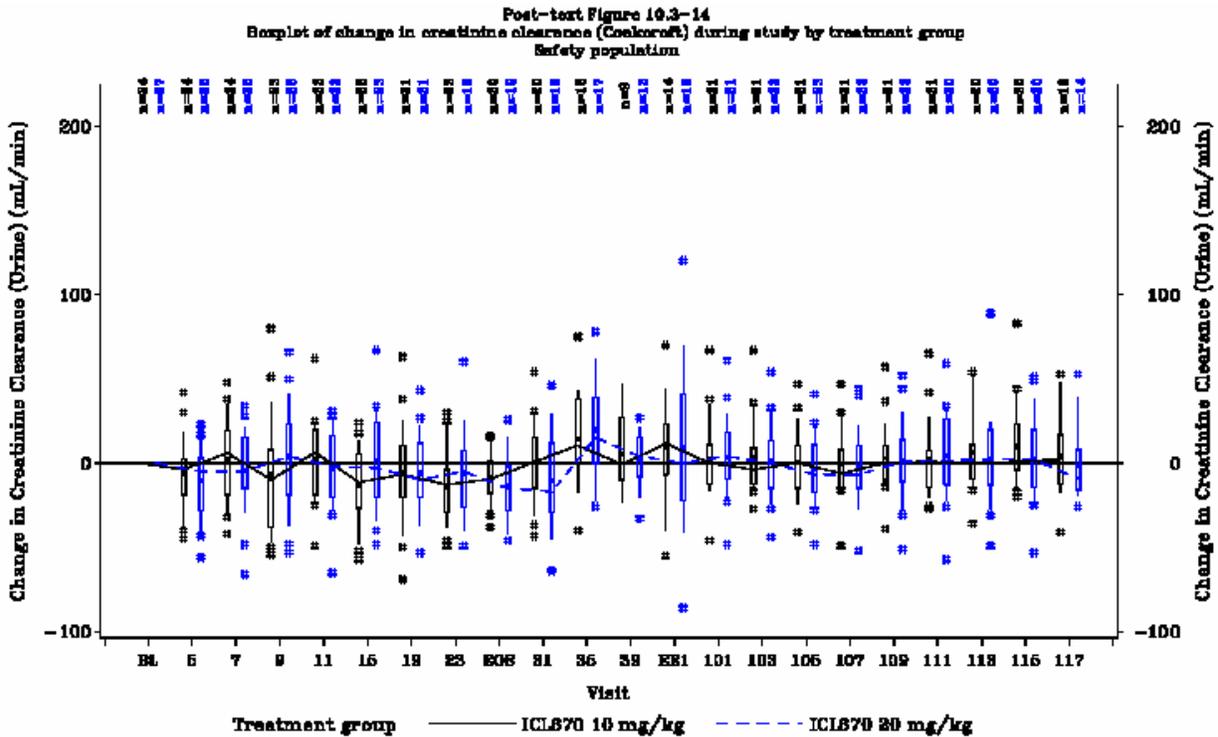
Source: Sponsor submission page 619.

About half of the patients had an elevated NAG (as a marker of renal tubular function) at baseline and almost all patients at both dose levels had an elevated NAG sometime during the study. There was no progressive increase in NAG during the study.

About one-third of patients had an elevated urinary protein/creatinine ratio at baseline. Almost all patients had an increase in this ratio sometime during the course of the trial but this did not seem to be progressive and did not appear to be dose related as shown in the following 2 figures.

Post-text Table 10.3-3 (Page 2 of 3)
Urinary parameters shift table (low/normal/high) by treatment
Safety population
Urinary parameter: Protein(Urine)/Creatinine ratio

		Baseline		Extreme lab value					
				Low		Normal		High	
Treatment		n	(%)	n	(%)	n	(%)	n	(%)
ICL670 10mg/kg (N=24)	Low	0		0		0		0	
	Normal	16	(66.7)	0		2	(8.3)	14	(58.3)
	High	8	(33.3)	0		0		8	(33.3)
	Total	24	(100)	0		2	(8.3)	22	(91.7)
ICL670 20mg/kg (N=27)	Low	0		0		0		0	
	Normal	19	(70.4)	0		2	(7.4)	17	(63.0)
	High	8	(29.6)	0		0		8	(29.6)
	Total	27	(100)	0		2	(7.4)	25	(92.6)
All treatments (N=51)	Low	0		0		0		0	
	Normal	35	(68.6)	0		4	(7.8)	31	(60.8)
	High	16	(31.4)	0		0		16	(31.4)
	Total	51	(100)	0		4	(7.8)	47	(92.2)

Source: Sponsor submission page 782.

