1 SCIENTIFIC DISCUSSION

1.1 Introduction

Iron overload

Iron overload is the result of many disorders and can lead *per se* to the development of organ damage and increased mortality. In humans total body iron stores is maintained within the range of 200-1500 mg by adequate adjustment of intestinal iron absorption, since no excretory mechanisms exist [1]. In normal individuals, feedback mechanisms inhibit iron absorption as storage iron increases [1]. Each condition that induces an increased net entry of iron within the body inevitably leads to iron overload. It can be classified as primary or secondary depending whether it results from a primary defect in the regulation of iron balance or is secondary to other genetic or acquired disorders. A known example of primary iron overload is hereditary hemochromatosis (HHC), in which iron is absorbed in excess because of increased iron transfer from the enteral cells to the blood. The secondary includes iron overload either due to, or associated with, ineffective erythropoiesis, chronic liver diseases, parenteral administration or ingestion of excessive amounts of iron. Thalassemia major and sideroblastic anemia are the two best studied examples of iron overload secondary to blood transfusions and ineffective erythropoiesis. Frequent blood transfusions lead to excessive accumulation of iron with a toxic accumulation in 3 to 10 years.
The toxicity of iron results from two related events: 1) excess iron deposits in various tissues of the body, particularly in liver, heart and endocrine organs with the consequence of liver diseases, diabetes mellitus and other complications, and 2) free iron that catalyzes the formation of highly reactive hydroxyl radicals which lead to membrane damage and denaturation of proteins. Once iron exceeds a certain level, these effects lead to significant morbidity and mortality. Without specific chelation therapy to remove the iron, in 3 to 10 years almost all regularly transfused patients will have acquired a toxic accumulation of iron. The main cause of death is due to cardiac complications.

Treatment of iron overload

The aim of treatment of iron storage disease is to remove from the body the excess iron that has accumulated. In the case of patients without primary disorders of hematopoiesis (i.e. primary hemochromatosis), this is best achieved by phlebotomy, since regeneration of erythrocytes by the marrow utilizes iron, which is therefore withdrawn from various body pools. Phlebotomy is only occasionally feasible in patients who have augmented iron stores because of ineffective erythropoiesis and is generally precluded in those in whom the iron overload is the result of multiple transfusions. Such patients require treatment with an iron chelating agent to achieve safe levels of body iron. This is a slow process because only a small proportion of body iron is available for chelation at any moment. By increasing the doses of chelators in an attempt to speed up iron removal, there is a risk of increasing the toxicity of iron chelators by chelating iron, which is needed for normal tissue metabolism. Therefore, while the slow process of decreasing tissue iron to safe levels is being achieved, a second goal is to make the iron as safe as possible by binding the toxic iron pools responsible for causing tissue damage. Iron chelation therapy reduces iron-related morbidity, reduces and retards liver diseases, diabetes and other endocrine failures, normalizes growth and sexual development, prevents, and in some cases reverses, cardiac insufficiency and improves quality of life. Consequently iron chelation therapy dramatically reduces mortality.
Deferoxamine mesylate was introduced about forty years ago and remains the standard chelation therapy for the removal of excess iron. A clear and consistent evidence in the literature on the demonstrable clinical benefits of deferoxamine therapy was shown both on morbidity and mortality [2]. Due to the challenges of administering deferoxamine by slow subcutaneous or intravenous infusion over 8 to 12 hours, five to seven nights per week, compliance is often poor, leading to less than optimal efficacy of this therapy in preventing complications.
Due the limited data available on its efficacy and its safety profile, the oral iron chelator deferiprone is approved in Europe only for the treatment of iron-overloaded thalassemic patients who cannot adequately be treated with deferoxamine, or for whom deferoxamine is contraindicated.

About the product

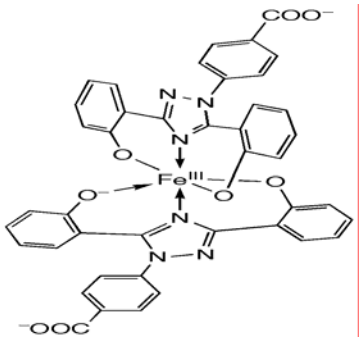
Exjade developed by Novartis Europharm contains the active substance deferasirox, an orally active iron chelator for the treatment of chronic iron overload due to blood transfusions.
Acronyms used during the development were ICL670, ICL670-NXA, ICL670-NXB, CGP72670 and the international non-proprietary name (INN) and the approved name in USA is Deferasirox.
With the present application, the applicant sought a marketing authorization for the "*treatment of chronic iron overload due to blood transfusion (transfusional haemosiderosis) in adult and paediatric patients (aged 2 years and over)*". The dose proposed by the applicant was an initial dose of 20mg/kg body weight for patients receiving blood transfusions (about 2/4 units/month of packed red blood cells) with changes for less or more transfusions and a maintenance dose dependent on the serum ferritin with a maximum dose of 30mg/kg deferasirox.

1.2 Quality aspects

Introduction

Exjade is presented as dispersible tablets containing 125 mg, 250 mg and 500 mg of deferasirox, as active substance. The three strengths can be differentiated by the size of the tablets and their imprints.
The other ingredients include lactose monohydrate, crospovidone type A, microcrystalline cellulose, povidone, sodium lauryl sulphate, silica colloidal anhydrous and magnesium stearate. The tablets are packed in PVC/PE/PVDC/Aluminium blisters. The tablets are to be dispersed in water, orange juice or apple juice prior to oral administration.

Active Substance
Deferasirox belongs to a novel class of tridentate iron chelators, the N-substituted bis-hydroxyphenyl-triazole.



Two molecules of deferasirox are needed to form a soluble complex with one Fe^{3+} ion. Satisfactory information has been provided on the structure/the stability of the complex at physiological pH and on the influence of other metal ions (see non-clinical and clinical sections).
The active is a white to slightly yellow and not hygroscopic powder. It has a good permeability and it is practically insoluble in water and in acid medium, the solubility increasing with pH. Therefore, the particle size is likely to be important to the rate and possibly to the extent of absorption.
Deferasirox is not chiral. Two polymorphic forms have been identified. The active is the thermodynamically stable polymorph A. The other polymorph cannot be formed under recommended storage conditions for the active substance/finished product and under conditions used to manufacture the finished product.

- Manufacture

Deferasirox is produced by two different manufacturers from commercially available starting materials in a two-step synthesis followed by purification by crystallisation and micronisation. Satisfactory specifications and associated methods have been provided for the starting materials, key intermediates, reagents and solvents.
The same process has been used from development to commercial production. However, the purification step was slightly modified (change in crystallisation solvent) resulting in three process versions A, B and C. Comparative batch analysis data provided show no major differences, especially in term of impurity profiles.
Deferasirox contains very low levels of process-related impurities and detectable amounts were only found in early development batches. The only impurity relevant at low levels is 4-hydrazinobenzoic

acid (starting material), which has a genotoxic and carcinogenic potential. An acceptable impurity limit based on batch analysis data provided and justified from a toxicological point of view (see non-clinical assessment) has been included in deferasirox specification.
Catalysts are not used in the synthesis. However the active being a complexing agent for several metal ions, their level in the active has been controlled and results showed that no heavy metals are extracted from the production equipment.
Deferasirox residual solvents limits are in accordance with the ICH guideline.

- Specification

The active substance specification includes tests for appearance, clarity and colour of solution (PhEur), identity (IR and XRPD), assay (HPLC), impurity content (HPLC), residual solvents (GC), particle size, water content, residue on ignition (PhEur), heavy metals (PhEur) and microbial limits (PhEur). Impurity limits in the specification are justified by toxicology studies. Batch analysis data provided for batches manufactured at both sites confirm satisfactory compliance and uniformity with the proposed specification.

- Stability

Stability data have been provided for three batches. Under long-term conditions (25°C/60% RH – intended packaging) and under accelerated conditions (40°C/75% RH – intended packaging) respectively up to 2-year data and 6-month data have been provided.
The parameters tested included appearance, clarity and colour of solution, identity (IR and XRPD), assay (HPLC), impurities and water content.
Deferasirox appears as a very stable drug substance in the solid state as degradation products were not observed under ICH conditions and they formed only under stress conditions.
The data provided support the propose retest period when deferasirox is stored in sealed double polyethylene bags placed in sealed drums.

Medicinal Product

- Pharmaceutical Development

The objective was to develop an oral formulation, which would ease administration to all age patients. In order to avoid a large tablet for swallowing due to a relatively high amount of drug substance per dosage unit, dispersible tablets were developed.
The different strengths have the same qualitative and proportional quantitative composition.
The physical characteristics of the drug substance resulting from micronisation (electrostatic tendency, poor flow and compression properties) have been compensated by a suitable choice of excipients and manufacturing process (aqueous granulation).
The excipients have been selected based on their compatibility with deferasirox by means of binary mixture tests and they are commonly used for tablet formulations. Regarding the TSE risk, the magnesium stearate is of vegetable origin and the lactose derived from milk of bovine origin has been considered in compliance with the current TSE requirements.
Satisfactory specifications have been set up for PVC/PE/PVDC/Aluminium blister.
Physico-chemical stability up to 24h has been confirmed when tablets are dispersed in water, apple and orange juice (see section 4.2 of the SPC). Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.
The commercial formulation of the finished product has been used in all pivotal studies.

- Manufacture of the Product

The manufacturing process consists of the standard following operations: blending, aqueous granulation, drying, screening, blending and compression.
The quantity of magnesium stearate in the formulation had to be reduced during development in order to meet PhEur disintegration time requirements. Validation data on 3 consecutive full-scale batches per strength have been provided and confirm the robustness and reproducibility of the manufacturing process.

- Product Specification

The finished product specification includes tests for appearance, identity (UV and HPLC), assay (HPLC), degradation products (HPLC), uniformity of dosage units (PhEur), mean mass, fineness of dispersion (PhEur), dissolution , disintegration and microbial limits (PhEur).

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for its intended purpose.
Batch analysis data provided for the validation batches confirm satisfactory compliance and uniformity with the proposed specification.

- Stability of the Product

Stability data have been provided for production-scale batches manufactured using the commercial manufacturing process according to a bracketing program as the three strengths have comparable compositions *pro rata*. The parameters tested included: appearance, dissolution, fineness of dispersion, disintegration time, assay, degradation products and microbial quality.
Under long-term conditions (25°C/60% RH - commercial packaging) and under accelerated conditions (40°C/75% RH - commercial packaging) respectively 24-month and 6-month data are available. The observed changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SPC
The photostability study performed shows that the finished product is not light sensitive.
The data provided support the proposed shelf life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The active substance is well characterised and documented. The pharmaceutical form selected is adequate taking into account the properties and the stability of the drug substance. The excipients are commonly used for this kind of formulation and the packaging material is well documented. The manufacturing process enhances to obtain reproducible finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life. At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Risk-benefit balance of the product. The applicant committed to resolve it as Follow Up Measure after the opinion, within an agreed timeframe.

1.3 Non-clinical aspects

Introduction

While most of the pharmacology studies predate the ICH guidelines S7A [10] and S7B [4], all toxicological pivotal studies were conducted in accordance to Good Laboratory Practices (GLPs). The non-clinical studies were conducted in mouse, rat, marmoset, rabbit and dog and were performed using the oral route, as recommended for clinical use. The analytical methods (HPLC-UV or HPLC-MS-MS) were validated and the limit of quantification was ≤ 0.670 µmol/l for deferasirox and ≤0.314 µmol/l for Fe-[deferasirox]$_2$, the biological matrix used was plasma since a major part of deferasirox (68-95%) and Fe-[deferasirox]$_2$ (≤91%) was confined to the plasma compartment.

Pharmacology

The objectives of the pharmacology program were to establish the affinity and selectivity of deferasirox for iron.

- Primary pharmacodynamics

In vitro studies

Deferasirox is a tridentate chelator, hence two molecules are needed to fully coordinate one atom of (hexa-coordinate) Fe(III). The formation of Fe(III) complexes with deferasirox was studied in H_2O/DMSO by potentiometric and spectrophotometric methods. The major species identified under physiologic conditions (pH 7.4) and clinically attainable deferasirox concentrations of 10 µmol/l, and an assumed iron concentration of 1 µmol/l was Fe(deferasirox)$_2^{3-}$. In these conditions, the affinity of deferasirox for Fe(III) was less than deferoxamine but higher than deferiprone. Deferasirox had a low affinity for Fe(II). In a biological system at physiological conditions, if there were Fe(II) in solution, deferasirox would weakly bind it and convert it to a stable [FeIII(L)$_2$] complex.
Deferasirox was highly selective for Fe(III). The ranking according to affinities was typical for selective iron chelators: Fe(III)>Al(III)>>Cu(II)>>Zn(II)>Fe(II)>>Mg(II)>Ca(II).
The ability of deferasirox to remove iron from cells was studied in cultured iron-loaded rat heart cells. In direct comparison with DFO, up to a concentration of clinically relevant 80 µmol/l, the efficiency for the removal of radioactive iron was similar with the two compounds. At 160 and 320 µmol/l,

deferoxamine (DFO) was more efficient by removing approximately 73% and 82% compared to deferasirox, which removed approximately 46% and 56% of the radioactivity from cells.

In vivo studies

In rats, oral administration of 25, 50 and 100 mg/kg deferasirox in bile duct-cannulated showed promotion of iron excretion within the first three hours (h) post-dose with a dose dependent maximum mean iron excretion occurring between 4 and 12 h. A protracted action of deferasirox was observed for 30 hours after the administration of a dose of 25 mg/kg, and for 33 hours after doses of 50 mg/kg and 100 mg/kg of deferasirox.
The amount of excreted iron as percentage of the theoretical (stoichiometric) iron binding capacity of the 25, 50 and 100 mg/kg doses were 18.3±2%, 16.7±6% and 14.6±4%, respectively. The decrease of efficiency with higher doses was linear.
To define the sources of iron chelated *in vivo* by orally administered deferasirox, a comparative study with intraperitoneally administered DFO and orally administered deferasirox was performed in rats using radio-iron probes selective for hepatocellular and reticulo-endothelial iron stores. Deferasirox was more effective than DFO, particularly with mobilizing iron from the hepatocellular pool. With deferasirox, all iron was cleared by the liver and excreted through the bile.
The potential dissociation of iron chelator complexes prior to excretion was studied in an experimental rat model. Following i.v. (intravenous) administration into rats of ^{59}Fe-complexes of deferasirox pre-formed *in vitro*, 40% of the ^{59}Fe given was excreted within 48 hours, mostly in feces.
The ability of deferasirox to reduce body iron burden was further evaluated in iron-overloaded rats. Treatment with deferasirox at 59.7 mg/kg p.o. (80 µmole Iron Binding Equivalent (IBE)/kg) for 12 weeks was compared with DFO (98.4 mg/kg) and deferiprone (62.5 mg/kg), both at 150 µmole IBE/kg. in terms of iron binding equivalents, deferasirox (80 µmol/kg IBE) was similarly effective as an approximately two-fold higher dose of DFO (150 µmol/kg IBE).

Marmosets, which differ from rodents in their iron metabolism (uptake, pools, fluxes and excretion), were iron-overloaded by 3 intraperitoneal (i.p.) injections of iron-dextran, separated by a 14 day interval after each injection (200 mg iron/kg twice, 100 mg/kg at the third injection). The equilibration period after loading was at least 8 weeks. Seven days before and during the experiment with a chelator, marmosets were maintained on a low-iron diet to reduce fecal iron background.
After oral administration of 14, 28, 56 and 112 mg/kg of deferasirox, excretion of iron was primarily through the feces. High amounts of iron were still excreted in the 24 to 48 hour period, particularly at the two higher dosages. The "effective oral dose" (ED) is defined as the dose which mobilizes 500 µg of iron per kg body weight, the targeted, daily mobilization rate for iron chelation therapy in highly transfused β-thalassemia patients. The ED in marmosets was estimated to be about 22 mg/kg. The calculated in vivo efficiency of iron chelation for deferasirox, (i.e. the amount of excreted iron as percentage of the theoretical, stoichiometric iron binding capacity of the dose), was 29% at the dose of 56 mg/kg (150 µmol IBE/kg).

Treatment male and female marmosets with deferasirox at once daily oral doses of 20, 40 or 80 mg/kg decreased liver iron content by an average of 70%, 87% and 95%, respectively, in males. In females, liver iron reductions of 67% and 82% were observed in the 40 and 80 mg/kg dose groups, respectively. Females receiving 20 mg/kg had no reduction in liver iron. No decreases of liver copper or zinc were observed in animals. Kidney iron concentrations were reduced in both male and female treatment groups, albeit to a lesser extent than in the liver. A reduction of approximately 30% in females and 40% in males was noted only in the 80 mg/kg dose group. Treatment with deferasirox for 39 weeks had very marginal effects on kidney copper and zinc.
The effects of deferasirox on heart and liver iron have been studied in iron loaded gerbil, best available animal model [5], and were compared to the effects of deferiprone. At 5-fold the clinical dose (deferasirox 100 mg/kg once a day; deferiprone 375 mg/kg/day in three divided doses) deferasirox and deferiprone were equally effective in removing heart iron. Deferasirox removed double the amount of liver iron as compared to deferiprone [6]. This data were further supported by studies performed in cultured cardiac cells that showed removal of iron *in vitro* [6-9].

- Secondary pharmacodynamics

No specific study has been conducted to evaluate secondary pharmacodynamics.

- Safety pharmacology programme

Following evaluation of possible effects of deferasirox on the central nervous system *in vivo*, only a transient marginal to weak ataxia (0.5 to 6 hours following 100, 300 or 1000 mg/kg) and a marginal head tremor were observed in the mouse. Single intraduodenal doses of 100, 300 and 1000 mg/kg deferasirox in the anaesthetized rat had no effect on respiratory rate, tidal and minute volumes. In the conscious rat there were no effects on renal excretion of sodium, chloride and potassium, or urine volume over 6 hours after oral dosing up to 1000 mg/kg. The design of the studies investigating the cardiovascular effects of deferasirox are summarised in the table below:

Table 1: Summary of cardiovascular safety studies

Study type	Route	Major Findings
Isolated guinea pig atria (GLP)	*in vitro*	↑ force of contraction ≥ 100 µmol/l ↓ heart contractions at 300 µmol/l
Isolated sheep Purkinje fiber assay (GLP)	*in vitro*	↓ APD and maximum rate of depolarization at > 21 µM and reduced upstroke amplitude > 64 µM.
Isolated rabbit heart (non GLP)	*in vitro*	small ↑ APD, squaring of action potential at 30 µmol/l
HERG (non GLP)	*in vitro*	no effects up to max concentration of 250 µmol/l
Anesthetized rat study (GLP)	*in vivo* intraduodenal	No effects at single doses up to 1000 mg/kg
Dog telemetry study (GLP)	*in vivo* oral (gavage)	↑ heart rate at 300 mg/kg with no change in QTc

- Pharmacodynamic drug interactions

No specific pharmacodynamic drug interactions study has been conducted.

Pharmacokinetics

The plasma concentrations of total deferasirox (corresponding to the sum of free deferasirox and iron-bound deferasirox), and iron complex Fe-[deferasirox]^2 were measured by HPLC-UV or HPLC-MS-MS analytical methods. Metabolites were characterized by mass spectrometry (LC-MS and LC-MS-MS), LC-^{1}H-NMR or by co-elution with non-radiolabeled reference compounds.

- Absorption - Bioavailability

Single oral doses of deferasirox were rapidly and highly absorbed in all animals. High oral doses as used in toxicity studies in mice (300 mg/kg) or rats (100 mg/kg) led to a delayed absorption and distribution displaying Cmax values of deferasirox that were reached at up to 8 hours post-dose. Table 2 summarises the key PK parameters in rats, marmosets and humans (studies 0115 and 2101).

Table 2: Pharmacokinetic parameters of total deferasirox

	Human	**Marmoset**	**Rat** [b, f]
Single oral dose (mg/kg)	**~ 20** [a]	**25**	**10**
AUC (µmol·h/l)/(mg/kg) [c]	35.5	8.72 [h]	2.71 [h]
C_{max} (µmol/l)/(mg/kg) [c]	1.53	1.85	0.76
t_{max} (h)	4-6	0.5	0.5
Bioavailability (% of dose)	73 ± 20 [d]	88 [b]	32 [b]
deferasirox (% of 14C-AUC)	91	25	67
$t_{½\alpha}$ of deferasirox (h)	11 ± 5	0.7 ($t_{½z}$ 35) [e, f]	0.8
	Human [d]	**Marmoset**	**Rat** [b, f]
Intravenous dose (mg/kg)	**1.65**	**10**	**10**
AUC (µmol·h /l)/(mg/kg) [c]	63.4	9.96 [b, k]	8.45 [j]
V_{ss} (l/kg)	0.18	8.1 [e, f]	0.64

Single oral dose (mg/kg)	Human ~ 20 [a]	Marmoset 25	Rat [b, f] 10
Clearance CL (ml/min/kg)	0.74	3.2 [f]	5.6
Hepatic extraction ratio E_H (%) [g]	8	12	23
$t_{½\alpha}$ of deferasirox (h)	4.1 ± 1.5	0.5 ($t_{½z}$ 51) [e, f]	0.7

[a] an oral dose of 1000 mg ^{14}C-labeled deferasirox was given as a drink suspension in water to thalassemia patients at steady-state (daily 1000 mg non-radiolabeled deferasirox); [b] calculations based on: deferasirox $_{total}$ = deferasirox $_{free}$ + Fe-[deferasirox]$_2$; [c] multiply µmol/L or µmol·h/l with 373.37 to obtain µg/l or µg·h/l, respectively; [d] healthy volunteers, 130 mg, 90 min i.v. infusion *versus* 375 mg, p.o.; [e] value very high, probably due to substantial contribution by enterohepatic recirculation evident in the terminal elimination phase after 8 h; [f] parameter calculated by the author of this overview; [g] E_H= CL/hepatic plasma flow, where hepatic plasma flow = hepatic blood flow · hematocrit (HCT ~ 0.45); [h] $AUC_{0\text{-}72h}$; [i] $AUC_{0\text{-}24h}$; [j] $AUC_{0.083\text{-}24h}$; [k] $AUC_{0.083\text{-}72h}$.

Analysis of the binding kinetics of deferasirox in *in vitro* mechanistic transport studies in Caco-2 cell monolayers, showed a K_m value of about 14 µmol/l and a maximal transporter-mediated flux (J_{max}) of 94 nmol/min·cm^2. Inhibition studies with efflux inhibitors (verapamil, cyclosporin A, probenecid, imatinib) suggested deferasirox to be most likely a substrate for MRP2 or MXR (also called BCRP, breast cancer-resistant protein).
Transporter system(s) involved in carrier-mediated drug uptake of ICL670 were tested, using cRNA-injected Xenopus laevis oocytes. The human organic anion transporting polypeptides OATP1A2 (gene: SLC21A3, also called hOATP1), OATP1B1 (gene: SLC21A6, also called hOATP2), OATP1B3 (gene: SLC21A8, also called hOATP8) or the human organic cation transporter hOCT1 (gene: SLC22A2) were tested at deferasirox concentrations from 1 to 100 µmol/l. cRNA-injected transportocytes and water-injected control oocytes displayed a similar concentration-dependent linear increase of deferasirox uptake between 1 and 100 µmol/l.

The data obtained in purified membrane vesicles from insect or mammalian cells expressing high levels of human ABC transporter proteins indicated an interaction of deferasirox with MXR (BCRP) and MRP2 efflux pumps suggesting deferasirox to be actively transported by these transporter proteins, although with distinctly higher affinity for MXR (~ 8-fold) than for MRP2. In contrast, no transport by MDR1 (P-gp) efflux protein was observed. Experiments revealed deferasirox to inhibit endogeneous substrates of these transporters: [^{3}H]LTC_4 (leukotriene C_4) and [^{3}H]E_1S (estradiol 17β-D-glucuronide) transport mediated by MRP2 (IC_{50} ≅ 50 µmol/L) and MXR (IC_{50} ≅ 1 µmol/L), respectively.

Bioavailability of deferasirox was tested in male Beagle dogs, comparing three oral formulations (A and B: dispersible tablet, C: sachet) *versus* an intravenous reference formulation (D: PEG 400 solution). In an additional PK study, the clinical service form [quadri-divisible dispersible tablet of total mass 1 g containing 250 mg of deferasirox (25% loading)] was compared with the market formulation [dispersible tablet of total mass 850 mg containing 250 mg of deferasirox (30% loading)]. The oral bioavailability of 10 mg/kg ICL670 was approximately 100% of dose.

The effect of food on the PK of 125 mg dosage strength (12 mg/kg) of deferasirox was studied in dogs. One group was pre-treated with an oil in-water emulsion (goat milk), another group was pretreated with oil (corn oil glycerides). The reference group remained fasted.

The enterohepatic recirculation of deferasirox and its metabolites was investigated in male bile duct-cannulated rats. A first group received an IV dose of 10 mg/kg ^{14}C-labeled deferasirox. Within 6 and 24 hours post-dose, 61.5% and 78.2%, respectively, of the radioactive dose was collected in bile. A second group received the bile from donor rats from the first group, as an infusion into the duodenum. The total mean recovery of [^{14}C]deferasirox -related radioactivity in bile, urine and carcass was 39% of the infused radioactivity.

- Distribution

In vitro plasma protein binding studies were performed in plasma of mice, rats, rabbits, dogs, marmosets and humans. [^{14}C]deferasirox as well as its iron complex Fe-[deferasirox]^2 were bound from 98.2 to 99.6% to plasma proteins. The species ranking of unbound fraction was similar for deferasirox and its iron complex: human (0.3-0,5%) ~ rat ~ dog < rabbit ~ mouse ~ marmoset (0.9-

1.8%). *In vitro* plasma protein binding of deferasirox to human serum albumin (40 g/l) was 98%-99% for deferasirox concentrations of 10 and 105 µg/ml (27-281 µmol/l). Binding to α_1-acid glycoprotein was moderate and decreased from 85% to 8% with deferasirox concentrations from 0.5 to 105 µg/ml (1.34-281 µmol/l), respectively. Binding to γ-globulins was negligible. Deferasirox was mainly confined to the plasma compartment of all species including human (blood/plasma distribution value for was 70% to 85% in mice and 78% to 93% in rabbits).

After an oral dose of 100 mg/kg [^{14}C]deferasirox to male albino rats, maximal concentrations of radioactivity in the tissues were reached at 4 hours. Highest radioactivity concentrations were observed in the liver (765 nmol/g) and kidney cortex (631 nmol/g). Kidney medulla 245 nmol/g was comparable to blood (213 nmol/g). The volume of distribution was 0.18 to 0.98 l/kg in mice, rats, dogs and humans, 8.1 l/kg in marmosets. Clearance in plasma was 2.9 to 8.0 ml/min/kg in the animals, and 0.74 ml/min/kg in humans. The volume of distribution of Fe-[deferasirox]$_2$ was 0.086 l/kg in rats. Its clearance in plasma was 3.9 ml/min/kg.

Pregnant rats were administered a single oral dose of 30 mg/kg of [^{14}C] deferasirox at days 13 and at day 17 of gestation. At day 13 between 1 and 24 hours post-dose, the mean ^{14}C concentrations in the fetuses were 12- to 26-fold, and at day 17 at 2 hours post-dose about 6-fold lower than in maternal blood and lower than in maternal tissues, respectively. Pregnant rabbits were given a single oral dose of 40 mg/kg [^{14}C]deferasirox at day 17 of gestation. At 24 hours post-dose the ^{14}C concentrations in the fetuses represented 1-2% of the concentrations found in the corresponding plasma of the dam.

Following a single oral dose of 10 mg/kg ^{14}C-labeled ICL670 to female lactating rats, C_{max} of radioactivity in plasma and milk was reached at 0.5 hours. The milk/plasma ratio of ^{14}C radioactivity at 4 to 8 hours post-dose was 17 to 24. Within 24 hours post-dose, about 3.3% of the administered radioactivity in the milk was recovered as unchanged drug.

- Metabolism

In vitro metabolism

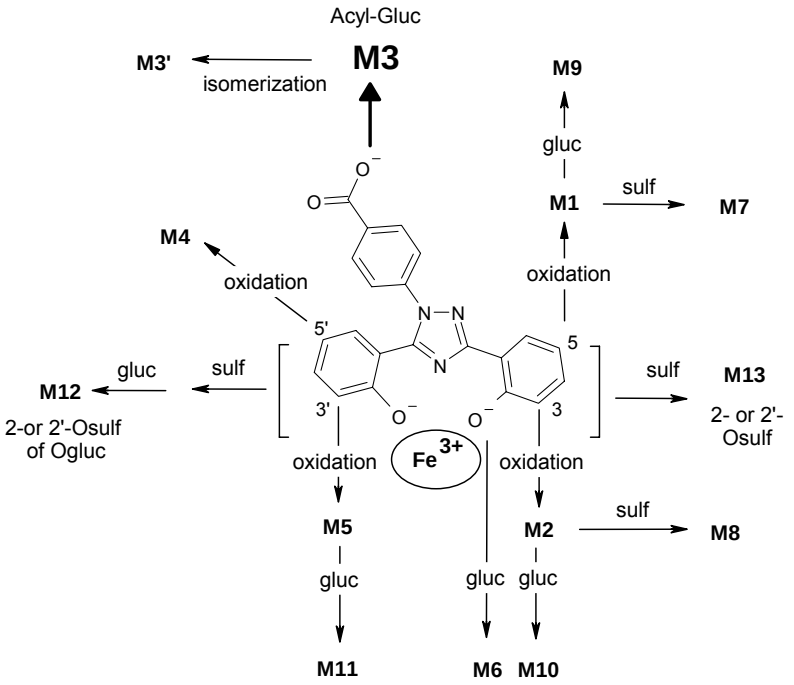
The *in vitro* biotransformation of [^{14}C]deferasirox was investigated using liver microsomes from the rat, rabbit, dog, marmoset and human. In rat, rabbit, marmoset and human liver microsomes, the metabolism of deferasirox was qualitatively comparable, whereas dog liver microsomes did not metabolize the compound under the experimental conditions studied. Four polar metabolite peaks were seen, which consisted of regio-isomers of mono-hydroxylated deferasirox. They were identified as M1, M2, M4, M5 by LC-MS and LC-^{1}H-NMR. These metabolites were also found to be present as glucuronic acid conjugates in the bile and as aglycons in feces of rats and marmosets treated with a single dose of deferasirox. Oxidative metabolism of deferasirox was fast in rabbit and marmoset, and slow in rat and human liver microsomes. The iron complex Fe-[deferasirox]$_2$ yielded similar metabolite patterns in marmoset liver microsomes indicating that iron complexing of deferasirox had a minor influence on the *in vitro* metabolism of deferasirox. After incubations with recombinant human cytochrome P450 isoenzymes, the metabolite formation was mainly catalyzed by CYP1A1 and CYP1A2 forming metabolites M1 and M2, and CYP2D6 forming metabolites M4 and M5. CYP1A2 contributes to the oxidative metabolism of deferasirox by 6- to 8-fold more than CYP2D6
The direct glucuronidation of deferasirox was investigated in vitro using human liver microsomes in the presence of UDPGA. Glucuronic acid conjugation was also tested with a panel of recombinant human UGT isoenzymes produced in insect cell membranes. Direct glucuronidation of deferasirox was catalyzed predominantly by UGT1A1 (K_m= 52.1 µmol/l) and UGT1A3 (K_m= 72.6 µmol/L) accounting together for about 95% of the glucuronide formation. Minor contributions originated from of UGT1A7 and UGT1A9. Only trace activities were observed with UGT1A4, UGT1A6, UGT1A8, UGT1A10, UGT2B4, UGT2B7, UGT2B15 and UGT2B17.

The formation of the acyl-glucuronide (M3) was an important biotransformation pathway observed in human and rat hepatocytes (50 µmol/l, 3 hours incubation time). Additionally, M7 (5-O-sulfate metabolite) and M4 (5'-hydroxy metabolite) were observed. M6 (2-O-glucuronide metabolite) was only seen in human hepatocytes. Metabolites M3, M4, M6 and M7 were also seen in 0-48 h bile of bile duct-cannulated rats (10 mg/kg, i.v.).

In vivo metabolism

The metabolism of ^{14}C-labeled deferasirox was studied in male and female mice (10 mg/kg, i.v.; 10 and 300 mg/kg, p.o.), male rats (10 mg/kg, i.v, 10 and 100 mg/kg, p.o.) and male marmosets (10 mg/kg, i.v.; 25 mg/kg, p.o.). Additionally, the metabolism of the ^{14}C-labeled iron complex Fe-[deferasirox]$_2$ was studied in male rats after an intravenous dose of 10 mg/kg. In humans, the metabolism of deferasirox was investigated in thalassemia patients at steady-state by non-radiolabeled deferasirox (1000 mg/day), who were given a single oral dose of 1000 mg (~ 20 mg/kg) of ^{14}C-labeled deferasirox. The Biotransformation pathways of deferasirox in animals and humans are summarised in Table 3.

Table 3: Biotransformation pathways of deferasirox in animals and humans



Metabolite	Occurrence in species
M1	M, R, Ma, H
M2	M, R, Ma, HLM
M3	M, R, Ma, H
M3'	M, R, Ma, H
M4	M, R, Ma, H
M5	M, R, Ma, HLM
M6	M, R, Ma, H
M7	M, R, Ma, H
M8	M, R, Ma
M9	R
M10	R
M11	R
M12	R
M13	R

Abbreviations: Acyl-Gluc: acyl-glucuronide of deferasirox; gluc: O-conjugation with glucuronic acid; sulf: O-conjugation with sulfuric acid; Fe^{3+}: position of the Fe^{3+} ion in the Fe-(deferasirox)$_2$ complex; M: mouse; R: rat; Ma: marmoset monkey ; H: human; HLM: human liver microsomes.

In all species including human, biotransformation was extensive, the major metabolic pathways being hydroxylation, glucuronidation and sulfation. In mice and rats, depending on dose and dosing route, deferasirox represented 80%-95% of the ^{14}C-AUC$_{0\text{-}8h}$. In mice, deferasirox represented 66%-81% of the ^{14}C-AUC$_{0\text{-}24h}$. The acyl-glucuronide (M3) and the 2-O-glucuronide metabolite of deferasirox (M6) accounted for 2.9%-13.3% and 1.0%-5.8% of exposure respectively. In marmoset plasma (25 mg/kg, p.o.), deferasirox amounted to 23% of ^{14}C-AUC$_{0\text{-}24h}$. Additionally, a significant amount of about 27% consisted of the acyl-glucuronide (M3), 20% of the 5-O-glucuronide metabolite (M7) and about 2% of the 2-O-glucuronide metabolite of deferasirox (M6).