Post-text Figure 10.3-19
Boxplot of change in urinary total protein/CREA ratio during study by treatment group
Safety population
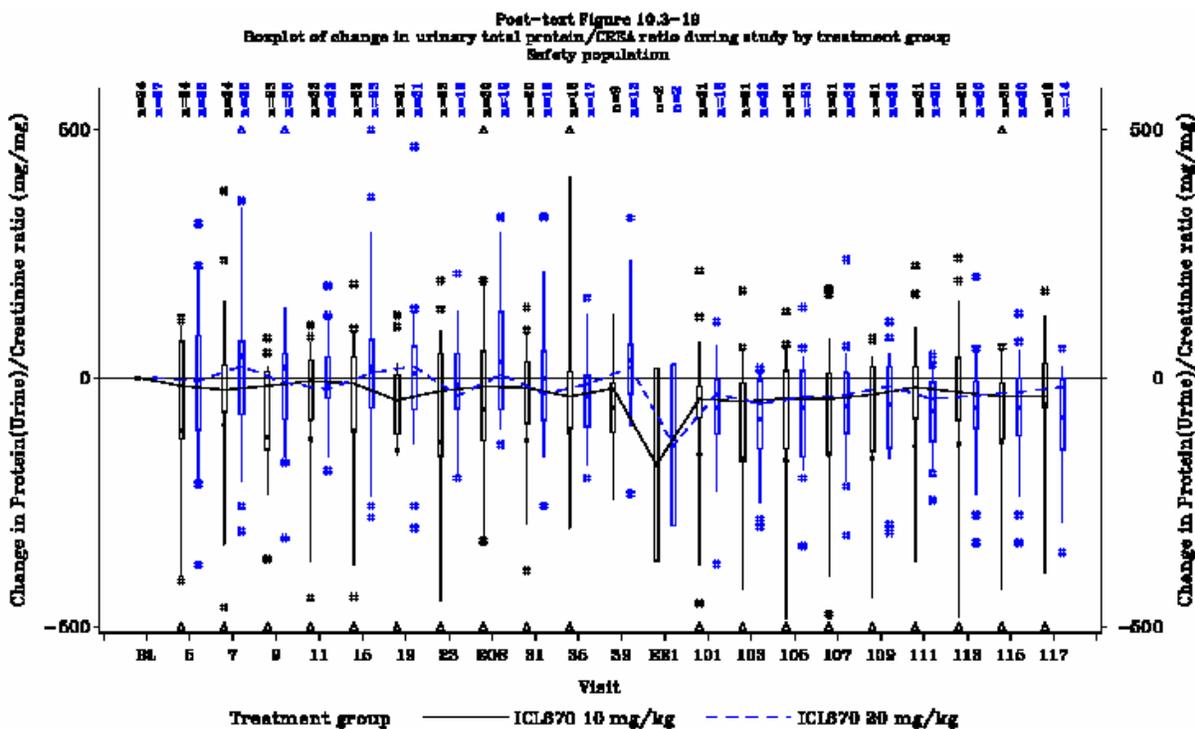
Source: Sponsor submission page 624.

- Trace elements. Low levels of serum copper were present in 24% of patients at baseline and were detected in 76% of patients at some time during the trial. These changes were not progressive. Low levels of serum zinc were present in 4% of patients at baseline and

were detected in 32% of patients at some time during the trial. These changes were not progressive.

- ECGs. There were ECG changes that occurred during Study 0105E2.
- Ophthalmologic evaluations. One patient (4/15) who had been receiving Exjade at a dose of 40 mg/kg/d for 4 months developed severe retinal degeneration of the left eye. The patient had stopped Exjade 2 days prior to the event because of lack of efficacy.
- Audiometric evaluations. No patients developed hearing loss during Study 0105E2.
- Liver echography. No patients developed echographic abnormalities during Study 0105E2.

Reviewer's Comments. The sponsor has provided an interim analysis of Study 0105E2, which extended the use of Exjade for up to 3 years in patients with β-thalassemia who had participated in earlier trials with Exjade. Although the number of patients (43) in the study is small, the data are useful as a preliminary evaluation of the safety of the long term use of Exjade. This is important because the drug is likely to be used for an indefinite period of time in most patients treated.

Although patients were initially assigned to Exjade at either a dose of 10 or 20 mg/kg/d, most of the patients in the 10 mg group actually received higher doses because of lack of efficacy during the trial. This demonstrates that the dose of 10 mg/kg/d is inadequate for the long term management of iron overload in chronically transfused patients.

The determination of efficacy was not the primary endpoint of this trial and its evaluation by SQUID measurement of LIC makes its interpretation difficult. The LIC was stable over the period of the trial and iron balance studies showed a ratio of intake to excretion of 1:1. However, since both of these evaluations were based on the SQUID results, their validity is uncertain. It is of note that serum ferritins continued to rise over the time of the trial suggesting that the correlation between LIC and serum ferritin is not direct.

The findings regarding safety are little different from those observed in the previously reviewed studies. Gastrointestinal complaints and skin rash, probably dose related, occurred but appeared manageable. There were no deaths or serious AEs believed related to the drug. Drug interruption was occasioned by a rise in transaminases in one patient and for renal colic in another. Transient increases in AST/ALT were common, but for most patients, their relation to Exjade was uncertain. The changes in renal function noted in previous studies did not appear to progress over the time of the trial. The remaining evaluations did not demonstrate progressive abnormalities, and there was a single case of retinal damage described.

Study 0109
Reviewed Primarily for Safety Data and Analysis

Study 0109 is an ongoing, randomized, multicenter, open label, phase II study designed to evaluate the safety, tolerability, pharmacokinetics and effects on LIC of repeated doses of Exjade compared to deferoxamine in adult and children sickle cell disease patients with transfusional hemosiderosis. The data provided by the sponsor covers the period from May 27, 2003 through the cut-off date of January 14, 2005.

Design

One hundred and seventy patients were to be randomized at a 2:1 Exjade/DFO ratio stratified into 3 age groups: children aged 2 to less than 12; adolescents aged 12 to less than 16; and, adults aged 16 and greater. Oral doses of Exjade from 5-40 mg/kg/d and parenteral doses of DFO from 20-60 mg/kg/d were determined by LIC measured by SQUID. The treatment period was one year. The study design is shown in the following table.

Table 3-1   Study design

← Run-in period ⟶		← —	Treatment and observation period				⟶
Prior to Amendment 3							
Screening	Washout						EOS*
−28 to −6 days	−5 to -1	Day 1	Week 2 & 4	Week 6 & 8	Week 10 & 12	Weeks 14 to 50	Week 52
Visit 1	Visit 2	V3	V4-V5	V6-V7	V8-V9	Visits 10 to 28	Visit 29
After Amendment 3							
−28 to −6 days	−5 to -1	Day 1	Week 2 & 4	Week 6 & 8	Week 10 & 12	Weeks 16 to 48	Week 52
Visit 1	Visit 2	V3	V4-V5	V6-V7	V8-V9	Visits 10 to 18	Visit 19

* EOS = End of study; Visit 29 (19) was numbered visit 777 (EOS) in the clinical database

Source: Sponsor's submission page 19

The visit schedule is shown in the following table.