In thalassemia patients who were treated with a single oral dose of 1000 mg (~ 20 mg/kg) of ^{14}C-labeled deferasirox at steady-state (1000 mg/day ICL670), the predominant radiolabeled component in plasma was deferasirox (about 91% of AUC). Thus systemic exposure was largely to deferasirox. Exposure to the acyl-glucuronide metabolite (M3) was minimal (3% of the ^{14}C-AUC).

- **Elimination and excretion**

The first elimination phase of deferasirox and ^{14}C radioactivity ranged from about 0.5 hours in mice (10 mg/kg, i.v.) to 1.9 hours in marmosets (25 mg/kg, p.o.). In male dogs following single doses of non-radiolabeled deferasirox (11-14 mg/kg, p.o.), the elimination half-lives were about 1-3 hours. In marmosets, the terminal elimination half-lives for deferasirox and ^{14}C radioactivity were 35 and 42 hours after p.o. dosing, and 51 and 41 hours after i.v. dosing, respectively. After intravenous administration of 10 mg/kg ^{14}C-labeled iron complex Fe-[deferasirox]$_2$ to male albino rats the ^{14}C concentrations in plasma declined with an initial half-life of about 0.5 hours (period: 0.5-2 h).

Independent of the route of administration, in all investigated species, excretion of radioactivity occurred mainly via bile/feces and was virtually complete within 3 days (mice) or 7 days (rats, marmosets). In rats, 58-76% of the dose was excreted in the bile. Renal excretion generally accounted for less than 12% of dose. After high oral doses (up to 300 mg/kg) male mice showed higher renal excretion (18% of the dose) and delayed excretion of radioactivity, in line with delayed elimination of radioactivity from the systemic circulation.

Deferasirox, its iron complex and metabolites of deferasirox are mono-, di- or tri-anionic molecules. Their elimination from the systemic circulation is most probably governed by anion-transport processes, largely in the liver. Biliary excretion of ^{14}C-radioactivity (10 mg/kg, i.v.), representing [^{14}C] deferasirox and its metabolites, was impaired in bile duct-cannulated Mrp2-deficient TR¯rats (the rat transporter Mrp2 corresponds to MRP2, multidrug-resistance-associated protein 2 in humans), although about 43% of the dose was still excreted into the bile.

Iron excretion was analyzed in urine and bile following a single intravenous dose of 50 mg/kg non-radiolabeled deferasirox, or its metabolites M1 or M2. The ability of deferasirox to remove iron from rats was 6-fold higher than for the two metabolites.

- **Pharmacokinetic drug interactions**

*In vitro d*rug-drug interaction study of deferasirox and its complex Fe-[deferasirox]$_2$ on comedications, showed that deferasirox weakly inhibited cytochrome P450 activities with IC_{50} values ranging from 100 to >500 µmol/l. Deferasirox displayed partial noncompetitive inhibition of acetaminophen glucuronidation in human liver microsomes (K_i = 204.8 µmol/l). Hydroxyurea was evaluated *in vitro* as a potential inhibitor of the metabolism of deferasirox in pooled human liver microsomes with NADPH and UDPGA as cofactors for cytochrome P450 and UGT metabolism, respectively. The results indicated that the metabolism of [^{14}C] deferasirox (50 µmol/l) was not inhibited by hydroxyurea concentrations between 0.01 to 5 mmol/l. For hydroxyurea up to 100 µmol/L no activation and no inhibition of the MDR1, MXR, or MRP2 proteins could be observed. The marker probe ligands for the two main drug binding sites on albumin, warfarin (1 and 5 µg/mL) and diazepam (0.1 and 1 µg/mL), were displaced to a very low extent by deferasirox and Fe-[deferasirox]$_2$ (5 and 100 µg/mL).

Toxicology

- Single dose toxicity

The acute toxicity of deferasirox was assessed in mice and rats receiving oral (0-1000 mg/kg) or intravenous (0-150 and 0-75 mg/kg, respectively) single dose. The minimum lethal oral doses were 1000 and 500 mg/kg in mice or male rats and female rats, respectively. The minimum lethal intravenous doses were 150 and > 75 mg/kg in mice and rats, respectively.
Discolored urine, body weight reductions with or without concomitant food consumption deceases were observed. Deaths occurred immediately post dose in the intravenous mouse study, but typically occurred on subsequent days (days 2-9).

- Repeat dose toxicity (with toxicokinetics)

Studies in rats

Deferasirox was administered orally to iron overloaded and/or non-overloaded Han Wistar rats (10/sex/group) at 0 or 100 mg/kg. Clinical signs in non-iron overloaded males were sedation, ptosis, piloerection, red discoloration of feces, diarrhea, labored breathing and chromorhinorrhea, while females were generally unaffected. Hematology revealed morphological changes of the red blood cells. Zinc protoporphyrin was increased and platelets and hemoglobin were slightly decreased in all treated groups. Urinalysis revealed a slightly reduced creatinine clearance in all treated groups. Following treatment, the liver/kidney iron concentration was reduced by 47-81% in deferasirox treated non iron overloaded animals compared to non iron overloaded controls; whereas the liver/kidney iron concentration was reduced by 16-46% in iron overloaded animals compared to iron overloaded controls. Pathology investigations revealed that deferasirox was nephrotoxic at 100 mg/kg/day although the nephrotoxic potential was less pronounced in animals pre-loaded with iron. The liver/kidney iron concentration was still higher in iron overloaded deferasirox treated rats after the 4-week treatment period than in non overloaded controls (17 fold in males, 10 fold in females).

Deferasirox was administered orally to Wistar Hannover rats (16/sex/group) at daily doses of 10, 30 and 100 mg/kg for at least 4 consecutive weeks. Deferasirox-related findings were observed at 100 mg/kg and included mortality; decreases in mean cell volume, hemoglobin, mean corpuscular hemoglobin and hematocrit and increases in red cell distribution width; decreases in serum iron with concomitant increases in total and unsaturated iron-binding capacity (TIBC and UIBC); decreases in urinary pH; decreases in liver and kidney iron content at all doses; gross necropsy findings of red lesions in the stomach, red contents in the intestine and urinary bladder and red mesenteric lymph nodes, in the early deaths; decreases in adrenal weights, and decreases in thymus weights; and microscopic findings of tubular vacuolation and necrosis in the kidney, vacuolation of the adrenal gland, focal degeneration, inflammation and myocarditis in the heart, erosion, hemorrhage and/or inflammation in the stomach and intestine and lymphoid depletion and/or necrosis in the thymus and spleen. Most of the treatment-related effects were reversible by the end of a 4-week recovery period.

In a 4-week oral exploratory study in male rats, a daily dose of 100 mg/kg/day to animals fed with a standard diet was not tolerated based on mortality, reductions in body weight and food consumption parameters and histopathological changes in the kidneys, adrenals and stomach. Deferasirox was well tolerated in animals fed with an iron supplemented diet at the same dose level, based on the absence of any toxicological findings.

In a 26-week oral toxicity study in rats, deferasirox was administered to Wistar Hannover rats (20 or 30/sex/group) at daily doses of 30, 80 and 180 mg/kg. These animals also received an iron supplemented diet. One control group received iron supplemented rodent diet; the second control group received standard rodent diet. Chronic oral administration of deferasirox to rats produced pharmacologic and/or toxicologic effects at all dose levels. The high dose of 180 mg/kg/day exceeded a maximally tolerated dose as evidenced by test article-induced mortality. Histopathological changes were evident in the eyes and stomach at doses $\geq$ 80 mg/kg/day and in the kidneys, adrenals and spleen at 180 mg/kg/day. All changes were at least partially reversible with the exception of the cataracts. Minimal clinical pathology, organ weight and early lenticular changes were observed in males at 30 mg/kg/day. The no effect level for females was 30 mg/kg/day. A no-observed-adverse-effect level (NOAEL) was not achieved for males.

Studies in marmosets

In a 2-week oral toxicity study three groups of two male and two female marmosets received deferasirox at dosages of 100, 200 or 400 mg/kg/day. The administration of deferasirox was associated with kidney alteration (cortical proximal tubular epithelial vacuolation) and changes (increase in urine and plasma iron concentration. The NOAEL was 100 mg/kg/day, corresponding to a Cmax of 235 µmol/l in the male and 129 µmol/l in the female.

In a 2-week oral toxicity study, deferasirox or control article were consequently given to marmosets with an initial iron overload. A group of ten male and ten female marmosets received deferasirox at a dose of 400 mg/kg/day for 14 days. No deferasirox-related changes of the kidney were present at microscopic examination. The NOAEL was 400 mg/kg/day, corresponding to a Cmax of 195 µmol/l in the male and 214 µmol/l in the female.

In a 4-week oral toxicity study in marmosets, administration of deferasirox at a dose of 130 mg/kg/day was associated with changes in the kidney, liver and gallbladder in males. After a 4-week recovery period, the only remaining change was a small number of protein casts in renal cortical tubular cells of a single male animal. The NOAEL was considered to be 65 mg/kg/day for males and 130 mg/kg/day for females.

In a 4-week oral palatability and toxicity study in marmosets, two groups of two male received deferasirox at a dose of 200 mg/kg/day. One of these treated groups received normal diet and one received an iron-supplemented diet. One of the control groups received normal diet and one received iron-supplemented diet. Animals receiving iron-supplemented diet did not tolerate the treatment with deferasirox as well as the animals receiving normal diet. Plasma concentrations of total deferasirox in the surviving animal given an iron-supplemented diet were lower than in the two animals given a normal diet (Cmax 78.8 µmol/l instead of 194 µmol/l in males and 662 µmol/l instead of 2266 µmol/l in females). No AUC were reported. A high inter-animal variability of C_{max} and $AUC_{(0\text{-}24h)}$ in animals given a normal diet was stated in the application.

In a 39-week oral toxicity study in marmosets, deferasirox was administered to groups of four male and four female marmosets at doses of 20, 40 or 80 mg/kg/day and a dose volume of 5 ml/kg, once daily. An additional group receiving 80 mg/kg/day deferasirox was given an iron supplement in the diet to attenuate possible adverse effects due to iron deprivation. At 80 mg/kg/day there were clinical signs, body weight and food consumption effects resulting in the premature sacrifice of three animals, and evidence of toxic changes in the gallbladder, hepatic bile ducts and kidneys. Marked depletion of liver and kidney iron stores was apparent at all dosages with the exception of females at 20 mg/kg/day. Excluding this finding, changes at 40 mg/kg/day were minimal and this was considered to be the No-Toxic-Effect Level.

Table 4: Deferasirox exposure multiples in toxicity studies

Species/ Study number	NOAEL[b] (mg/kg)	Sex	$AUC_{0\text{-}24h}$[c] (µmol·h/L)	C_{max}[c] (µmol/L)	Exposure multiples: Based on $AUC_{0\text{-}24h}$	Exposure multiples: Based on C_{max}
4-wk rat [974080] [d]	10 10	male female	25.8 27.6	6.43 13.1	0.02 0.02	0.05 0.11
4-wk rat [987066] [e]	100 -	male female	1095 -	276 -	0.78 -	2.3 -
26-wk rat [987037] [e]	30 [f] 30 [f]	male female	98 166	19.5 72.3	0.07 0.12	0.16 0.60
2-wk marmoset [971974]	100	male female	- -	235 129	- -	1.04 1.07
4-wk marmoset [974194] [d]	65 130	male female	520 541	92.7 72.6	0.37 0.38	0.77 0.60
39-wk marmoset [982027] [d,]	40 40	male female	164 195	32.0 37.0	0.12 0.14	0.27 0.31

[a] based on 20 mg/kg, multiple dose, day 12, C_{max} = 120.5 µmol/l, $AUC_{0\text{-}24h}$ = 1404 µmol·h/l; [b] No-Observed-Adverse-Effect-Level; [c] based on day 1 data; [d] Standard diets; [e] Iron-supplemented diets; [f] Lowest dose in study, not NOAEL

- Genotoxicity

The design of the genotoxicity studies performed is provided in the table below:

Table 5: Deferasirox in vitro and in vivo genotoxicity studies

In vitro test/study ID/GLP	strains	Concentrations/ Concentration range/ Metabolising system	Results
Ames (GLP)	S. typhimurium TA1535, TA97a, TA98, TA100, TA102	Up to 5000 µg/plate +/- S9	negative
Chromosomal aberration (GLP)	Human peripheral blood lymphocyte	Up to 143.0 µg/mL +/- S9	negative
In vivo test/study ID/GLP	**species**	**Concentrations/ Concentration range/ Metabolising system**	**Results**
Bone marrow Micronucleus test (GLP)	rat	50, 158, 500 mg/kg	positive result at 500 mg/kg
Bone marrow Micronucleus test	rat	A - 500 mg/kg twice with a recovery period up to 10 days B – 500 mg/kg with ICL670-iron complex	A: + after 1, 2, 3 days; - after 6 and 10 days B: positive
Bone marrow Micronucleus test (GLP, excepted the tissue iron analysis)	Iron-overloaded rats (40 mg/kg IP iron twice per week)	300 or 500 mg/kg	negative
Liver micronucleus test (GLP)	rat	200, 350 or 500 mg/kg	negative

- Carcinogenicity

In a 104-week oral carcinogenicity study in rats, the animals received doses of 0 (control feed), 0 (iron supplemented feed), 25, 50 and 100 mg/kg/day of deferasirox. These dose were subsequently decreased to 15, 30 and 60 mg/kg/day beginning on day 29. At study termination, 72-84% survival was observed in the males and 58-68% survival was observed in the females. There were no statistical differences in survival between the control groups and deferasirox -treated dose groups. There were no test article-related neoplastic or non-neoplastic pathological changes. Based on the extent of tissue iron depletion with corresponding increases in serum iron concentrations, the maximum tolerated dose was 100→60 mg/kg/day.

In a 26-week oral carcinogenicity study in p53 heterozygous mice, deferasirox was administered to 25 male at daily doses of 0 (feed supplemented with iron), 0 (standard feed), 20, 100 and 200 mg/kg/day (feed supplemented with iron), and 30 mg/kg/day (standard feed) and to 25 female at daily doses of 0 (feed supplemented with iron), 0 (standard feed), 30, 100 and 300 mg/kg/day (feed supplemented with iron) and 100→60 mg/kg/day (standard feed, dose decrease effective day 50). Deferasirox was also administered to p53 wild type mice (25/sex/group). Excessive moribundity/mortality was observed. The cause of moribundity was test article-related stomach and kidney lesions. There were no test article-related neoplastic findings.

- Reproduction Toxicity

In a fertility and early embryonic development study in rats, deferasirox administered orally at daily doses of 7.5, 25 or 75 mg/kg to male and female rats resulted in no effects on sperm count, sperm motility, or fertility in males and there were no treatment-related effects noted in females at any dose level.

In an oral embryo-fetal development study in 25 female rats (10-100 mg/kg), the following changes were observed at 100 mg/kg: 1) mortality with associated gastrointestinal lesions; 2) clinical signs; 3) decreases in food consumption, body weight parameters; 4) increases in the number of fetuses with skeletal variations without an apparent indication of teratogenicity. The systemic exposure of pregnant rats to ICL 670 increased over-proportionally with the dose between 10 and 100 mg/kg, based on AUC values. The maternal liver iron was depleted by deferasirox in a dose-dependent manner, but there were no effects on the fetal iron level. The NOEL was 30 mg/kg.

In an oral embryo-fetal development study in 20 female rabbits (5-50 mg/kg), deferasirox had no effect on the reproductive parameters and no effect on the fetal external, visceral or skeletal development. Deferasirox had no effect on the iron and zinc levels in the maternal liver and in the fetuses. The NOEL for the rabbit maternal toxicity was 20 mg/kg. The NOEL for the rabbit embryo-fetal development was 50 mg/kg.
In an oral pre- and postnatal development study in 25 female rats (10-90 mg/kg), the NOEL for F_0 maternal toxicity and fetal growth and viability was 30 mg/kg/day. There were deferasirox -related effects on body weight, morphological, functional, learning/memory or fertility parameters investigated for offspring at doses ≤ 30 mg/kg/day. Thus, the NOEL for F_1 effects was > 30 mg/kg/day.

- Studies in juvenile animals

In an oral neonatal and juvenile development study, deferasirox administered to rats on days 7-70 post partum at a dose of 40 mg/kg/day produced mortality with and without iron supplementation. Test article-related lenticular changes (cataracts) developed during the study and these increased in incidence and severity as the study progressed. These lenticular changes remained the same showing no detectable progression during the recovery period examinations. The no-observed-adverse-effect level (NOAEL) was considered to be 20 mg/kg/day for neonatal/juvenile males and 10 mg/kg/day for neonatal/juvenile females.

In a subchronic oral toxicity study of in juvenile mice, administration of deferasirox at ≥ 15 mg/kg/day produced mortality (with and without iron supplementation). There were effects on lymphocyte populations in the blood at each dose level and in the spleen and thymus at 35 mg/kg/day (with or without iron supplementation).

- Local tolerance

The local tolerance of deferasirox was assessed in the rabbit when administered by a single intravenous administration. At necropsy there were a few instances of discoloration or blood vessel dilation in both groups and at both saline and test item treated sites. Microscopic examination revealed no evidence of local intolerance to either deferasirox or placebo.

- Other toxicity studies

In a immunotoxicity study, deferasirox was administered to groups of rats (10/sex/group) at dosages of 6, 20 or 60 mg/kg/day for four weeks. Hematological changes in the erythron and a dose-related decrease in white cell parameters for immunized males when compared with immunized controls was observed. Histopathological changes corresponding to immune stimulation were observed in the spleen and in the lymph nodes of immunized animals. A lower production of IgG was observed for immunized males administered 60 mg/kg/day, with reduced B cell counts in peripheral blood and to a lesser extent the spleen and lymph nodes.

The mechanism of deferasirox nephrotoxicity was investigated in cell cultures from kidney proximal tubule and in rat kidney slices. In pig cell line and human renal proximal tubular epithelium cells, deferasirox induced a concentration dependent increase of LDH leakage. In both cellular systems this effect was statistically significantly different from controls at deferasirox concentrations ≥ 100 µM and was not detected in the presence of an equimolar amount of Fe^{3+}. Treatment with the stable iron complex did not increase LDH leakage significantly. Rat kidney slices were treated with 1 mM of deferasirox for 4.5 hours in the presence or absence of 0.5 and 1 mM Fe^{3+}. In the absence of iron, deferasirox significantly increased LDH leakage by a factor of 2-3 compared to control. The ATP dependent para-aminohippuric acid (PAH) uptake as a parameter of function integrity of proximal tubular cells was decreased by 71-78%. In parallel ATP content and energy charge were decreased. These effects were prevented in the presence of a twofold molar excess of Fe^{3+}. Co-incubation of deferasirox with a stoichiometric amount of Fe^{3+} impeded the increase of the LDH leakage completely and partly the reduction of the PAH-accumulation.

The effects of iron and deferasirox on cultured lenses was performed in an *in vitro* cataract study with isolated rat lenses. The lenses were incubated with deferasirox at concentrations of 2-200 µM for 14 hours or 6 days in the presence and absence of additional iron. The major finding was that exposure to

deferasirox at high concentrations for prolonged period of 6 days led to both loss of transparency and glutathione. No change in effect was observed when iron was added to the experiment.

Deferasirox has been shown in ICH compliant stability experiments to be chemically stable when exposed to ultraviolet/visible light as drug substance or drug product. Based on this information, nonclinical phototoxicity studies were not conducted.

4-Hydrazinobenzoic acid (4-HBA) is an impurity of deferasirox, which is carried over from synthesis and not a degradation product formed during processing or storage. 4-HBA was evaluated for mutagenic activity in a GLP test using *Salmonella typhimurium* strains. In strain TA97a, a clear and dose-dependent mutagenic effect was seen after treatment with 4-hydrazinobenzoic acid (doses of up to 5000 µg/plate, with or without S9), up to a factor of 5.86 over the control value.
The clastogenic potential of 4-HBA was assessed *in vitro,* on human peripheral blood lymphocytes, up to 1498.7 µg/ml with metabolic activation and up to 928.3 µg/ml without metabolic activation. No increased chromosome aberration frequencies above the historical control range were found in any of the experiments.

Ecotoxicity/environmental risk assessment

Based on the calculated PEC (predicted environmental concentration) in surface water, the predicted concentration of deferasirox in the environmental was 42 ng/l. The PEC/PNEC ratio (algae, EC_{50} 0.32 mg/l) was < 1. The relative weight of dry sludge in waste water was estimated to be approximately 0.5 %. The predicted concentration of deferasirox in the environmental was 56 ng/kg, as calculated below:

PECs grassland (ng/kg) = (Cs*As)/(D*ä) = (84480*0.1)/(0.1*1500) = 56.32ng/kg soil

Cs = Concentration of substance adsorbed to sludge particles (ng/kg dry sludge); As = Amount of sludge spread on grass (0.1 kg/m2/year) or arable land (0.17 kg/m2/year); D = Incorporation of sludge into soil (10 cm for grass land and 20 cm for arable land); ä = Density of soil (1500 kg/m3)

The PEC was 178-fold below the action limit (PEC >10 µg/kg soil) recommended in the draft guideline [EMEA, Released for consultation January 2005 (http://www.emea.eu.int/pdfs/human/swp/519902en.pdf) #8] on environmental risk assessment of medicinal products for human use. Therefore, no further analysis was performed.

Discussion on the non-clinical aspects

Discussion on non-clinical phamacodynamics

The primary pharmacodynamic program, including *in vitro* and *in vivo* studies conducted in rats and marmosets, investigated the affinity, the selectivity and the efficiency of deferasirox regarding the iron overload. The major species under physiologic conditions, deferasirox concentrations of 10 µmol/, and iron concentration of 1 µmol/l was $Fe(deferasirox)_2^{3-}$. In these conditions, the affinity of deferasirox was less than DFO but higher than deferiprone. Deferasirox showed low affinity for Fe(II). The ranking according to affinities was: Fe(III)> Al(III)>> Cu(II)>> Zn(II)> Fe(II)>> Mg(II)> Ca(II). Up to 80 µmol/l of deferasirox (plasma concentration range observed in patients receiving deferasirox at dose ≥ 20 mg/kg), the efficiency of deferasirox, defined as the amount of iron excreted as a percentage of the theoretical iron binding capacity of the dose, was approximately 40%. This efficiency was similar to that of DFO (50%). Beyond this concentration, a reduced potency as compared to DFO was seen (at 320 µmol/l, deferasirox showed an efficiency of 56% as compared to 82% with DFO). In animal models tested, iron excretion was dose proportional and protracted, indicating dose dependent pharmacodynamic effects for up to 24 hours. The bulk of the iron was excreted in bile, while urinary excretion was consistently low (< 15%). The efficiency of the chelator, was around 18% and 29% for rat and monkey, respectively (efficiencies of DFO given subcutaneously and deferiprone given orally ranged between 2 to 4% in rats and monkeys).

The effective daily dose of deferasirox in marmosets was calculated as approximately 22 mg/kg (the effective dose is based on the clinical objective of eliminating up to 500 µg/kg/day in highly transfused β-thalassemia patients). Daily administration of deferasirox up to 80 mg/kg to non iron-loaded marmoset monkeys (male/female) for 39 weeks resulted in average reductions of liver iron up to approximately 85%. Elevation in liver copper level has been observed in a limited number of marmoset chronically treated with deferasirox. This phenomenon remained unexplained but was not

expected to have any significant clinical consequences. Liver iron was used throughout the development program as a robust marker of total body iron load and as model target for iron mobilization by chelation. However, deferasirox was shown to remove iron from the heart.
The preclinical investigations to assess for effects on the cardiovascular system were conducted to aid in the clinical investigation on potential cardiovascular effects (see clinical safety). The dog study did not provide any relevant findings.

Discussion on non-clinical phamacokinetics

Pharmacokinetics of deferasirox, its metabolites, and the respective iron complex Fe-[deferasirox]$_2$ were investigated in mice, rats, marmosets, dogs and rabbits. The fate of deferasirox and Fe-[deferasirox]$_2$ were similar in all species investigated including human. Data obtained in rats were the most similar to those from human, in terms of disposition and metabolism of deferasirox.

In rodents, but not in marmosets and humans, bioavailability increased dose over-proportionally, probably due to saturation of elimination processes. Based on *in vitro* permeability studies across Caco-2 cell monolayers, deferasirox was identified as a well permeable compound being a substrate for a prominent efflux system. Uptake of deferasirox was not significantly different from uptake values into water-injected control oocytes, indicating deferasirox to have no affinity for the human organic anion transporting polypeptides OATP1A2, OATP1B1, OATP1B3 or the human organic cation transporter hOCT1. All oral test formulations and the market formulation were virtually completely absorbed and their mean plasma profiles were almost similar. No differences in absorption rate was observed. Dog model was of limited value concerning modelling of food effect in humans. Following studies performed in bile duct-cannulated rats, the total extent of enterohepatic circulation was 30.5% of the originally administered intravenous dose. Unchanged deferasirox, several sulfate and glucuronide conjugates contributed to the enterohepatic circulation of ICL670-related compounds.

The volume of distribution of deferasirox was low to moderate (V_{ss}= 0.18 to 0.98 l/kg in the mouse, rat, dog and human). The volume of distribution of Fe-[deferasirox]$_2$ was very low (V_{ss}=0.086 l/kg in the rat). Up to 8 hours post-administration, most organs and tissues showed ^{14}C concentrations close to or below that in blood. Highest ^{14}C levels were seen in the gastrointestinal tract, the heart and excretory organs, i.e. liver, kidney and intestine. Deferasirox and/or its metabolites passed the blood-brain barrier to a very low extent. Deferasirox and/or its metabolites did not show any affinity to melanin-containing structures of the eye (choroid) of the pigmented rat. Similar tissue distribution patterns were observed in rats after i.v. administration of ^{14}C-labeled deferasirox and its iron complex. The placental barrier was passed in pregnant rats and rabbits to a very limited extent. It can be assumed that also the human placenta will be crossed to a very limited extent. Deferasirox was found to be rapidly and extensively secreted into maternal milk. Therefore, breast-feeding while taking deferasirox is not recommended (see SPC section 4.6).

Metabolism data indicated that glucuronidation of deferasirox was a key biotransformation pathway. Direct glucuronidation of deferasirox was catalyzed predominantly by UGT1A1 and UGT1A3 accounting together for about 95% of the glucuronide formation. Minor contributions originated from of UGT1A7 and UGT1A9. Only trace activities were observed with UGT1A4, UGT1A6, UGT1A8, UGT1A10, UGT2B4, UGT2B7, UGT2B15 and UGT2B17. Data available from the literature show that UGT induction is generally low. However, no induction study of UGT was performed. Monthly safety and efficacy (serum ferritin) monitoring are recommended in the SPC (see section 4.2) to tailor the dose of deferasirox to the individual patient's response (see also clinical pharmacokinetics).

Deferasirox was the predominant systemically available component in all species including humans. Essentially the same metabolites of deferasirox in humans were formed by at least one of the animal species *in vivo* and/or *in vitro*, supporting the selection of the toxicological test species. Exposure to metabolites after oral dosing of [^{14}C]deferasirox was high in marmosets (~ 80% of ^{14}C-AUC) and moderate to low in mice (~ 30%), rats (~ 20%) and low in humans (~ 9%). In line with the *in vitro* studies in liver microsomes and hepatocytes, the main oxidative metabolic pathways were aromatic hydroxylation accompanied by conjugation with glucuronic acid and/or sulfuric acid. The common systemically available metabolite across species was the acyl-glucuronide (M3) constituting about 27% of ^{14}C-AUC$_{0\text{-}24h}$ in marmosets, about 3% in humans, and about 0.8% in mice and rats. Deferasirox being the major active circulating moiety, it was considered to contribute to most of the

pharmacological activity (iron mobilization). The hydroxy metabolites M1 and M2 were considered to negligibly contribute to the overall iron elimination *in vivo*.

Radioactivity was eliminated from blood and most tissues with apparent half-lives ranging from 2 to 7 hours, except in the skin where a half-life of about 21 hours was seen. Biliary elimination could be studied in rats only, but the findings were assumed to apply to other animal species. According to the data assessed, accumulation of deferasirox and/or its metabolites in the excretory organs or in any tissue is not expected after multiple oral administration of deferasirox to humans.

Given the relatively high expected therapeutic concentrations of deferasirox (100-200 µmol/l, reached after daily oral dosing of 20-30 mg/kg), inhibition by deferasirox of metabolic reactions that are catalyzed by CYP2C8, CYP1A2, CYP3A4/5, CYP2A6, CYP2C9 is possible in theory. Though, considering the very high plasma protein binding of deferasirox (>99%), significant inhibition by deferasirox is not likely to occur. Oxidative metabolism by cytochrome P450 enzymes (hydroxylation) to M1 (presumably by CYP1A) and M4 (by CYP2D6) is a minor elimination process, as only 6% and 2% of the dose, respectively, underwent this type of metabolism. Therefore, any inhibition or induction of those enzymes by co-medications is not expected to significantly affect the pharmacokinetics of ICL670. If any interaction *via* CYP450 enzymes were to occur, the change in ICL670 pharmacokinetics would most likely be much smaller than the normal interindividual variability. Genetic polymorphism (e.g. CYP2D6 poor metabolizer status) is not expected to have an impact either. In combination with the very high plasma protein binding of deferasirox, significant drug-drug interactions due to inhibition of paracetamol glucuronidation by deferasirox were considered unlikely. Interaction of deferasirox and Hydroxyurea in sickle cell anemia patients was also considered unlikely. The potential for a clinically relevant interaction on the protein binding level appears to be very unlikely with warfarin and diazepam.

Discussion on toxicology

The most relevant finding observed in the repeated dose toxicity studies included renal effects, lenticular changes, effects on hepatobiliary tract and myocardial changes.

A nephropathy consisting of renal tubular degeneration, cytoplasmic vacuolization of cortical tubular epithelial cells and tubular necrosis was observed in all species and contributed to the mortality observed in these studies. In the rat, renal tubular degeneration was observed at exposure (AUC) that was 1.4-1.7 and 1.5-4.8 fold the human exposure. *In vivo* and *in vitro* data suggested that the renal findings are a consequence of the pharmacological action of iron chelators under conditions of normal tissue iron levels. According to this hypothesis, a scale in renal toxicity should be observed in patients, depending on the degree of iron-overload due to transfusion. However, in animals on iron supplemented diets, exposure to circulating deferasirox was reduced, suggesting that renal effect observed *in vivo* was due to the lack in exposure rather than to the lack of iron depletion. As the safety margin was very low and would be lower after administration of the maximal therapeutic dose of 40 mg/kg, it was anticipated that the effect might occur in the patient. The applicant committed to explore the extent and mechanisms of potential renal injury following deferasirox administration.

Cataracts were first observed high-dose repeated toxicity study in rats. The changes varied in morphology from early cortical striations or vacuoles to mature cataracts. Cataracts were also observed in the rat neonatal/juvenile toxicity and 26-week transgenic mouse carcinogenicity. In contrast, in the two-year rat carcinogenicity, in which the dose and exposure in the mid and high doses overlapped the dose and exposure in the low and mid dose in the 26-week study, no lenticular lesions were observed at any dose level. Cataracts were also not observed in any marmoset toxicity study, even though exposure at the high dose used in the 39 week marmoset was greater than that in the low dose chronic rat study where early lesions were observed. An *in vitro* study with rat lenses suggested that the stress induced by deferasirox is oxidative in nature rather than disruptive of membrane integrity. These lenticular effects occurred at exposures less than human exposure.
Animal assessments are not capable of detecting subtle changes in auditory function nor indicate the type of deficit (e.g. high frequency). The sensitive and routine measurements employed in humans will be able to detect these types of changes. Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of the treatment and at regular intervals thereafter (every 12 months). If

disturbances are noted during the treatment, dose reduction or interruption may be considered (see section 4.4 of the SPC).

Inflammatory and degenerative changes in the gallbladder and bile ducts were seen in some marmosets at high doses and at doses that resulted in morbidity/mortality. Similar findings were observed in intrahepatic bile ducts in transgenic mice. Inflammatory changes in the gallbladder were generally seen in all treatment groups including control animals in most of the marmoset toxicity studies with ICL670. While the severity of these observations was greater in individual animals treated with high doses of deferasirox, the increased severity may represent a secondary effect on a pre-existing condition of the marmoset gallbladder. As the primary elimination route of deferasirox is via bile, the exacerbation of background lesions may be caused by excretion/concentration of deferasirox iron complexes in bile.

Myocardial changes (primarily myocarditis) were observed in rats and mice studies without iron supplementation. These changes were observed concurrently with and might be secondary to severe anemia observed in these animals. Cardiac changes were not detected in any marmoset study. These types of observations are expected to be of no or little clinical relevance in patients with increased iron tissue burden.

Gastrointestinal erosions/ulceration, and cytoplasmic vacuolization of the adrenal medulla were observed in rats and transgenic mice at high doses that were generally associated with morbidity or mortality, and as such are of little clinical relevance. Anemia, lymphoid depletion, and decreased adrenal and thymus weights were observed in rats, possibly due to depletion of tissue iron since changes were less marked in studies in iron-loaded animals. As these effects were most pronounced at higher doses and in the shorter term studies in which severe effects on animal health were observed, these findings were considered of little or no relevance to humans.

Deferasirox was not found mutagenic *in vitro* experiments. A positive result was observed in the micronucleus test in rats following oral adminsitration of 500 mg/kg. Following an additional micronucleus test performed on iron-overloaded rats giving negative results, deferasirox was considered not genotoxic up to the maximum tolerated dose of 500 mg/kg.

The oral administration of deferasirox to rats fed an iron supplemented diet for at least 104 weeks was not carcinogenic at doses up to 100→60 mg/kg/day. Deferasirox administered orally for 26 weeks was not carcinogenic in p53 heterozygous or wild type mice at doses up to 200 mg/kg/day for males and 300 mg/kg/day for females. Due to the sensitivity of the animal models relative to humans, doses at multiples of exposure as presented in the ICH S1C guideline [11] were not possible. Consequently, doses were selected based on existing data to estimate a maximum tolerated dose as the high dose, as also described in the ICH S1C guideline [11] . As expected, the administration of p-cresidine caused proliferative changes notably in the urinary bladder of p53 heterozygous mice (see section 5.3 of the SPC).