Table 3-2 Visit schedule and evaluations since Amendment 3

	Run-in −28 to −6	Run-in −5 to −1	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	EOS 52
VISIT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
CRF Visit	1	2	3	4	5	6	7	8	9	11	13	15	17	19	21	23	25	27	29
Informed consent	x																		
Incl./excl. criteria	x																		
Randomization			x																
Physical exam.	x				x				x			x			x				x
Medical history/ current conditions	x																		
Liver function and tranfusion history	x																		
SQUID	x											x							x
MRI subgroup	x											x							x
Biopsy subgroup	x																		x
Liver echography	x											x							x
Vital signs	x			x		x		x	x	x	x	x	x	x	x	x	x	x	x
Weight/height	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x								x			x			x				x
Echocardiography	x											x							x
Holter monitoring	x								x			x			x				x
Ocular/audiometric examination	x								x			x			x				x
Urinalysis			x						x			x			x				x
Renal function	x	x		x	x		x		x	x	x	x	x	x	x	x	x	x	x
Hemoglobin	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hb Electrophoresis	x		x		x		x		x	x	x	x	x	x	x	x	x	x	x
Hematology, biochemistry, iron metabolism	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hepatitis serology	x																		
Cystatin C	x	x	AS REQUIRED																
Blood/urine for proteomics			x						x			x			x				x
Blood for pharmacogenetics		x																	
Health care resource utilization			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Global assessment	x			x					x			x							x
QoL (EQ-5D)	x								x			x							x
PK trough samples					x				x			x							x
PK profile samples												x							x

	Run-in		1	Treatment and observation — 2-weekly visits until Week 12, 4-weekly visits thereafter															EOS
Days	-28 TO -6	-5 TO -1	1																	
Weeks				2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
VISIT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
CRF Visit	1	2	3	4	5	6	7	8	9	11	13	15	17	19	21	23	25	27	29
Concomitant med.		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pediatric patients additional evaluations																			
Stature assessment	x											x							x
Growth velocity assessment												x							x
X-ray (bone age)	x																		x
Pubertal staging	x											x							x
School attendance			x		x		x			x	x	x	x	x	x	x	x	x	x
School performance	x																		x

Source: Sponsor's submission page27-28

Patients

Patients included in this study had common variants of sickle cell disease (e.g., SS, Sβ-thal, SC, etc). Inclusion criteria were:
- History of repeated blood transfusion with iron overload
- Patients already receiving chelator therapy or patients without contraindications to the use of chelator therapy
- History of regular transfusion requirement or history of receiving at least the simple transfusion of at least 20 units of packed red cells
- Serum ferritin ≥1000µg/L
- LIC ≥2 mg Fe/g dw if receiving simple transfusions during trial
- LIC ≥5 mg Fe/g dw if receiving exchange transfusions during trial
- For women capable of bearing children, adequate contraception
- Written informed consent from adults or from guardians if children

Exclusion criteria were:
- Chronic anemias other than SCD (SS, SC, SD, S HPFH and Sβ0 thal or Sβ+ thal)
- Serum creatinine above the upper limit of normal
- Significant proteinuria as indicated by a urinary protein/creatinine ratio greater than 0.5 (mg/mg) in second-void urine samples taken at both Visits 1 and 2. A third sample was to be taken from patients in whom one ratio was greater than 0.5 (mg/mg) and one was less than or equal to 0.5 (mg/mg) and patients in whom the urinary protein/creatinine ratio greater than 0.5 (mg/mg) in two of the three determinations were also to be excluded
- Serological evidence of active hepatitis B (presence of HBe Ag, HBsAg, HBcAg-IGM, in the absence of HBsAb)

- Clinical evidence of active hepatitis C (HCVAb positive and RNA positive with abnormal liver transaminase level)
- Other clinically relevant laboratory abnormalities
- Unstable concurrent medical conditions not controlled by standard therapy
- Patients with 2nd or 3rd A-V block, clinically relevant Q-T interval prolongation as well as patients requiring treatment with digoxin or similar compounds or drugs which may induce prolongation of the A-V conduction time or prolongation of the Q-T interval other than β-adrenoceptor antagonists.
- Patients with a diagnosis of clinically relevant cataract or a previous history of clinically relevant ocular toxicity related to iron chelation

Treatment

The initial ICL670 dose was dependent on the LIC determined at screening:
- Patients with a screening LIC of 2-3 mg Fe/g dw received 5 mg/kg
- Patients with a screening LIC of >3-7 mg Fe/g dw received 10 mg/kg
- Patients with a screening LIC of >7-14 mg Fe/g dw received 20 mg/kg
- Patients with a screening LIC of >14 mg Fe/g dw received 30 mg/kg

The selection of the initial DFO dose also took account of the baseline LIC:
- Patients with a screening LIC of 2-3 mg Fe/g dw received 20-30 mg/kg/day
- Patients with a screening LIC of >3-7 mg Fe/g dw received 25-35 mg/kg/day
- Patients with a screening LIC of >7-14 mg Fe/g dw received 35-50 mg/kg/day
- Patients with a screening LIC of >14 mg Fe/g dw received ≥50 mg/kg/

Patients with a baseline LIC of 2-7 mg Fe/gm dw who were already receiving DFO were allowed to continue on their previous dose.

Dose adjustments for both agents could be made on the combined evaluation of safety markers indicative of over- or under-chelation. All dose adjustments had to be approved by the sponsor after consultation with the Study Monitoring Committee.

Concomitant therapy to treat other symptoms was permitted and was recorded on the eCRF. The use of hydroxyurea during the trial was prohibited. Blood transfusions were continued as necessary.