No effects on sperm count, sperm motility or fertility in males, or on fertility in males and females were observed at any dose level. Deferasirox was not teratogenic in rats or rabbits but caused increased frequency of skeletal variations and stillborn pups in rats at high doses that were severely toxic to the non-iron-overloaded mother (see section 5.3 of the SPC).

There was a weak reduction in the secondary immune response in male rats at the highest dosage tested. Deferasirox was locally well tolerated in a local intravenous tolerance study in the rabbit. The assessments of auditory function were limited to measurement of the startle effect.

Based on the results of the environmental risk assessment report, deferasirox is expected to be of negligible risk to the environment.

1.4 Clinical aspects

The development program of deferasirox was based on three pivotal studies (one phase III trial [study 107], one non-controlled phase II efficacy trial [108] and one controlled phase II safety trial [109]). These studies were supported by a small long-term trial in adults (study 0105) and a small trial in pediatrics (study 0106) with β-thalassemia, and by several short-term pharmacokinetic, pharmacodynamic, and safety studies in patients with β-thalassemia and in healthy volunteers. The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Deferasirox must be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions. It is recommended that treatment be started after the transfusion of approximately 20 units (about 100 ml/kg) of packed red blood cells or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin > 1,000 µg/l). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size. The recommended initial daily dose is 20 mg/kg body weight. An initial daily dose of 30 mg/kg may be considered for patients who require reduction of elevated body iron levels and who are also receiving more than 14 ml/kg/month of packed red blood cells (approximately >4 units/month for an adult). An initial daily dose of 10 mg/kg may be considered for patients who do not require reduction of body iron levels and who are also receiving less than 7 ml/kg/month of packed red blood cells (approximately <2 units/month for an adult). The patient's response must be monitored and dose increase should be considered if sufficient efficacy is not obtained. For patients already well managed on treatment with deferoxamine, a starting dose of deferasirox that is numerically half that of the deferoxamine dose could be considered (e.g. a patient receiving 40 mg/kg/day of deferoxamine for 5 days per week (or equivalent) could be transferred to a starting daily dose of 20 mg/kg/day of EXJADE). When this results in a daily dose less than 20 mg/kg body weight, the patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained. It is recommended that serum ferritin be monitored every month and that the dose of deferasirox be adjusted, if necessary, every 3 to 6 months, based on the trends in serum ferritin. Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). Doses above 30 mg/kg are not recommended because there is only limited experience with doses above this level. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered (see SPC, section 4.2 and section 4.4). Instructions for use and handling are detailed in the SPC (see section 6.6).

Pharmacokinetics

The concentrations of total deferasirox (corresponding to the sum of free deferasirox and iron-bound deferasirox), as well as the iron complex Fe-[deferasirox]$_2$ were determined in plasma by HPLC-UV or HPLC-MS-MS analytical methods. The HPLC-UV method and HPLC method with Turbo Ion Spray Mass Spectrometry (MS) detection were used for the analysis of the plasma and urine samples of the clinical trials. The limit of quantification was ≤ 0.670 µmol/l for deferasirox and ≤ 0.314 µmol/l for Fe-[deferasirox]$_2$.

- Absorption

The absolute oral bioavailability of deferasirox was assessed in one study in healthy adult volunteers. The absolute oral bioavailability of deferasirox estimated by the dose-normalized geometric mean ratio for $AUC_{0-\infty}$ following a single 375 mg oral dose (tablet) compared to a 130 mg 90-minute intravenous infusion was 0.70 [90% CI (0.62, 0.80)]. Bioequivalence studies between intermediate development formulations were not performed.

$AUC_{0-\infty}$ for deferasirox 0.5 hour before high fat breakfast and standard breakfast was 13 % [90% (CI 1.02, 1.25)] and 25% [90% CI (1.13, 1.38)] higher, respectively, compared to deferasirox under fasting conditions. The total exposure (AUC) to deferasirox increased by a factor of two if taken after

a high-fat breakfast in comparison to fasted condition. The total exposure increased by about 50% if administered concomitantly with a standard breakfast compared to fasted condition.
An open label, randomized, four-way crossover study evaluated in 28 subjects, the bioequivalence of a single oral dose of 20 mg/kg deferasirox administered 4 hours before a standard lunch when dispersed in orange juice, apple juice or non-dispersed in water compared to the reference treatment, tablets dispersed in non-carbonated commercially bottled water. The $AUC_{(0-t)}$ and C_{max} for deferasirox dispersed in apple juice were 10% and 12% lower respectively, compared to deferasirox dispersed in water. The $AUC_{(0-t)}$ and C_{max} for deferasirox dispersed in orange juice were 3% and 8% higher respectively compared to deferasirox dispersed in water. The $AUC_{(0-t)}$ and C_{max} for deferasirox non-dispersed were 1% higher and 2% lower respectively, compared to deferasirox dispersed in water.

- Distribution

Deferasirox is highly bound to plasma proteins (~99%), almost exclusively to serum albumin (see non-clinical section on distribution). The *in vitro* distribution of deferasirox between blood cells and plasma showed, that the mean fraction in blood cells was only 5% over the concentration range of 4-80 µg/ml (10-200 µmol/l).

- Elimination

After a single oral dose of [^{14}C]deferasirox, about 8% of administered radioactivity was excreted in urine and 84% in the feces. Most of the administered radioactivity was recovered in feces as unchanged drug formed by de-conjugation of the glucuronide metabolite in the intestine. Deferasirox was eliminated mainly by conjugation with glucuronic acid, followed by hepatobiliary elimination of the conjugate. Oxidative metabolism was about 8% of the dose eliminated by this pathway. The total excretion of deferasirox and its metabolites over 7 days was 91.5% of the dose. Enterohepatic recirculation slowed down drug elimination and increases drug exposure. In an ADME radiotracer study in thalassemia patients, pharmacokinetics in some patients displayed a second maximum or a shoulder of deferasirox in plasma at 24 hours post-dose.

- Dose proportionality and time dependencies

In a single escalating doses in sequential dose (2.5, 5, 10, 20, 40, 80 mg/kg, 18 patients), the pharmacokinetic of deferasirox was linear and drug exposure was dose proportional in patients at steady state. There was no change in the main PK parameters derived from plasma profiles over a one-year study duration in β-thalassemia patients treated with deferasirox in the dose range 5-30 mg/kg/day. In β-thalassemia patients, peak plasma concentrations of deferasirox were achieved with a median $t_{max,ss}$ between 1.5 and 4.3 hours in the dose range 5-30 mg/kg. Mean terminal elimination half-life was in the range of 7 to 16 hours. The accumulation ratio of deferasirox (10 and 20 mg/kg/day) calculated as the ratio of the average AUC between Day 15 and Day 360 to Day 1 AUC was 1.43 [90% CI (1.19, 1.73)].

- Special populations

A population pharmacokinetic model included several covariates to describe the inter-subject variability. Weight, sex, serum creatinine and study effects were included on both clearance of deferasirox and of (Fe-[deferasirox]$_2$). Weight and study effect were selected as covariates on deferasirox volume of distribution, and age as a covariate on the absorption rate constant. The inter-subject and inter-occasion variability on apparent deferasirox clearance were characterised by a coefficients of variation of 44% and 42%, respectively.
The PK characteristics of deferasirox was obtained in 19 paediatric patients (9 children and 10 adolescents) from an exploratory multicentre, open-label and non-comparative study conducted in patients with transfusion-dependent β-thalassemia major, previously treated with DFO for ≥4 weeks, stratified into two age groups (adolescents, 12 - ≤17 years and children, 2 - <12 years). The PK profile of deferasirox (10mg/kg/day) analysis revealed that, after single and multiple doses were similar PK characteristics in the adolescents and children, associated with an important inter-individual variability. There was accumulation in both age groups, deferasirox total exposure (AUC) was 60% higher after 2 weeks of treatment compared to Day 1 (90% CI for the ratio: 1.38, 1.85). After 4 weeks of treatment, AUC_{0-24} had doubled compared to Day 1 (90% CI for the ratio: 1.72, 2.31), with a 25% further increase in the last 2 weeks (90% CI for the ratio: 1.08, 1.45). Based on the population PK

analysis, the exposure of young children (ages 2 to < 6 years) was about 50% lower than in adults, although there was variability, with some children in this age range experiencing a drug exposure that was similar to adults. Drug exposure increases between age 2 to 18 years to reach adult levels. Females had a lower apparent clearance (by 17.5%) for deferasirox compared to males. Patients of Oriental, Black and Caucasian were involved in the clinical trials. There were very few data comparing the pharmacokinetics of deferasirox in the different ethnic groups. The pharmacokinetics of deferasirox were not studied in elderly patients (≥ 65 years), in patients with impaired liver or renal function.

- Pharmacokinetic interaction studies

In vitro studies

Interaction with CYP450 isoenzymes

The inhibitory potential of deferasirox and its ferric complex form to inhibit specific cytochrome (CYP) P450 activities was investigated in human liver microsomes in a concentration range of 0-500 µM. The iron chelator deferasirox inhibited cytochrome P450 (CYP) activities with IC_{50} values ranging from 100 to 500 µM. Deferasirox inhibited CYP2C8 paclitaxel hydroxylation activity with the lowest IC_{50} of 100 µM, followed by CYP1A2 phenacetin O-deethylation activity with IC_{50} of 175 µM. CYP2A6, 2C19, 2D6 and 3A4/5 were inhibited with IC_{50} values of 200 µM, 210 µM and 340 µM respectively. CYP2E1 (chlorzoxazone 6-hydroxylation) was inhibited with an IC_{50} > 500 µM. The ferric complex of attenuated phenacetin O-deethylation (CYP1A2) and coumarin 6-hydroxylation (CYP2A6) both with IC_{50} values of 100 µM. All other CYP450 activities examined were inhibited by ferric complex form with IC_{50} values ≥160 µM. Induction of CYP450 isoenzymes by deferasirox has not been investigated.

Interaction with UGT isoenzymes

Deferasirox was mainly metabolised by glucuronidation with the acylglucuronide being the major metabolite (see clinical and non-clinical metabolism). Glucuronidation was found to be performed predominantly by UGT1A1 and, UGT1A3 (accounting together for about 95% of the glucuronide formation) with minor contributions of UGT1A7 and UGT1A9. Only trace activities were observed with UGT1A4, UGT1A6, UGT1A8, UGT1A10, UGT2B4, UGT2B7, UGT2B15 and UGT2B17.

As patients treated with deferasirox may also take acetaminophen as co-medication, an *in vitro* study using human liver microsomes was conducted to investigate the potential inhibition of acetaminophen glucuronidation by deferasirox. The relative contributions of UGT enzymes for glucuronidation of acetaminophen were calculated to be 60% for UGT1A9, 30% for UGT1A6 and 10% for UGT1A1 at therapeutic drug levels. At toxic concentrations of acetaminophen (> 1 mM), the relative contributions by UGT1A1 increased to 30%, UGT1A6 dropped to 10% and UGT1A9 remained unchanged at 60%. At therapeutic oral doses of up to 40 mg/kg/day deferasirox, the K_i values was more than two-fold higher than the C_{max} for deferasirox reached in the patients.

Interaction with hydroxyurea

The potential inhibitory effect of hydroxyurea comedications on deferasirox metabolization was investigated in a *in vitro* study using human liver microsomes. The concentrations of hydroxyurea ranged between 10 µM and 5 mM (twice the highest human *in vivo* concentrations). Hydroxyurea did neither change the metabolite pattern nor the metabolisation rates up of deferasirox.

Interaction with P-gp transporter

Human intestinal cell line Caco-2 grown on permeable filter support was used to identify the inhibitory potential of deferasirox on P-gp transporter. The concentration dependant compound transport [1,5,10 and 50 µM] across Caco-2 cell monolayers was measured from the apical to basolateral as well as from the basolateral to apical side. For 1µM deferasirox apical to basolateral transport studies were also performed in the presence of the potent efflux system inhibitors ciclosporin and verapamil at concentration of 10µM and 100µM respectively. Deferasirox was identified as a highly permeable compound (intrinsic permeability > 80%). The significant differences between apical-to-basolateral and basolateral-to-apical permeability data suggest strong efflux transporter involvement. Presence of the efflux transporter inhibitor Verapamil did not influence deferasirox

permeability. Addition of the efflux inhibitor CsA, however, increased apical-to-basolateral permeability slightly but significantly.

Displacement of warfarin and diazepam from human plasma proteins

In human plasma displacement in human plasma of both [14C]diazepam (0.1 and 1 µg/ml) and [14C] warfarin (1 and 5 µg/ml) by deferasirox was observed. In presence of 100 µg/ml of deferasirox (268 µM) the unbound fractions of [14C] diazepam and [14C] warfarin in human plasma were 3.4-3.6 % and 1.5-1.6 %, respectively, as compared to 2.3-2.4 % and 1.1-1.2 % in absence of deferasirox.

In vivo studies

A randomized, single centre, open-label, two-period cross-over study was conducted in 15 healthy male volunteers to determine the effect of a single 20 mg/kg oral dose of deferasirox on multiple dose digoxin pharmacokinetics (single oral dose of 0.5 mg on day 1 and day 22, and 0.25 mg oral dose once daily on day 2-8 and days 23-29). In terms of C_{max} and AUC, the 90% confidence intervals around the geometric mean ratio were within the limits of [0.8 - 1.25] with AUC ratio of 0.908, 90% CI [0.827-0.997] and C_{max} ratio of 0.933, 90% CI [0.822-1.059].

Discussion on clinical pharmacology

Clinical pharmacokinetics

The estimate of the absolute bioavailability of deferasirox from oral formulation was about 70% compared to an intravenous formulation. There was no correlation observed between the individual absolute bioavailability data and subjects' body weight, body height, or body surface area.
The possibility of two pathways working together (i.e. improved oral absorption and enhanced entero-hepatic recycling of drug once absorbed), provides a plausible basis that the increased oral bioavailability observed when taking the drug with a meal can exceed the absolute bioavailability established under fasting conditions. It is therefore recommended that deferasirox is taken on an empty stomach at least 30 minutes before food, preferably at the same time each day (see SPC, sections 4.2, 4.5 and 5.2). The bioequivalent exposure to deferasirox when tablets were dispersed in orange or apple juice was considered comparable with the exposure to deferasirox dispersed in water. No difference in bioavailability was observed whether the tablets were administered fully dispersed in water or non-dispersed (see SPC, sections 4.2).
Deferasirox has not been studied in patients with hepatic impairment and must be used with caution in such patients. The initial dosing recommendations for patients with hepatic impairment are the same as for adult patients (see SPC section 4.2). Hepatic function in all patients should be monitored before treatment then every month (see clinical section and SPC section 4.4). In the clinical studies, treatment has been initiated only in patients with baseline liver transaminase levels up to 6 times the upper limit of the normal range. Deferasirox is not recommended in patients with severe hepatic impairment, as it has not been studied in such patients (see section 4.4 and 5.2). Deferasirox has not been studied in patients with renal impairment and must not be used in patients with pre-treatment estimated creatinine clearance below < 60 ml/min (see clinical safety, SPC sections 4.2, 4.3 and 4.4). Age was not found to affect the pharmacokinetics of deferasirox in adult patients. The pharmacokinetics of deferasirox in geriatric individuals 65 years of age and older have not been investigated. However safety in the elderly population indicated no substantial difference from other age groups (see clinical safety). The dosing recommendations for elderly patients are the same as for adult patients. Since the SPC advises frequent assessments of renal and hepatic function with dose adjustments if necessary, it is considered to be sufficient for a physician to monitor and manage elderly patients. A clinical study is currently ongoing with deferasirox in elderly patients with myelodysplastic syndrome and transfusional iron overload, in which PK is being assessed. The dosing recommendations for paediatric patients (2 to 17 years of age) are the same as for adult patients (see SPC section 4.2). In children aged between 2 and 5 years, may require higher doses than are necessary in adults (see SPC section 5.2). However, the initial dose should be the same as in adults, followed by individual titration.
Glucuronidation was the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox was mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. A decrease of deferasirox plasma concentration cannot be excluded when administered with potent

UGT inducers such as rifampicin, phenobarbital or phenytoin. The patient's serum ferritin should be monitored during and after the combination, and the dose of deferasirox adjusted if necessary (see SPC section 4.5). The applicant has agreed to assess, post authorization, the magnitude of the effect of potent UGT inducers (such as rifampicin) on deferasirox plasmatic exposure.
Oxidative metabolism by CYP enzymes (hydroxylation) to M1 (presumably by CYP1A) and M4 (by CYP2D6) was a minor elimination process (about 8%). Therefore, any inhibition or induction of those enzymes by co-medications is not expected to significantly affect the pharmacokinetics of deferasirox.
Based on an *in vitro* study, the concentration of deferasirox leading to a CYP2C8 inhibition was close to the human concentration at a dose of 30 mg/kg/day. Although, CYP2C8 is not, quantitatively, the major isoenzyme of the cytochrome system, several compounds are mainly metabolised by this isoenzyme as paclitaxel or repaglinide. Due to the variability of deferasirox concentration and AUC after a dose of 30 mg/kg, a clinical drug-drug interaction study was requested to exclude the potential risk of interaction between deferasirox and CYP2C8 substrates. A clinical study in healthy volunteers to investigate a potential induction effect of deferasirox on single dose pharmacokinetics of midazolam is planned. Based on the results obtained, if inductive changes in midazolam exposure by deferasirox are observed, the applicant has committed to perform further studies with appropriate probe-substrates for each cytochromes (e.g. repaglinide with CYP2C8). Pending clarification, SPC section 4.5 mentions that an interaction between deferasirox and CYP2C8 substrates like paclitaxel and repaglinide can not be excluded.
In case of any interaction *via* CYP450 enzymes, the change in deferasirox pharmacokinetics would be negligible. Genetic polymorphism (*e.g.,* CYP2D6 poor metabolizer status) is not expected to have an impact either.
No inhibition of deferasirox metabolism by hydroxyurea was observed *in vitro*. Deferasirox was not P-gp dependent, but MRP2 and MXR, two multidrug resistance associated proteins, were involved in biliary excretion of deferasirox. Considering the compensatory elimination and excretory pathways, the therapeutic window and the slow mode of action of deferasirox, any relevant interactions on the transporter level when deferasirox is given concomitantly with other drugs are not expected. Combination of deferasirox with other iron chelator therapy has not been studied and is contra-indicated in view of the high potency of deferasirox and the increased risk of adverse effects associated with rapid or extensive chelation (see SPC section 4.3 and 4.5). Although deferasirox has a lower affinity for aluminium than for iron, it is not recommended to take deferasirox with aluminium-containing antacid preparations (see SPC section 4.4 and 4.5). Displacement of both warfarin, diazepam or other compounds binding to the same site on albumin cannot be excluded in patients treated with deferasirox. However, a clinically significant effect is very unlikely in case of warfarin and diazepam. No interaction was observed between deferasirox (20 mg/kg) and digoxin in healthy adult volunteers. The concomitant administration of deferasirox and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg per day have not been associated with adverse consequences (see SPC section 4.5).