Assessments

Efficacy
- LIC by SQUID measurement
- Iron balance
- Surrogate markers (serum ferritin, iron, transferrin, transferrin saturation)

- Substudy to evaluate the relationship of LIC as measured by SQUID, liver biopsy and MRI

Safety
- AEs and SAEs
- Vital signs and physical examinations
- ECGs, echocardiograms
- Audiometry and ophthalmological examinations
- Liver echograms
- Laboratory parameters (hematology, chemistry, urinary)
- In pediatric patients, growth and development

Protocol amendments

Four amendments were made to the protocol (February 27, 2003, June 26, 2003, November 24, 2003, December 21, 2004). None of provisions of these amendments affected fundamental aspects of the trial or the interpretations of the results. The significant aspects of the changes included:

- The level of proteinuria permitted to enroll in the trial and to cause a change in dosing of Exjade during the trial was raised.
- Incorporation of an interim analysis 6 months after completion of enrollment.
- Changes in dosing of Exjade based on changes in creatinine levels during the trial.
- Abandonment of the initial doses of Exjade at 5 and 10 mg/kg/d for all patients. All patients entering the trial were to be commenced at a dose of 20 mg/kg/d. This amendment was instituted at the same time as the database was being locked for the interim analysis and, therefore, did not affect any of the patients whose results were analyzed in this report.

Statistics

The data from all centers were pooled for statistical analysis. All data was analyzed by treatment group and for a number of subgroups. This interim report represents the safety analysis after all patients enrolled in the trial had completed 6 months on the study.

In this interim report, only the safety population, defined as all patients who received at least one dose of study medication, is analyzed.

Safety evaluation was based on the frequency of AEs and the number of laboratory values that fell outside of pre-determined ranges. Other safety data (ECGs, audiometry, ophthalmological examination, etc) were considered as appropriate. Laboratory values considered notable are shown in the following table.

Table 6-1   Definition of notable and extended ranges for selected laboratory parameters

Laboratory parameter	Criteria for notable and extended ranges
Platelet count	<100 x 10^9/L
Absolute neutrophils	<1.5 x 10^9/L
Serum creatinine	>33% increase from baseline at two consecutive post-baseline measurements (extended range: >50% increase)
Urinary protein/creatinine ratio	≥1.0 (mg/mg) in a second-void morning urine sample
SGOT/AST and SGPT/ALT	>5 x ULN (extended range: >10 x ULN)

Source: Sponsor submission page 43

Patient narratives were provided for all deaths, SAEs with a suspected relationship to study medications, and for all discontinuations of study drug due to an AE with a suspected relationship to study drug.

With a population of 90 subjects, events not seen and having an underlying event rate higher than 3.3% can be ruled out with a 95% confidence. The sample size of 170 patients was believed sufficient to allow for dropouts and maintain the required number of patients to achieve adequate evaluation of the study's endpoint.

Patients studied

The following table shows the overall disposition of patients at data cut-off. A greater percentage of patients receiving Exjade discontinued from the study because of AEs and withdrawal of consent.

Table 7-1   Patient disposition

Disposition Reason	ICL670 N=132 n (%)	DFO N=63 n (%)	All patients N=195 n (%)
Completed	13 (9.8)	5 (7.9)	18 (9.2)
Ongoing	109 (82.6)	53 (84.1)	162 (83.1)
Discontinued	10 (7.6)	5 (7.9)	15 (7.7)
Adverse events	4 (3.0)	1 (1.6)	5 (2.6)
Lost to follow-up	-	1 (1.6)	1 (0.5)
Withdrawal of consent	6 (4.5)	1 (1.6)	7 (3.6)
Unsatisfactory therapeutic effect	-	2 (3.2)	2 (1.0)

Source: Sponsor submission page 48

The demographic characteristics of the patients by treatment group are shown in the following table. The groups were well matched. About half the patients were <age 16 years.

Table 7-5   Patient demographics

Variable / Statistic	ICL670 N=132	DFO N=63	All patients N=195
Age (years)			
N	132	63	195
Mean ± SD	19.1 ± 10.7	19.4 ± 11.25	19.2 ± 10.85
Median	15	16	15
Min [-Max	3 – 54	3 - 51	3 – 54
Age group (years)			
< 6	4 (3.0%)	3 (4.8%)	7 (3.6%)
6 - < 12	30 (22.7%)	15 (23.8%)	45 (23.1%)
12 - < 16	33 (25.0%)	13 (20.6%)	46 (23.6%)
16 - < 50	63 (47.7%)	31 (49.2%)	94 (48.2%)
50 - < 65	2 (1.5%)	1 (1.6%)	3 (1.5%)
Sex			
Male	52 (39.4%)	28 (44.4%)	80 (41.0%)
Female	80 (60.6%)	35 (55.6%)	115 (59.0%)
Race			
Caucasian	8 (6.1%)	3 (4.8%)	11 (5.6%)
Black	118 (89.4%)	59 (93.7%)	177 (90.8%)
Others	6 (4.5%)	1 (1.6%)	7 (3.6%)
Height (cm)			
N	130	62	192
Mean ± SD	153.9 ± 17.84	154 ± 19.18	153.9 ± 18.23
Median	156	159.5	157
Min – Max	98 - 190	96 - 185	96 - 190
Weight (kg)			
N	130	63	193
Mean ± SD	51.6 ± 19.39	52.3 ± 20.54	51.8 ± 19.72
Median	52.6	52.6	52.6
Min – Max	16 – 105	16.5 - 125.3	16 - 125.3
Weight group (kg)			
15 - <35	31 (23.5%)	15 (23.8%)	46 (23.6%)
35 - <55	39 (29.5%)	20 (31.7%)	59 (30.3%)
55 - <75	46 (34.8%)	21 (33.3%)	67 (34.4%)
>=75	14 (10.6%)	7 (11.1%)	21 (10.8%)

Source: Sponsor submission page 51

There was a history of hepatitis B in 1.0%, hepatitis C in 7.2 % and both hepatitis B and C in 1.0% of all patients. Splenectomy ad been performed in 12.8% of patients.   Sixty one percent (61%) of patients had received DFO prior to entry into the trial.

Study medication

The average daily dose of Exjade and DFO categorized by the initially assigned dose is shown on the following table.

Table 8-2   Average daily dose of ICL670 and DFO during study – by initial dose

	Initial dose of ICL670 (N=132)			
	5 mg/kg N=4	10 mg/kg N=64	20 mg/kg N=46	30 mg/kg N=18
Initial dose of ICL670 (N=132)				
Mean ± SD	4.9 ± 0.29	11.0 ± 3.15	19.4 ± 1.97	28.9 ± 2.15
Median	5.0	10.0	20.0	30.0
Minimum-Maximum	4.4 - 5.0	4.0 - 23.9	10.0 - 20.0	23.2 - 30.0
	Initial dose of DFO (N=63)			
	<25mg/kg N=6	25-<35mg/kg N=21	35-<50mg/kg N=19	≥50mg/kg N=17
Initial dose of DFO (N=63)				
Mean ± SD	22.5±3.82	28.8±2.98	36.4±9.64	51.0±5.67
Median	21.0	29.0	35.0	50.0
Minimum-Maximum	19.6-29.5	24.4-34.1	7.0-51.3	39.7-62.0

Source: Sponsor submission page 54

Although drug interruptions were somewhat more frequent and their lengths somewhat greater in patients treated with Exjade compared to DFO, the relative dose intensity of drug administration was similar in both arms. Dose interruptions were more commonly due to AEs in patients treated with Exjade than in those treated with DFO. Dose increases for efficacy were more common in patients treated with Exjade than in those treated with DFO. The durations of exposure for Exjade and DFO were similar (mean ± SD, 28.7 ± 10.54 weeks, median, 25.6 weeks).

Efficacy

Efficacy is not the primary evaluation for this interim analysis and the study remains ongoing. However, preliminary data suggest that at week 24 there was little difference in LIC (mean ± SD, -0.5 ± 2.31 mg Fe/g dw) from baseline and that there was no difference in patients treated with Exjade compared to those treated with DFO. There were no changes in serum ferritin in either treatment group.

Safety

The safety information collected included AEs, laboratory evaluations, physical examinations, vital signs and weight. Special attention was given to renal function which was monitored by the regular measurement of creatinine and BUN in the blood, and of total protein, α-1 M, β-2 M, RBP, NAG, albumin and IgG in the urine. Creatinine clearance was also calculated at each visit where serum creatinine was measured. In addition, monitoring of auditory and visual function was carried out and serial liver echograms and ECGs were performed. In pediatric patients, stature, growth velocity, bone age, pubertal stage and school performance were determined.

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Adverse Events

AEs occurred in 90% of all patients enrolled in the study. The most common were related to the gastrointestinal tract and infections. AEs affecting the skin, GI tract, renal, urinary, hepatobiliary disorders and investigations were more common in patients receiving Exjade as compared to DFO, while injuries were more common in patients receiving DFO. The overall experience with AEs is shown in the following table.

Table 10-1   Number (%) of patients with AEs overall and by primary system organ class

Primary system organ class Preferred term	ICL670 N=132 n (%)	DFO N=63 n (%)	All patients N=195 n (%)
Any primary system organ class	119 (90.2)	56 (88.9)	175 (89.7)
Gastrointestinal disorders	68 (51.5)	23 (36.5)	91 (46.7)
Infections and infestations	62 (47.0)	28 (44.4)	90 (46.2)
Nervous system disorders	45 (34.1)	22 (34.9)	67 (34.4)
General disorders	44 (33.3)	22 (34.9)	66 (33.8)
Congenital disorders (SCD with crisis)	34 (25.8)	17 (27.0)	51 (26.2)
Musculoskeletal disorders	34 (25.8)	17 (27.0)	51 (26.2)
Respiratory disorders	33 (25.0)	13 (20.6)	46 (23.6)
Skin disorders	27 (20.5)	8 (12.7)	35 (17.9)
Eye disorders	19 (14.4)	8 (12.7)	27 (13.8)
Injury etc.	11 (8.3)	15 (23.8)	26 (13.3)
Investigations	18 (13.6)	2 (3.2)	20 (10.3)
Metabolic and nutritional disorders	9 (6.8)	2 (3.2)	11 (5.6)
Reproductive disorders	9 (6.8)	2 (3.2)	11 (5.6)
Ear and labyrinth disorders	5 (3.8)	5 (7.9)	10 (5.1)
Renal and urinary disorders	9 (6.8)	1 (1.6)	10 (5.1)
Vascular disorders	6 (4.5)	4 (6.3)	10 (5.1)
Psychiatric disorders	6 (4.5)	2 (3.2)	8 (4.1)
Blood disorders	5 (3.8)	1 (1.6)	6 (3.1)
Surgical and medical procedures	4 (3.0)	2 (3.2)	6 (3.1)
Cardiac disorders	3 (2.3)	2 (3.2)	5 (2.6)
Endocrine disorders	-	1 (1.6)	1 (0.5)
Hepatobiliary disorders	7 (5.3)	-	7 (3.6)
Neoplasms	2 (1.5)	-	2 (1.0)
Pregnancy*	2 (1.5)	1 (1.6)	3 (1.5)
Immune system disorders	2 (1.5)	-	2 (1.0)
Social circumstances	-	1 (1.6)	1 (0.5)

Source: Sponsor submission page 65

The most frequently occurring AEs are shown in the following table.