Pharmacodynamics

- **Mechanism of action**

Deferasirox is an orally active iron chelator belonging to a new class of tridentate iron chelators, the N-substituted bis-hydroxyphenyl-triazoles. Deferasirox is claimed to mobilize tissue iron and promote its excretion, primarily in the feces (see non-clinical pharmacology).

- **Primary and secondary pharmacology**

In a randomized, double-blind, placebo-controlled, dose-escalation study (0104) the PK and cumulative iron balance (including urinary and fecal iron excretion) were assessed in 24 adult thalassemia patients receiving deferasirox, at doses of 10, 20 or 40 mg/kg, or placebo, during 12 days. The efficiency of chelation was based on average daily net iron excretion, and was calculated as the ratio between the amount of iron that could theoretically have been chelated, and the amount of iron actually excreted, relative to body weight. The theoretical amount of iron was obtained from the consideration that two molecules of deferasirox are needed to chelate a single atom of iron. The molecular weight of deferasirox is 373.4, and that of iron 55.85. Negative iron balance was achieved at all 3 doses of active drug, and averaged approximately 0.119 mg/kg/day at the 10 mg/kg dose,

0.329 mg/kg/day at the 20 mg/kg dose, and 0.445 mg/kg/day at the 40 mg/kg dose. The fraction of iron excreted in urine was on average for each active dose approximately 2-5% of the total.

In a randomized, open-label, phase II study (0105) was performed a to evaluate the effects on liver iron concentration of repeated doses of 10 and 20 mg/kg/day of deferasirox in comparison with 40 mg/kg/day deferoxamine in adult patients with transfusion-dependent iron overload. Hepatic iron stores (measured by means of SQUID) and urinary iron excretion (UIE) were examined in the exploratory analysis of the exposure-response relationships. AUC_{δ} and the trough concentrations for both deferasirox and its iron complex were the exposure PK parameters used in the PK/PD analysis. The relationships between the deferasirox chelation to iron *versus* dose were examined. There was a trend for patients with higher AUC values and patients with higher trough concentrations to show greater reductions in LIC from baseline. No PK/PD relationship could be established between the AUC and the changes in LIC. No PK/PD relationship could be established with the trough concentrations. No significant amounts of iron were found in urine and therefore, in contrast to DFO, UIE could not be used as an efficacy marker. The relationship between the total iron excretion and Cmax was more variable than with AUC, and thus the correlation was weak ($r2 = 0.464$, $P < 0.001$). There was a marked relationship between the total iron excretion and the trough concentrations ($r2 = 0.7378$, $P < 0.0001$).

Clinical efficacy

- Dose response studies

Two dose-finding trials were performed. Study 0104 was 12 days randomized placebo-controlled trial *versus* placebo, conducted in 23 frequently transfused adult patients with β-thalassemia, receiving deferasirox 10, 20, 40 mg/kg, and aiming at providing initial pharmacokinetic and pharmacodynamic data. This study was followed by a phase II (study 0105) multi-center, one-year, open-label, randomized controlled trial in 71 adult β-thalassemia patients in which surrogate markers for iron burden, such as serum ferritin, were explored and liver iron concentration (LIC) changes over a one year interval, were determined every 3 months by a non-invasive method [magnetic susceptometry by superconducting quantum interference device (SQUID)].

Study 0105 was used as the basis for the formulation of the dosing algorithm used in the pivotal and supportive studies of ICL670. Patients were randomized to receive oral deferasirox at doses of 10 or 20 mg/kg/day, or subcutaneous (s.c) infusions of DFO 40 mg/kg/day for five days each week (n= 24, 24 and 23, respectively). Patients were male or female, at least 18 years of age, with LIC values as determined by SQUID of 5 to 15 mg Fe/g dry weight (dw) at study entry. Dose adjustments were permitted during the additional phase of the trial if strongly indicated, based on clinical response.

The groups were well balanced for demographic characteristics at baseline. There were no protocol violations. The mean exposure time for the initial part of study was similar for the two deferasirox arms (10 mg/kg, 49 weeks; 20 mg/kg, 47 weeks) and slightly less for the DFO arm (45 weeks). In patients with LIC available at 12 months (per protocol population, PP) the mean LIC in the group treated with ICL670 10 mg/kg was 8.7 and 8.4 mg/g dw liver at baseline and 12 months respectively. The corresponding figures for the deferasirox 20 mg/kg and the DFO groups were 8.7 and 6.6, and 7.9 and 5.9 mg/g dw liver. A categorical analysis of the percentage change in LIC showed that the responder rates (>10% fall in LIC) were 73 % and 76 % in the groups treated with deferasirox 20 mg/kg and DFO, respectively, and 46% in patients treated with deferasirox 10 mg/kg. No consistent changes were seen in serum ferritin, iron, transferrin and transferrin saturation.

- Main study(ies)

Three study reports of clinical trials pertinent to the claimed indication were submitted. Study 0107 was a phase III randomised, active-controlled, open-label clinical trial to evaluate deferasirox in frequently transfused patients with β-thalassemia. Study 0108 was a phase II open-label trial to evaluate deferasirox 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. Study 0109 was a phase II

randomised, active-controlled, open-label trial to evaluate the safety of deferasirox in patients with sickle cell disease (SCD) and transfusional hemosiderosis requiring chelation therapy.

Study 0107

METHODS

Study Participants

This was a multicenter, randomised, active-controlled phase III clinical trial. The main inclusion criteria were patients older than 2 years, with β-thalassemia and transfusional hemosiderosis, 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 (≥ 8 transfusional events per year). The main exclusion criteria were: transfusion-dependent anemias other than β-thalassemia; 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 enrolment, including measurements during the run-in) and ALT or AST variations >300% (CV of mean value) during 12-months preceding enrolment; clinical evidence of active hepatitis C; serum creatinine above the upper limit of normal (ULN); significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 (mg/mg) in a 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 > 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; 2nd or 3rd degree A-V block, Q-Tc interval prolongation, cataract or a history of relevant ocular toxicity related to iron chelation; pregnant or breast-feeding patients; pediatric patients body weight which prevented the use of the smallest tablet strength for dosing.

Treatments

Deferasirox tablets were to be dispersed in a small glass of water and taken daily every morning 30 minutes before breakfast. DFO was selected as the active comparator since it was the reference chelator in patients with transfusional hemosiderosis. DFO was administered as s.c. infusions for ≥8 hours at doses between 20 and 60 mg/kg/day for five consecutive days/week.

The initial dose of deferasirox or DFO was dependent on the LIC determined at screening: patients with a screening LIC of 2 - 3 mg Fe/g c dry weight (dw) received deferasirox 5 mg/kg or DFO 20-30 mg/kg/day; patients with a screening LIC of >3 - 7 mg Fe/g dw received deferasirox 10 mg/kg or DFO 25-35 mg/kg/day; patients with a screening LIC of >7-14 mg Fe/g dw received deferasirox 20 mg/kg or DFO 35-50 mg/kg/day; patients with a screening LIC of >14 mg Fe/g dw received deferasirox 30 mg/kg or DFO ≥50 mg/kg/day.

The initial dose of deferasirox 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 deferasirox was 125 mg. Patients with a baseline LIC of 2-7 mg Fe/g dw were allowed to continue their previous doses of DFO, even if doses were greater than those specified above. The allowance regarding the weekly schedule was limited to at least three and up to seven days/week. The initial dose of DFO was to remain unchanged during the study period, provided that the evaluation of safety and efficacy markers did not indicate that a dose adjustment was needed.

Dose adjustments for both deferasirox and DFO were based on the combined evaluation of safety markers indicative of over- or under-chelation. Secondary efficacy parameters (potential surrogate markers such as serum ferritin) were also considered. The majority of deferasirox dose adjustments were to be performed in steps of 10 mg/kg/day up to a maximum of deferasirox 40 mg/kg/day. In individual cases (e.g. paediatric patients), if prompted by safety concerns, or where baseline LIC levels have 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 (see table 6).

Table 6: Average daily dose by LIC category in study 0107

	Baseline LIC in mg Fe/g dw (regardless of method)

	Baseline LIC in mg Fe/g dw (regardless of method)			
	<= 3	**>3-7**	**>7-14**	**>14**
deferasirox (N=296)	**N=15**	**N=78**	**N=84**	**N=119**
Protocol assigned 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 assigned 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

Objectives

The primary objective was to demonstrate non-inferiority of deferasirox compared to DFO in its effects on liver iron content (LIC) as assessed by liver biopsy after one year of treatment in patients with β-thalassemia and transfusional hemosiderosis. The main secondary objectives were to evaluate the safety profile of deferasirox, to estimate the absolute and relative change in LIC and total body iron excretion (TBIE) rate for subgroups [LIC (2 - <7 and ≥ 7mg 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 deferasirox as well as safety markers possibly indicative of over chelation.

Outcomes/endpoints

The primary endpoint was based on changes in LIC measured by liver biopsy or superconducting quantum interference device (SQUID), a noninvasive technology and in a subset of patients by liver biopsy and MRI [12, 13] , in pediatric patients or those with contraindication to liver biopsy; the success rate was determined and analyzed primarily for the PP-1 population, i.e. all patients who had either LIC measurements at baseline and EOS using liver biopsy or SQUID, or who discontinued due to safety reasons. The primary endpoint was based on the following success criteria:

Table 7: Succes rate for the primary endpoint in study 0107

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

Liver samples for iron content and pathology studies were obtained by ultrasound-guided percutaneous biopsy of the center of the right lobe of the liver [14] . Iron quantification was performed in a central laboratory using atomic absorption spectrometry [15]. All patients who were randomized were included in the intent to treat population (ITT). Patients in the per protocol (PP) population for the primary efficacy analysis (PP-1) were those that had received study drug and who had an LIC determination at baseline and at EOS, using the same technique as at baseline. Also included were patients who had to permanently discontinue study medication due to any of the following: adverse event; abnormal laboratory value; abnormal test procedure results; iron overload related death. Patients prematurely discontinued due to any other reason were excluded from this population. Secondary endpoints measures included absolute and relative change in LIC, total body iron excretion (TBIE) and surrogate markers of efficacy and iron metabolism including serum iron, ferritin, TRF and TRF saturation as well as liver pathology evaluations in patients with biopsy. For the

secondary efficacy parameters, the PP population (PP-2) was used and included patients for whom an LIC determination at EOS was available, using the same technique as at baseline.

Sample size

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 deferasirox treatment arms (probability of success =0.5) have 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. The power calculations (non-inferiority margin: 0.15) at different success rates (0.6, 07 and 08) in the ICL670 and DFO arm was 92.8%, 95.5% and 98.7% respectively.

Randomisation

Patients were assigned a sequential patient number in each center. Eligible patients were randomized in a 1:1 ratio to receive either oral dereasirox once daily, or s.c. infusions of DFO on five consecutive days each week, using an interactive voice response system. Randomization was stratified by age groups: 2 to <12 years, 12 to <18 years and >=18 years.

Blinding (masking)

Study 0107 was an open-label study as it was considered impractical and unethical to use blinding which would have required the long-term self-administration of a parenteral placebo in patients randomized to deferasirox.

Statistical methods

Non-inferiority was to be shown if the 2-sided 95% CI (using normal approximation) of the difference in success rate between deferasirox and DFO was above -15% in the PP-1 population. For groups of less than 12 patients, exact CIs were calculated using Pearson-Clopper limits. To test the reduction in LIC in patients on deferasirox with a baseline LIC of >=7 mg Fe/g dw, Student's t-test at a one-sided alpha level of 0.025 was used. For comparison of LIC reduction between patients treated with deferasirox and DFO, a covariance model with baseline value as covariate, and treatment-group as main effect was fitted.
Additional analyses were done for efficacy and safety assessment for the following subgroups: Age category: (<6 years, 6-<12 years, 12-<16 years, 16-<50 years, 50-<65 years, >=65 years) based on derived age at visit 1; gender (Male/Female); ethnic groups (Caucasian, Black, Oriental, Other); country; dose cohort (the initial dose recorded in the eCRF): 5 mg/kg deferasirox / < 25 mg/kg DFO, 10 mg/kg deferasirox / 25 - <35 mg/kg DFO, 20 mg/kg deferasirox / 35 - <50 mg/kg DFO, 30 mg/kg deferasirox / >= 50 mg/kg DFO; baseline LIC category, by method: <7 mg Fe/g dw (SQUID), <7 mg Fe/g dw (Biopsy), >=7 mg Fe/g dw (SQUID), >=7 mg Fe/g dw (Biopsy).
The following subgroups were used for additional efficacy analyses: average planned daily dose during study: <7.5 mg/kg ICL670 / < 25 mg/kg DFO, 7.5 - <15 mg/kg ICL670 / 25-<35 mg/kg DFO, 15 - <25 mg/kg ICL670 / 35-<45 mg/kg DFO, >=25 mg/kg ICL670 / >=45 mg/kg DFO; average iron intake category: none, >0 and <0.4 mg Fe/kg/day; 0.4 and <=0.5 mg Fe/kg/day; >0.5 mg Fe/kg/day; baseline LIC category: < 7 mg Fe/g dw or >=7 mg Fe/g dw; baseline LIC method: SQUID or biopsy; baseline LIC dosing category: <=3 mg Fe/g dw; >3 - 7 mg Fe/g dw; >7 - 14 mg Fe/g dw; >14 mg Fe/g dw.

RESULTS

Participant flow

A total of 591 were randomized (297 in the deferasirox arm; 294 in the DFO arm); of these, 5 patients never started treatment. Of the 586 patients who started treatment (296 in the deferasirox arm; 290 in the DFO arm), premature discontinuation occurred in 17 patients receiving deferasirox and 12 receiving DFO. The reasons for discontinuation are provided in table 8.

Table 8- Patient disposition in study 0107 and reasons for discontinuation

Disposition	deferasirox 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)

The number of patients included in the PP-1 population was 276 in the deferasirox arm and 277 in the DFO arm. There were 20 patients in the deferasirox arm and 13 patients in the DFO arm excluded from PP-1 population (11 *vs* 5 due to not available LIC; 2 in both arms excluded for protocol violation; 7 *vs* 6 excluded for withdrawal of consent).

Recruitment

The first patient was randomized in February 2003 and the last one in November 2004.

Conduct of the study

Three amendments of the protocol were made during the study. Amendment 1 revised the exclusion criterion for the permitted level of proteinuria [urinary protein/creatinine ratios >0.5 (mg/mg) in a minimum of two urine samples]. In addition the amendment specified that treatment with deferasirox 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 deferasirox at the same dose. Amendment 2 introduced dose adjustments for patients on deferasirox in whom serum creatinine levels increased by >33% from baseline values at ≥2 consecutive visits. Amendment 3 added central ECG and quantitative QT/QTc analysis in order to comply with the ICH draft guideline E14 (2004) [16]. The amendment also retrospectively addressed changes to the liver biopsy procedures (most importantly, the sample weight threshold for the analysis of liver biopsies was reduced from 1 mg dw to 0.5 mg dw; the number of stains used in the pathology analysis was reduced to three; review by a second pathologist was eliminated).

Baseline data

Baseline demographic characteristics are provided by treatment, in the following table:

Table 9: Demographic characteristics (study 0107, PP-1 population)

Variable / Statistic	Deferasirox (N=276)	DFO (N=277)	All patients (N=553)
Age (years)			
N	276	277	553
Mean ± SD	16.7 ± 9.26	16.9 ± 9.84	16.8 ± 9.55
Median	15	15	15
Min - Max	2 – 49	2 - 53	2 – 53
Age group (years)			
< 6	28 (10.1%)	28 (10.1%)	56 (10.1%)
6 - < 12	63 (22.8%)	67 (24.2%)	130 (23.5%)
12 - < 16	57 (20.7%)	49 (17.7%)	106 (19.2%)
16 - < 50	128 (46.4%)	132 (47.7%)	260 (47.0%)
50 - < 65	0 (0.0%)	1 (0.4%)	1 (0.2%)
Sex			
Male	130 (47.1%)	138 (49.8%)	268 (48.5%)
Female	146 (52.9%)	139 (50.2%)	285 (51.5%)
Race			
Caucasian	245 (88.8%)	239 (86.3%)	484 (87.5%)
Black	2 (0.7%)	1 (0.4%)	3 (0.5%)
Oriental	9 (3.3%)	10 (3.6%)	19 (3.4%)
Others	20 (7.2%)	27 (9.7%)	47 (8.5%)
Height (cm)			
N	275	277	552
Mean ± SD	144.9 ± 20.76	144.4 ± 21.55	144.6 ± 21.14
Median	150	149	150.0
Min – Max	84 - 186	84 - 181	84 - 186
Weight (kg)			
N	275	277	552
Mean ± SD	42.8 ± 16.61	42.4 ± 16.71	42.6 ± 16.65
Median	43.5	44.8	44.1
Min – Max	11.4 – 87.9	12.0 – 90.2	11.4 – 90.2
Weight group (kg)			
<15	7 (2.5%)	8 (2.9%)	15 (2.7%)
15 - <35	86 (31.2%)	87 (31.4%)	173 (31.3%)
35 - <55	114 (41.3%)	111 (40.1%)	225 (40.7%)
55 - <75	60 (21.7%)	66 (23.8%)	126 (22.8%)
≥75	8 (2.9%)	5 (1.8%)	13 (2.4%)

Of the 586 patients treated, 15 (2.6%) were chelator naïve: 7 patients on the deferasirox arm and 8 patients on the DFO arm. Five patients (2 on the deferasirox arm *vs*. 3 on the DFO arm) received prior deferiprone treatment in addition to DFO.

Numbers analysed

The number of participants in each group included in each analysis is provided in Table 10.

Table 10: Number (%) of patients in analysis populations

Analysis Population	Deferasirox 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)

Outcomes and estimation

Primary efficacy results

As shown in the table 11, the results of study 0107 obtained in the PP-1 population did not show that deferasirox is non-inferior to DFO in reducing or maintaining LIC levels, with a difference in success rates of -13.5 [-21.6, -5.4].

In a open label subgroup analysis of 381 patients with LIC ≥ 7 mg Fe/g dw, the difference was -0.3 [-10.2, 9.6] and thus non-inferioritiy was achieved when comparable doses were used.

Table 11 - Success rates based on change in LIC (study 0107, PP-1 population)

	Deferasiro x 5 mg/kg N=15	**Deferasiro x 10 mg/kg N=70**	**Deferasiro x 20 mg/kg N=79**	**Deferasiro x 30 mg/kg N=112**	**Deferasiro x all patients N=276**	**DFO all patients 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,

	Deferasiro x 5 mg/kg N=15	Deferasiro x 10 mg/kg N=70	Deferasiro x 20 mg/kg N=79	Deferasiro x 30 mg/kg N=112	Deferasiro x all patients N=276	DFO all patients N=277
						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]

Abbreviations: CI = confidence interval; DFO = deferoxamine; LIC = liver iron content; SQUID = superconducting quantum interference device.

Secondary efficacy results

Results of secondary efficacy analysis of study 0107 are provided in tables 12,13,14.

Table 12 - Absolute changes in LIC, serum ferritin, and iron balance (PP-2 and safety populations)

LIC in mg Fe/g dw	Median dose mg/kg/day Deferoxamine / DFO		Iron burden at end of study (based on available values)	n	Mean ± SD deferoxamine	n	Mean ± SD DFO
LIC <= 3	5	30	Change in serum ferritin (µg/l)	15	+1189 ± 700	13	+211 ± 459
			Change in LIC (mg Fe/g dw)	15	+4.8 ± 3.77	13	+0.5 ± 1.11
			Ratio iron excretion/intake	15	0.58 ± 0.328	13	0.95 ± 0.101
LIC >3-7	10	35	Change in serum ferritin (µg/l)	73	+833 ± 817	77	+32 ± 585
			Change in LIC (mg Fe/g dw)	68	+3.8 ± 3.85	75	0.0 ± 2.36
			Ratio iron excretion/intake	68	0.67 ± 0.365	75	0.98 ± 0.217
LIC >7-14	20	41	Change in serum ferritin (µg/l)	80	-36 ± 721	89	-364 ± 614
			Change in LIC (mg Fe/g dw)	77	-0.4 ± 4.70	87	-1.9 ± 2.93
			Ratio iron excretion/intake	77	1.02 ± 0.398	87	1.13 ± 0.241
LIC >14	30	51	Change in serum ferritin (µg/l)	115	-926 ± 1416	101	-1003 ± 1428

LIC in mg Fe/g dw	Median dose mg/kg/day Deferoxamine / DFO	Iron burden at end of study (based on available values)	n	Mean ± SD deferoxamine	n	Mean ± SD DFO
		Change in LIC (mg Fe/g dw)	108	-8.9 ± 8.07	98	-6.4 ± 6.93
		Ratio iron excretion/intake	108	1.67 ± 0.716	98	1.44 ± 0.596

Table 13 - Change in LIC in patients with LIC >= 7 mg Fe/g dw at baseline (PP-2 population)

Statistics	deferoxamine N=185	DFO N=186	Difference (deferoxamine - 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)**

* 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 no significant difference in absolute change in LIC between patients (with LIC >= 7 mg Fe/g dw at baseline) treated with ICL670 and DFO.

Table 14 summarises the iron excretion (based on LIC measurements at baseline and EOS) and the iron excretion/intake ratio by treatment group in the PP-2 population. There were no marked differences in these parameters between the treatment groups.

Table 14 - Iron balance during treatment (study 0107, PP-2 population)

	Deferasirox N=268	DFO N=273
Biopsy	**n=224**	**n=230**
Average iron intake (mg/kg/day)		
Mean ± SD	0.38 ± 0.109	0.40± 0.113
Minimum - Maximum	0.13 - 0.71	0.17 – 0.80
P25 - P75	0.30- 0.47	0.32 - 0.47
Median	0.37	0.38
Average iron excretion rate (mg/kg/day)		

Mean ± SD	0.45 ± 0.252	0.47 ± 0.194
Minimum - Maximum	-0.16 - 1.3	-0.18 - 1.36
P25 - P75	0.27 - 0.62	0.35 - 0.57
Median	0.43	0.47
Ratio Fe excretion/Fe intake		
Mean ± SD	1.21 ± 0.745	1.21 ± 0.476
Minimum - Maximum	-0.78 - 4.47	-0.55 - 3.78
P25 - P75	0.71 -1.64	0.96 - 1.39
Median	1.07	1.14
SQUID	**n=44**	**n=43**
Average iron intake (mg/kg/day)		
Mean ± SD	0.40 ± 0.097	0.44± 0.107
Minimum - Maximum	0.17 – 0.63	0.23 – 0.82
P25 - P75	0.34- 0.46	0.36 - 0.51
Median	0.38	0.43
Average iron excretion rate (mg/kg/day)		
Mean ± SD	0.36 ± 0.085	0.46 ± 0.113
Minimum - Maximum	0.14 - 0.53	0.18 - 0.81
P25 - P75	0.31 - 0.42	0.39 - 0.53
Median	0.37	0.49
Ratio Fe excretion/Fe intake		
Mean ± SD	0.95 ± 0.24	1.05 ± 0.145
Minimum - Maximum	0.44 - 1.64	0.80 – 1.45
P25 - P75	0.81 -1.06	0.96 - 1.13
Median	0.91	1.02

Serum ferritin levels mirrored the changes observed with LIC. In patients treated with deferasirox 5 or 10 mg/kg in whom LIC increased, ferritin levels also increased progressively. In deferasirox patients treated at 20 mg/kg, LIC and ferritin levels remained stable, and in patients treated at 30 mg/kg there was a fall in both LIC and serum ferritin.
In DFO-treated patients, ferritin behaved in a similar way. At lower doses, ferritin levels remained relatively constant and in patients treated with doses of >=50 mg/kg, a progressive fall in ferritin was observed (data not shown).
An increase in serum iron was observed during the study in the highest dose category for both treatments. Although the variability of TRF concentrations was high, there were small increases in TRF concentrations in both treatment groups during the study, accompanied by a slight increase in TRF saturation.

- Supportive studies

Study 0108

This study was a multi-center, open-label, non-comparative phase II trial designed to evaluate the efficacy/safety of deferasirox in pediatric and adult patients with congenital and acquired anemia complicated by chronic iron overload who could not be appropriately or adequately treated with DFO. The study population included β-thalassemia patients unable to be adequately treated with DFO (n=85) and patients with various rare chronic anemias (n=99).

Deferasirox treatment was as detailed in study 0107. The primary efficacy assessment was liver iron content (LIC). The success rate was determined based on changes in LIC; (for secondary assessment: see study 0107). The primary objective of the study was to evaluate the effects of deferasirox treatment on LIC as assessed by liver biopsy (or SQUID) after one year treatment. Effective chelation with deferasirox in patients with either β-thalassemia unable to be adequately treated with DFO or with rare anemias was defined to be established if the success rate was above 50%.

The rare anemia stratum included patients with myelodysplastic syndrome (MDS, n=47), Diamond-Blackfan anemia (DBA, n=30), 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). Thirty-two patients discontinued prior to the completion of the 1-year study period [8 patients with β-thalassemia (4 adverse events; 4 withdrew consent) and 24 patients with rare anemias (9 adverse events, 5 deaths, 6 withdrew consent, 4 study drug no longer needed0]. The median daily dose during study was 26.9 mg/kg for patients with β-thalassemia and 21.0 mg/kg for patients with rare anemias. About 50% of patients required dose adjustments at least once during study.

In the ITT population, the success rate was significantly higher than 50%. In the PP-1 population the success rate was significantly higher than 50% in patients whose LIC was ≥ 7 mg Fe/g dw (biopsy + SQUID) at baseline. The same was observed in the ITT population with a baseline LIC >=7 mg Fe/g dw measured by biopsy (see table 15).

Table 15 - Success rates based on change in LIC (study 0108, 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)

Changes in LIC in patients [N=126 (β-thalassemia n=67 and rare anemias n=59)] with LIC available by either method (Biopsy and SQUID) at EOS (PP-2 population) and baseline LIC ≥ 7 mg Fe/g dw, showed a statistically significantly reduction in LIC (Mean ± SD = - 5.5 ± 7.37, p<0.001).

Changes in ferritin mirrored LIC changes. In patients with β-thalassemia or DBA treated with deferasirox 5 or 10 mg/kg, ferritin levels increased progressively, whereas ferritin levels remained constant or fell progressively with doses of 20 and 30 mg/kg respectively. For patients with MDS or other rare anemias, who had a lower average iron intake during study, constant levels of LIC and ferritin were observed with a dose of 10 mg/kg, and 20 mg/kg introduced an overall reduction of iron burden. Liver pathology showed no change in liver fibrosis in either disease group. In both groups, there was a decrease in Ishak grading [17] indicating a decrease in necro-inflammatory activity, most apparent in patients treated with deferasirox 30 mg/kg. Semi-quantitative assessment of changes in regional hepatic iron showed reductions in total and regional iron of similar magnitude in both disease groups.

Study 0109

A randomized, multicenter, open label, phase Il study designed to evaluate the safety, tolerability, pharmacokinetics and the effects on liver iron concentration of repeated doses of 10 mg/kg/day of deferasirox relative to deferoxamine in sickle cell disease (SCD) patients with transfusional hemosiderosis.

For treatment, see study 0107. Efficacy was a secondary objective and was assessed by estimating absolute and relative LIC change as well as the TBIE rate. LIC was assessed by SQUID. All patients

underwent a baseline SQUID assessment which was repeated at 24 and 52 weeks. In addition, a subgroup of 30 patients was planned to undergo liver biopsy at screening and 52 weeks and MRI at screening, 24 and 52 weeks. The goal of these additional assessments was to calibrate the LIC assessments obtained by SQUID with biopsy and MRI data. PK profiles were collected from patients receiving deferasirox in this subgroup. Independent of the randomized chelation therapy all patients in selected centers were potentially eligible to undergo liver biopsy and MRI as an additional method for LIC assessment until the required patient number had been reached. If a patient agreed to undergo the additional procedure he/she was included in this subgroup.
An average dose of about a 2:1 ratio were received by all 4 dose treatment groups. A significant reduction in LIC was observed in patients receiving deferasirox and with LIC ≥7 mg Fe/g dw at baseline. The difference in response to deferasirox or DFO treatment was not statistically significant (p=0.669, PP-2 population). The results were confirmed in the PP-1 population. In patients with sickle cell disease and baseline LIC <7 mg Fe/g dw, who received the lower doses of deferasirox and DFO, maintenance of mean LIC was observed.

- Discussion on clinical efficacy

The patients included in the main dose finding study had a liver iron concentration (LIC) >7mg Fe/g dry weight (dw), as measured by the SQUID method. In severely overloaded patients (taking into account the SQUID initial screening), the 20 mg/kg/day dosage was effective to reverse iron overload, which was not the case with the 10 mg/kg/day dosage. The 20mg/kg/day dosage was therefore selected in severely iron overloaded patients for efficacy studies.
The choice of the primary endpoint of the pivotal study, based on a success/failure criterion was supported by the literature. The primary objective could be interpreted as 1) prevention of increase of LIC above 7 mg Fe/g dw in patients with a LIC under this limit at baseline, and 2) decrease of LIC to a value <7 mg Fe/g dw in patients with a LIC above this limit at baseline. The possible loss of information using such categorical endpoint was acknowledged, as very different situations could be defined as "success" (e.g. a patient showing a LIC decrease from 6.9 to 1.0 mg Fe/g dw and a patient showing a LIC increase from 2.0 to 6.9 mg Fe/g dw).
Inclusion criteria and dose attribution were based on LIC, a parameter of limited availability in clinical practice. Posology and dose adjustment recommendations [based on patient's response and therapeutic goals (maintenance or reduction of iron burden)] are provided in the SPC, based on monitoring of serum ferritin (see SPC section 4.2 and 4.4) and in line with the SPC of the reference product. This proposal was considered acceptable from a practical point of view. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment is recommended.
It appeared during the pivotal trial that SQUID method underestimated LIC by 50% as compared to the actual values obtained from liver biopsy. The discrepancy was considered of limited impact as far as relative (percent) variations of LIC were assessed. However, absolute values of LIC and of LIC decreases were underestimated (errors in baseline categorization; false assessments of absolute LIC variations and of success/failure detection). Even if a limited number of patients were evaluated with the SQUID method (including children and patients with contra-indication to liver biopsy), the reliability of the clinical results was questioned.
The primary analysis of the overall PP-1 population failed to meet the prospectively defined criterion to establish non-inferiority based on the comparison of success rates in the PP-1 population (difference and 95% CI: -13.5 [-21.6, -5.4]). In a sub-group analysis of patients with baseline LIC levels ≥ 7 mg Fe/g dw, overall success rates were comparable (58.6% vs. 58.9%) and the lower limit of the 95% confidence interval (-10.2%) was above the predefined non-inferiority threshold of -15%.
Treatment adjustment, as described in the protocol and applied in the pivotal study, resulted in imbalance dosages that may have favoured the results in patients (especially in the less severely overloaded patients) treated with DFO: Patients receiving DFO before inclusion and randomized in the DFO group, could receive their pre-inclusion posology as soon as a dose increase was considered necessary. Therefore, the actual dose of DFO often exceeded the dose initially allocated, whereas patients allocated to deferasirox had to follow a pre-established schedule that produced limited dose increase as compared to the initial planning. These doses adjustments precluded a fair comparison between the two treatments and could partly explain why deferasirox failed to demonstrate non inferiority to DFO, especially in less overloaded patients.

Target organ damages have not been evaluated. Cardiologic consequences of iron overload being a major prognostic factor, the applicant has committed to further investigate, post-authorisation, the effect of deferasirox on cardiac iron overload and cardiac function.
Ten percent of the patients included in the pivotal trial were under 6 years of age. The efficacy results in this sub-group did not differ from the results observed in the general population. However, the applicability of the results observed in the whole population to children was questioned. Various concerns were raised: difficulty to apply the claimed non-inferiority to the small subgroup of very young children; the SQUID method was more frequently used in children than in adults [79/292 (27%) in patients under 16 years *versus* 11/261 (4%) after 16 years of age]. Among patients between 2 and 6 years of age, 9/56 (16%) were evaluated by SQUID; the renal disorders observed in the overall population (see clinical safety) remained a concern in very young patients.