Table 10-2   Most frequently reported AEs (>5% in any treatment group)

Preferred Term	ICL670 N=132 Total n (%)	ICL670 N=132 Moderate/ severe n (%)	DFO N=63 Total n (%)	DFO N=63 Moderate/ severe n (%)	All patients N=195 Total n (%)	All patients N=195 Moderate/ severe n (%)
Headache	33 (25.0)	13 (9.8)	17 (27.0)	5 (7.9)	50 (25.6)	18 (9.2)
SCD* with crisis	33 (25.0)	29 (22.0)	17 (27.0)	15 (23.8)	50 (25.6)	44 (2.6)
Nausea	27 (20.5)	8 (6.1)	7 (11.1)	2 (3.2)	34 (17.4)	10 (5.1)
Vomiting	19 (14.4)	6 (4.5)	7 (11.1)	3 (4.8)	26 (13.3)	9 (4.6)
Abdominal pain	17 (12.9)	8 (6.1)	3 (4.8)	-	20 (10.3)	8 (4.1)
Diarrhoea	17 (12.9)	5 (3.8)	2 (3.2)	-	19 (9.7)	5 (2.6)
Abdom. pain upper	16 (12.1)	3 (2.3)	4 (6.3)	2 (3.2)	20 (10.3)	5 (2.6)
URTI**	16 (12.1)	4 (3.0)	8 (12.7)	2 (3.2)	24 (12.3)	6 (3.1)
Back pain	14 (10.6)	8 (6.1)	7 (11.1)	-	21 (10.8)	8 (4.1)
Pyrexia	14 (10.6)	6 (4.5)	4 (6.3)	1 (1.6)	18 (9.2)	7 (3.6)
Nasopharyngitis	12 (9.1)	1 (0.8)	7 (11.1)	-	19 (9.7)	1 (0.5)
Arthralgia	11 (8.3)	5 (3.8)	7 (11.1)	3 (4.8)	18 (9.2)	8(4.1)
Chest pain	11 (8.3)	4 (3.0)	5 (7.9)	3 (4.8)	16 (8.2)	7 (3.6)
Rash	11 (8.3)	1 (0.8)	1 (1.6)	0	12 (6.2)	1 (0.5)
Constipation	10 (7.6)	4 (3.0)	5 (7.9)	1 (1.6)	15 (7.7)	5 (2.6)
Cough	10 (7.6)	1 (0.8)	4 (6.3)	1 (1.6)	14 (7.2)	2 (1.0)
Pain in extremity	10 (7.6)	6 (4.5)	5 (7.9)	-	15 (7.7)	6 (3.1)
Pharyngeal pain	10 (7.6)	-	3 (4.8)	-	13 (6.7)	-
Pain	7 (5.3)	4 (3.0)	3 (4.8)	2 (3.2)	10 (5.1)	6 (3.1)
UTI***	7 (5.3)	5 (3.8)	3 (4.8)	1 (1.6)	10 (5.1)	6 (3.1)
Viral infection	3 (2.3)	1 (0.8)	4 (6.3)	1 (1.6)	7 (3.6)	2 (1.0)

Source: Post-text Table 10.1-3
* Sickle cell disease **Upper respiratory tract infection *** Urinary tract infection
  Source: Sponsor submission page 66

Gastrointestinal complaints and skin rash were more common in patients receiving Exjade. Severe GI symptoms were seen in 4.5% of patients receiving Exjade and in 3.2% of patients receiving DFO. A dose-response effect for Exjade was seen for nausea, vomiting, diarrhea and abdominal pain, with a 3-fold increase in these complaints at 30 mg/kg/d compared to lower doses of Exjade, and occurred more frequently in females. Skin rash was not dose dependent.

The number of patients who experienced AEs suspected to be related to drug was 44 (33.3%) for Exjade and 16 (25.4%) for DFO. For Exjade, these were primarily gastrointestinal and skin rash. For DFO, these were primarily reactions at the site of administration.

Hearing loss was reported in 3 (4.8%) patients receiving DFO, 2 of which were believed to be drug related. No patients receiving Exjade suffered hearing loss. One patient receiving Exjade at a dose of 20 mg/kg/d developed a cataract on day 168. In that patient, the serum ferritin was stable at about 2400 ng/mL and the LIC had decreased from 7.3 to 4.5 mg Fe/g dw.

Deaths

No deaths occurred during the study.

Serious adverse events

SAEs occurred in 34.8% and 33.3% of patients receiving Exjade and DFO, respectively. SAEs leading to drug discontinuation occurred in 4 patients receiving Exjade and 1 patient receiving DFO. Two patients receiving Exjade and one receiving DFO became pregnant. One of the pregnancies in a patient receiving Exjade led to a therapeutic abortion.

Other significant adverse events

The following table shows the number of patients in whom AEs led to dose adjustment or interruption of therapy.

Table 10-5   Numbers (%) of patients with AEs requiring dose reduction or interruption by primary system organ class and preferred term

Primary system organ class Preferred term	ICL670 N=132 n (%)	DFO N=63 n (%)	All patients N=195 n (%)
Any primary system organ class*	33 (25.0)	14 (22.2)	47 (24.1)
Cardiac disorders	1 (0.8)	-	1 (0.5)
Ventricular hypertrophy	1 (0.8)	-	1 (0.5)
Congenital disorders	10 (7.6)	5 (7.9)	15 (7.7)
Sickle cell crisis	10 (7.6)	5 (7.9)	14 (7.2)
Ear and labyrinth disorders	1 (0.8)	3 (4.8)	4 (2.1)
Deafness	-	1 (1.6)	1 (0.5)
Hypoacusis	-	1 (1.6)	1 (0.5)
Tinnitus	-	1 (1.6)	1 (0.5)
Vertigo	1 (0.8)	-	1 (0.5)
Gastrointestinal disorders	11 (8.3)	2 (3.2)	13 (6.7)
Abdominal distension	1 (0.8)	-	1 (0.5)
Abdominal pain	2 (1.5)	1 (1.6)	3 (1.5)
Diarrhoea	5 (3.8)	-	5 (2.6)
Nausea	2 (1.5)	1 (1.6)	3 (1.5)
Vomiting	4 (3.0)	1 (1.6)	5 (2.6)
General disorders	7 (5.3)	2 (3.2)	9 (4.6)
Chest discomfort	-	1 (1.6)	1 (0.5)
Chest pain	2 (1.5)	-	2 (1.0)
Infusion site oedema	-	1 (1.6)	1 (0.5)
Oedema peripheral	1 (0.8)	-	1 (0.5)
Pyrexia	4 (3.0)	-	4 (2.1)
Hepatobiliary disorders	1 (0.8)	-	1 (0.5)
Hepatic function abnormal	1 (0.8)	-	1 (0.5)
Infections and infestations	4 (3.0)	2 (3.2)	6 (3.1)
Catheter related infection	1 (0.8)	-	1 (0.5)
Cellulitis	-	1 (1.6)	1 (0.5)
URTI*	1 (0.8)	-	1 (0.5)
Urinary tract infection	1 (0.8)	-	1 (0.5)
Pneumonia	1 (0.8)	-	1 (0.5)

Viral infection	-	1 (1.6)	1 (0.5)
Injury etc.	-	2 (3.2)	2 (1.0)
Arthropod sting	-	1 (1.6)	1 (0.5)
Transfusion reaction	-	1 (1.6)	1 (0.5)
Investigations	4 (3.0)	-	4 (2.1)
ALT increased	1 (0.8)	-	1 (0.8)
Creatinine increased	3 (2.3)	-	3 (1.5)
Musculoskeletal disorders	1 (0.8)	1 (1.6)	2 (1.0)
Arthralgia	1 (0.8)	-	1 (0.5)
Pain in extremity	-	1 (1.6)	1 (0.5)
Nervous system disorders	5 (3.8)	-	5 (2.6)
Headache	4 (3.0)	-	4 (2.1)
Intraventricular hemorrhage	1 (0.8)	-	1 (0.5)
Pregnancy	1 (0.8)	-	1 (0.8)
Reproductive disorders	1 (0.8)	-	1 (0.5)
Breast swelling	1 (0.8)	-	1 (0.5)
Respiratory disorders	4 (3.0)	-	4 (2.1)
Dyspnoea	1 (0.8)	-	1 (0.5)
Pharyngolaryngeal pain	3 (2.3)	-	3 (1.5)
Skin disorders	3 (2.3)	-	3 (1.5)
Rash papular	1 (0.8)	-	1 (0.5)
Rash vesicular	1 (0.8)	-	1 (0.5)
Swelling face	1 (0.8)	-	1 (0.5)
Vascular disorders	1 (0.8)	-	1 (0.5)
Vascular occlusion	1 (0.8)	-	1 (0.5)

* Subject with multiple adverse events within a primary system organ class is
counted only once in the total row.
Source: Sponsor submission page 71

The commonest reasons for dose modification in patients receiving Exjade were gastrointestinal disorders, infections, fever, headache, skin disorders and elevations of serum creatinine and ALT. A dose response relationship with Exjade was seen only for gastrointestinal disorders (4.7%, 8.7% and 16.7% of patients affected at 10, 20 and 30 mg/kg/d doses, respectively).

AEs led to drug discontinuation in four patients (1 skin rash, 1 diarrhea, 1 pregnancy and 1 acute pancreatitis with concomitant abnormal liver function tests) receiving Exjade and one patient receiving DFO (1 pregnancy). No patients discontinued drugs because of laboratory abnormalities.

Laboratory values

- Bone marrow function. One patient receiving Exjade at a dose of 10 mg/kg/d had neutrophil counts <1500/mL on days 58, 127 and 213 but recovered spontaneously without drug modification. No patient developed thrombocytopenia.
- Hepatic function. The number of patients with raised serum transaminases is seen in the following table.

Table 10-8   Number (%) of patients with transaminases greater than 5 x ULN

Laboratory parameter	ICL670 N=132 n (%)	DFO N=63 n (%)	All patients N=195 n (%)
SGOT/AST			
No. patients with SGOT/AST >5 x ULN at ≥2 post-baseline visits	1 (0.8)	-	1 (0.5)
No. patients with SGOT/AST >5 x ULN at ≥2 consecutive post-baseline visits	1 (0.8)	-	1 (0.5)
SGPT/ALT			
No. patients with SGPT/ALT >5 x ULN at ≥2 post-baseline visits	1 (0.8)	1 (1.6)	1 (0.5)
No. patients with SGPT/ALT >5 x ULN at ≥2 consecutive post-baseline visits	5 (3.8)	-	5 (2.6)

Source: Sponsor submission page 77

All of the patients whose transaminases were raised during drug administration also had had elevations of transaminases at baseline. However, transaminases were raised more frequently in patients receiving Exjade than in patients receiving DFO. One patient had a drug interruption because of the abnormal transaminases but no patients were discontinued from Exjade because of an abnormal transaminase.

- Renal function. The number of patients who had increases in serum creatinine that qualified for the notable range definition is shown in the following table.

Table 10-9   Number (%) of patients with increases in serum creatinine

Laboratory parameter	ICL670 N=132 n (%)	DFO N=63 n (%)	All patients N=195 n (%)
Serum creatinine			
No. patients with creatinine >33% at ≥2 consecutive post-baseline visits	32 (24.2)	4 (6.3)	36 (18.5)
No. patients with creatinine increase >33% and >ULN at ≥2 consecutive post-baseline visits	1 (0.8)	2 (3.2)	3 (1.5)

Patients are counted only once in each post-baseline category
Source: Sponsor submission page 78

Of the 33 patients who had an increase of >33% in serum creatinine compared to baseline, 3 underwent dose reduction. Most often, this was because the serum creatinine had fallen spontaneously at subsequent visits before dose reduction could be implemented or because they occurred in pediatric patients in whom dose adjustment was not required unless the 33% increase also resulted in a creatinine that was above the ULN. The changes in creatinine over the course of the study are shown in the following figure.

Post-text Figure 10.3-16
Boxplot of change in creatinine during study by treatment
Safety population
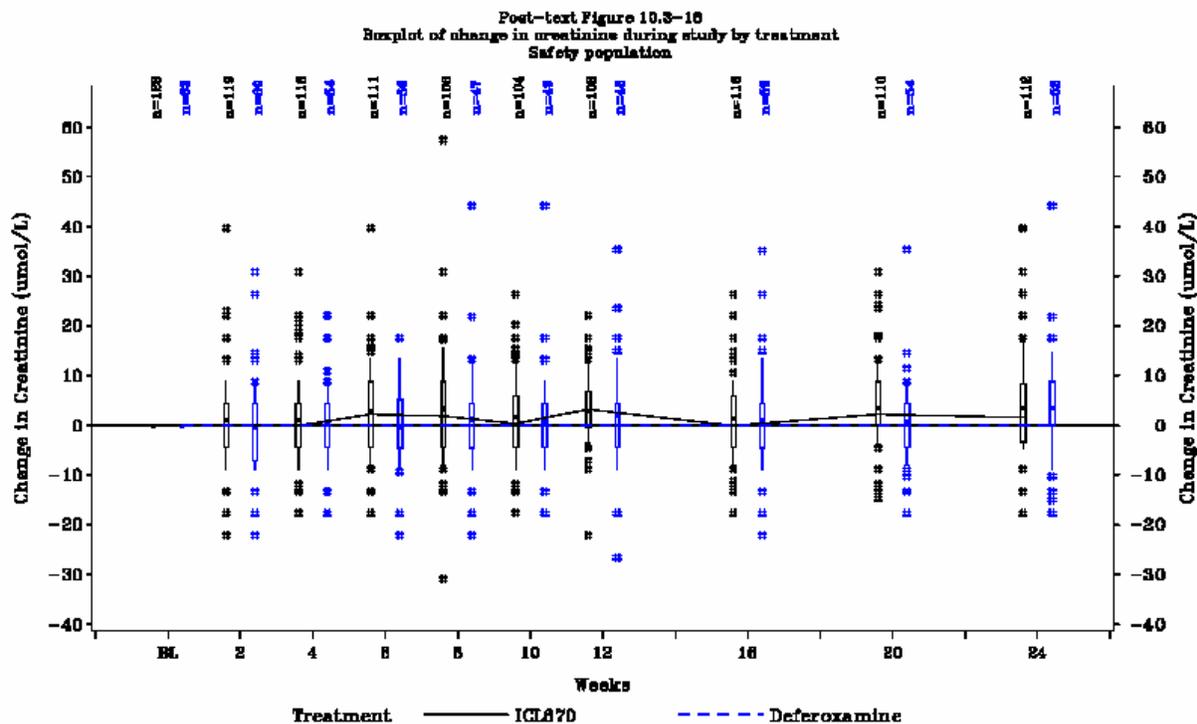
Source: Sponsor submission page 1771

About 30% of patients in both treatment arms had a urinary protein/creatinine ratio that was above the normal range at baseline. Transient increases during the study occurred with a similar frequency in both arms of the trial. No patients developed progressive proteinuria. The increases were not dose dependent. No patients had dose modifications because of the urinary findings. Increases in the urinary protein/creatinine ratio are shown in the following table.

Table 10-10   Number (%) of patients with increases in total urinary protein/creatinine ratio

Laboratory parameter	ICL670 N = 132 n (%)	DFO N = 63 n (%)	All patients N = 195 n (%)
Urinary protein/creatinine ratio (UPCR)			
No. patients with UPCR 0.2 - <0.4 mg/mg post-baseline	60 (45.5)	25 (39.7)	85 (43.6)
No. patients with UPCR 0.4 - <0.6 mg/mg post-baseline	11 (8.3)	3 (4.8)	14 (7.2)
No. patients with UPCR >=0.6 mg/mg post-baseline	14 (10.6)	6 (9.5)	20 (10.3)

Patients are counted only once in each post-baseline category

Source: Sponsor submission page 79

- Trace elements. Twenty five percent (25%) and 2% of patients had a low serum zinc and copper level at baseline, respectively. There were minor fluctuations of each of these elements during the trial in both study groups.

- Vital signs. There were no significant changes in vital signs in patients in either arm of the trial.

- ECGs. Four patients on ICL670 (1 case each of increased QT interval, AV block, sinus arrhythmia, left ventricular hypertrophy) and 3 on DFO (QT prolongation, 2 cases of left ventricular hypertrophy) developed new or worsening significant ECG abnormalities. These changes are considered to be related to the underlying disease.

- Ophthalmologic examinations. Four patients on ICL670 and 2 on DFO had new significant findings post-baseline, mainly related to blood vessel changes. No lens or retinal abnormalities were reported.

- Audiometric examinations. Two patients on ICL670 and 2 on DFO had newly reported significant findings after baseline. These episodes comprised 3 episodes of conductive deafness and one of fluid in the middle ear cavity.

- Liver echograms. No significant findings were noted.

- Anthropometric measurements and sexual development. Only preliminary data are available at 24 weeks, but there were no differences noted in these parameters between the two arms of the trial.

Reviewer's Comments. Study 0109 is a trial comparing the safety and efficacy of the use of Exjade and DFO over a one year period in a population of adult and children patients with sickle cell disease and its variants who have developed hemosiderosis because of transfusions. The information reviewed here is from an interim analysis of data after all enrolled patients had been enrolled for at least 6 months and is submitted by the sponsor for a review of the safety data in support of its application for approval of its indication. As in some of its other studies, the sponsor has relied on the use of SQUID to measure LIC. This does not affect this review other than to note that since the initial dose of Exjade and DFO were dependent on the SQUID measured LIC, the dose of study drug may have been given at less than required dose to achieve the goal of diminishing LIC.

Review of the safety data suggests that the use of Exjade in patients with sickle cell syndromes is associated with safety concerns that are similar those seen in patients with β-thalassemia. These include gastrointestinal symptoms (nausea, vomiting, diarrhea and abdominal pain), skin rash, cataract development, increases in serum transaminases, increases in serum creatinine and urinary protein, and diminution in hearing. Although dose interruptions and decreases with Exjade were more frequent than with DFO, almost all patients in the trial were able to continue on the study. Pregnancies occurred in 2 patients receiving Exjade, one of whom had a therapeutic abortion. The sponsor has not provided any information on the outcome of the second pregnancy.

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