Clinical safety

- Patient exposure

The key studies supporting the safety claim included data obtained in 1005 patients with transfusional hemosiderosis in various diseases (β-thalassemia, rare anemias, SCD) and derived from the four main safety and efficacy studies (0106, 0107, 0108, 0109).
Of these patients, 652 received deferasirox and 353 received deferoxamine (DFO). Among them, 488 (46.7%) were paediatric patients < 16 years of age. In patients receiving deferasirox, 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.
More than 93% of patients with β-thalassemia received deferasirox for ≥48 weeks and the mean exposure was about one year [Mean (± SD) = 51.6 ± 8.55]. Approximately 40% of patients were initially treated at the highest daily dose of 30 mg/kg and 17 of the 143 patients analyzed in the ≤10 mg/kg dose group received an initial dose of 5 mg/kg.
In the subgroups of patients with rare anemias (study 0108, n = 99), the initial dose of deferasirox was 5, 10, 20 or 30 mg/kg in 5 (5.1%), 11 (11.1%), 30 (30.3%) and 53 (53.5%) patients, respectively. About 70% of patients received study drug for ≥48 weeks, including 27 patients with MDS and 14 with other anemias. Thirty-three patients with MDS and 21 patients with other anemias received deferasirox for ≥24 weeks. In the subgroups of patients with SCD (study 0109, n = 195), 165 (84.6%) patients, including 114 (86.4%) on deferasirox, had received study drug for ≥48 weeks. Treatment duration in the core phase of study 0105 was three months and treatment could continue in an extension phase for a total duration of 48 weeks.

- Adverse events

Controlled studies

In study 0107, 500 patients developed AEs [254/296 (85.8%) in the deferasirox; 246/290 (84.8%) in the DFO group). General disorders were prominent among the DFO patients due to frequent reports of infusion site reactions. Gastrointestinal disorders (42.6% *vs.* 31.4%), skin and subcutaneous tissue disorders (22% *vs.* 15.5%), investigations (19.3% *vs.* 5.5%), hepatobiliary disorders (4.7% *vs.* 1.7%), psychiatric disorders (4.7% *vs.* 3.4%) were more frequent in the deferasirox group. The following AEs were reported more frequently in the deferasirox group: abdominal pain (13.9% *vs.* 9.7%), diarrhea (11.8% *vs.* 7.2%), nausea (10.5% *vs.* 4.8%), creatinine increased (11.1% *vs.* 0%), rash (8.4% *vs.* 3.1%), abdominal pain upper (7.8% *vs.* 5.2%), arthralgia (7.4% *vs.* 4.8%), acute tonsillitis (6.4% *vs.* 5.2%), fatigue (6.1% *vs.* 4.8%), dyspepsia (3% *vs.* 1.7%). Cholelithiasis, hepatitis and hepatic steatosis, ALT increased occurred more frequently in the deferasirox group compared to DFO group (respectively 1.7% *vs.* 0.7%; 0.7% *vs.* 0; 1% *vs.* 0; 2.0% *vs.* 0.3%). However, events such as viral infection, influenza like illness, pharyngitis, bronchitis, pyrexia, cough, headache, pharyngolaryngeal pain, back pain, asthenia, transfusion reaction, bone pain, epistaxis were more frequent in the DFO group. In study 0105, 68 patients reported AEs during [24 (100%) in the deferasirox 10 mg/kg/day group, 23 (95.8%) in the deferasirox 20 mg/kg/day group and 21 (91.3%) in the DFO group]. The respiratory system (87.5% in the deferasirox 10 mg/kg/day arm, 62.5% in the deferasirox 20 mg/kg/day arm, 56.5% in the DFO arm), including pharyngitis, rhinitis, pharyngolaryngeal pain, bronchitis, cough and the gastrointestinal system (respectively 70.8%, 58.3%, 47.8%) were the system

the most frequently affected, followed by general disorders (54.2%, 58.3%, 47.8%), infections (75%, 45.8%, 52.2%), and musculoskeletal complaints (50%, 50%, 52.2%). The frequency of skin/subcutaneous disorders was similar between groups (respectively 20.8%, 20.8%, 21.7%). Investigations were more frequently reported in the deferasirox groups and mainly concerned renal function tests abnormalities reported in the deferasirox 20mg/kg/day group (2 cases of β-2microglobulin increased, 3 cases of urinary β-2microglobulin increased, one case of blood creatinine increased, one case of creatinine renal clearance decreased *vs.* 0 in the others).

Adverse reactions ranked by frequency, are provided in table 16

Table 16: Adverse reactions among clinical trial (presented in order of decreasing seriousness)

Psychiatric disorders	
Uncommon:	Anxiety, sleep disorder
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness
Eye disorders	
Uncommon:	Early cataract, maculopathy
Ear and labyrinth disorders	
Uncommon:	Hearing loss
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Pharyngolaryngeal pain
Gastrointestinal disorders	
Common:	Diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia
Uncommon:	Gastritis
Hepatobiliary disorders	
Common:	Transaminases increased
Uncommon:	Hepatitis, cholelithiasis
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus
Uncommon:	Pigmentation disorder
Renal and urinary disorders	
Very common:	Blood creatinine increased
Common:	Proteinuria
Uncommon:	Glycosuria
General disorders and administration site conditions	
Uncommon:	Pyrexia, oedema, fatigue

Convention: very common: > 1/10; common: > 1/100, < 1/10; uncommon: > 1/1,000, < 1/100.

Uncontrolled studies

In study 108, 181 patients reported AEs [84/85 (98.8%) in the group with β-thalassemia and 97/99 (98.8%) in the group with rare anemias]. Gastrointestinal disorders (respectively 71.8% and 72.7%), infections and infestations (70.6% and 65.7%), general and administration site disorders (48.2% and 48.5%) were the most frequently reported. A total of 73/184 (39.7%) patients developed mild creatinine increases at some point during the study. One of the patients treated at 5 or 10 mg/kg had a

transient 33% increase in creatinine, whereas the percentages affected in the 20 and 30 mg/kg groups were 48.1% and 44.3% respectively, and were similar in the disease groups. In the group of patients with rare anemias, 4 cases of renal failure, 3 cases of renal impairment two cases of cholelithiasis, two cases of cataract (one in each group), one case of sudden hearing loss were reported. Eleven cases of tachycardia (8 patients with β-thalassemia, 3 patients with anemias) and 9 cases of palpitations (5 patients with β-thalassemia, 4 patients with anemias) were observed.
In study 0106, involving paediatric patients with transfusion dependent β-thalassemia major (n=40) receiving repeated dose of 10 mg/kg of deferasirox during 48 weeks, 14 children < 12 years (70%), developed GI disorders compared to 11 adolescents (55%), 27.5% patients reported skin disorders and 12.5% reported transaminases increased. No growth disorders or sexual development failure occurred during this study.

- Serious adverse event/deaths/other significant events

In study 0107, 52 patients (8.9%) experienced serious adverse events (SAEs) [27 (9.1%) in the deferasirox group *vs*. 25 (8.6%) in the DFO group]. Four deaths were reported during the study [1 in the deferasirox group (0.3%) *vs*. 3 in the DFO group (1%)]. In study 0109, 67 patients (34.8%) experienced SAEs [46 (34.8%) in the ICL670 group *vs*. 21 (33.3%) in the DFO group]. Digestive disorders (abdominal pain, nausea, vomiting, one case of pancreatitis), investigations (mostly liver function tests disorders), skin disorders (skin ulcer, swelling face) were more frequent in patients receiving deferasirox. Two SAEs were considered related to deferasirox (acute pancreatitis; severe nausea). In study 0105, 12 patients (16.9%) experienced SAEs [4 (16.7%) in the deferasirox 10mg /kg/day group vs. 3 (12.5%) in the deferasirox 20mg /kg/day group and 5 (21.7%) in the DFO group]. No cases were considered drug-related. During the extension phase (n = 67), 5 patients reported 8 serious adverse events, including one case of QTc prolongation in one patient receiving deferasirox, one case of nephrolithiasis and one case of transaminases increased in patients receiving DFO. In study 0108, 38 patients (20.7%) experienced SAEs [11 in patients with β-thalassemia and 27 in patients with rare anemias], of which 6 cases were considered to be drug related (including 1 case of abdominal pain with a positive rechallenge, 1 case of skin rash, 1 case of dizziness, vomiting, hypotension and arrhythmia which led the investigator to switch to DFO, 1 case of loss of consciousness). In study 0106, 1 serious case of pancreatitis and one serious case of cholelithiasis were reported in two adolescents.

Other significant events

Renal disorders: Table 17 summarizes the data from studies 0105, 0106, 0107, 0108 and 0109 on renal disorders.

Table 17- Renal disorders (studies 0105, 0106, 0107, 0108 and 0109):

	Study 107		**Study 109**		**Study 105**		**Study 108**	**Study 106**
	deferasirox N = 296 n(%)	DFO N=290 n(%)	deferasirox N=132 n(%)	DFO N=63 n(%)	deferasirox N=48 n(%)	DFO N=23 n(%)	deferasirox N=184 n(%)	deferasirox N=40 n (%)
Renal disorders	9 (3.0%)	10 (3.4%)	9 (6.8%)	1 (1.6%)	8 (16.7%)	4 (17.4%)	29 (15.8%)	1 (2.5%)
Serum creatinine increases > 33%	113 (38.2%)	41 (14.2%)	32 (24.2%)	4 (6.3%)	NA	NA	54 (29.3%)	0
Serum creatinine increases > 33% and > ULN	**7 (2.4%)**	**1 (0.3%)**	1 (0.8%)	2 (3.2%)	NA	NA	19 (10.3%)	1 (2.5%) > ULN, but < 33%
Renal SAEs	0	2 (0.7%)	0	0	2 (4.1%)	0	2 (1.1%)	0

Withdrawal due to renal AEs	0	0	0	0	0	0	1 (0.5%)	0
Dose interruption / adjustment due to renal AEs	2 (0.6%)	1 (0.3%)	0	0	1 (2.1%)	0	8 (4.3%)	1 (2.5%)
Dose interruption / adjustment due to serum creat. increased	**33 (11.1%)**	**0**	4 (3.0%)	0	1 (2.1%)	0	32 (17.4%) 5 patients discont.	0
UPCR 0.2 - < 0.4 mg/mg UPCR 0.4 - < 0.6 mg/mg UPCR ≥0.6 mg/mg	126 (42.6%) 56 (18.9%) 55 (18.6%)	169 (58.3%) 42 (14.5%) 21 (7.2%)	60 (45.5%) 11 (8.3%) 14 (10.6%)	25 (39.7%) 3 (4.8%) 6 (9.5%)	NA	NA	80 (43.5%) 30 (16.3%) 27 (14.7%)	17 (42.5%) 3 (7.5%) 1 (2.5%)
Urinary β2 M increased Urin. β2M≥10000 µg/l	1 (0.3%) NA	0	NA	NA	3 (6.2%) 2 (4.1%)	0 0	NA	NA
Nephrolithiasis / renal colic	0	3 (1.0%)	0	0	8 (16.6%)	1 (4.3%)	3 (1.6%)	1 (2.5%)
Preoteinuria	2 (0.7%)	3 (1.0%)	2 (1.5%)	0	NA	NA	6 (3.2%)	0

A total of 36.3% of patients on deferasirox experienced serum creatinine increases > 33% at ≥2 consecutive visits. In most of the cases, the serum creatinine stayed into normal ranges. However, 2.4% of patients in study 107, 2.3% in study 109 and 10.3% in study 108 receiving deferasirox had serum creatinine post-baseline > ULN at ≥2 consecutive visits. This increase was dose-related and occurred mainly with daily doses of 20 and 30 mg/kg. Lower doses (5-10 mg/kg) were better tolerated.
More than 50% of patients treated with deferasirox and who did not underwent dose reduction, were still experiencing serum creatinine increases > 33% at the end of study.
In studies 107, 109 and 105, among patients treated with deferasirox, 68 had dose reduction/adjustment due to serum creatinine increased. The study protocols did not require dose reductions for patients on DFO who experienced serum creatinine increases.

In 41.2% of patients (28/68), a dose reduction led to a decrease of the serum creatinine. However, in all these cases but two, the values remained higher compared to baseline, with the reduced dose.
In 50% of patients (33/68), the serum creatinine values remained stable after dose reduction, without decreasing. In 7 patients, some values remained therefore > ULN after dose reduction. In 7 patients, the serum creatinine values tended to increase later after dose was decreased.
In some pateints, a progressive increase in serum creatinine led to drug interruption. In 17 cases, the consequences of the interruption could not be evaluated, as the treatement was interrupted for a few days only.
In 8 patients, the interruption of treatment was longer (from 20 to 110 days): In one case, the first interruption led to a decrease of the serum creatinine to a value similar to baseline within 23 days. However, following the second interruption (three weeks), serum creatinine values remained higher compared to baseline values (+30%). In two cases, treatment interruptions were decided due to values

> ULN at 20 mg/kg dose. The values decreased after dose interruption; the values normalised in one situation, during the extension study at a lower dose (15 mg/kg), and after 40 days of drug interruption, in the other situation. In four cases, the serum creatinine decreased after dose interruption but remained >ULN. In one case, the serum creatinine values decreased after dose interruption, however, the patient experienced one value >ULN on day 95 following the interruption.
At the end of study, 63% of patients had more than 30% serum creatinine increased compared to baseline and 30% of patients had a 50% serum creatinine increase.
Urinary β2M (ULN < 100 µg/l) and the urinary protein/creatinine ratio (UPCR), which quantifies the proteinuria (ULN < 0.2 mg/mg) were also modified in patients receiving deferasirox.
Renal colic/nephrolithiasis were reported more frequently in patients treated with deferasirox (8/48 (16.6%)) than in patients treated with DFO (1/23 4.3%)) in the comparative study 105. these events were reported with equal frequency in the two remaining comparative studies 107 and 109".
Proteinuria, dysuria and nephropathy were also observed. Protein electrophoresis was not performed. Markers of tubular function (such as uricemia, kalemia, phosphoremia, glycosuria) and glycemia were measured in all studies. These results showed no clinically relevant abnormalities except a minimal (on average, a 5% reduction from baseline) in uric acid.

The explanation provided by the applicant for the mild, stable increase in creatinine (and cystatin C) in patients treated with deferasirox is a reduction in GFR, possibly as a consequence of an effect on renal haemodynamics. The applicant hypothesised that these haemodynamic changes are induced by an excessively rapid rate of removal of iron (over-chelation). In some patients there appears to be removal of iron that greatly exceeds the intake of iron from transfusion which might lead to the removal of iron from iron-dependent enzymes and transporters that are associated with the regulation of kidney function.

Hepatobiliary disorders and liver function tests changes: Table 18 summarizes the data from studies 107, 109, 105 and 108 on liver disorders. In study 106, transaminases increases were reported in 12.5% of the patients, and one adolescent experienced one serious case of cholelithiasis.

Table 18: Liver disorders (studies 107, 109, 105 and 108):

	Study 107		**Study 109**		**Study 105**		**Study 108**
	Deferasirox N=296, n(%)	DFO N=290, n(%)	Deferasirox N=132, n(%)	DFO N=63, n(%)	Deferasirox N=48, n(%)	DFO N=23, n(%)	Deferasirox N=184, n(%)
Hepatobiliary disorders	14 (4.7%)	5 (1.7%)	7 (5.3%)	0	1 (2.1%)	0	10 (5.4%)
AST > 5 ULN at consecutive post-baseline visits	1 (0.3%	1 (0.3%)	1 (0.8%)	0	NA	NA	0
ALT > 5 ULN at consecutive post-baseline visits	17 (5.7%)	5 (1.7%)	5 (3.8%)	0	NA	NA	14 (7.6%)
Hepatobiliary SAEs	2 (0.7%)	0	1 (0.8%)	0	1 (2.1%)	0	2 (1.1%)
Deferasirox withdrawal due to hepatobiliary AEs	4 (1.4%)	0	0	0	0	0	0
Cholelithiasis	5 (1.7%)	2 (0.7%)	3 (2.4%)	0	0	0	2 (1.1%)

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DFO: Deferoxamine; SAEs: Serious adverse events; ULN: Upper normal limit.

Hepatobiliary disorders and liver function tests changes: The number of patients who reported jaundice and hyperbilirubinemia was higher in the group receiving 30 mg/kg of deferasirox. The LIC values at baseline were higher on average in this dose group. However, the relationship could not be established due to fluctuation of the bilirubin rates. Almost 2/3 of the patients in the deferasirox groups had elevations of transaminases during the study. There was a significant difference with the DFO group which was not in line with a possible normal fluctuations in a patient population with pre-existing liver disease. The difference was more evident when considering SGPT/ALT (70,8% *vs.* 33%). Cases of negative dechallenge, or one case of improvement after deferasirox dose increase, have been reported. In 2 cases positive dechallenges/rechallenge were reported. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). A similar number of patients receiving 5, 10, 20 or 30 mg/kg of deferasirox experienced hepatobiliary disorders, suggesting the absence of dose-effect. However, some events could be due to either the underlying disease or to insufficient iron chelation. Cholelithiasis is a known complication in patients with thalassemia [21] and sickle cell disease [18-20]. However, in clinical studies, the incidence of hepato-biliary adverse events occurring as cholecystitis, biliary colic, cholelithiasis was higher in deferasirox group than in DFO group [14/703 (2.0%) *vs.* 3/353 (0.8%)]; 9/14 (64%) cases were reported in patients aged ≤ 19 years.

ECG abnormalities and rhythm disorders: Nine cases (1.3%) of serious AEs involving ECG abnormalities or rhythm disorders were reported in patients treated with deferasirox compared to one reported with DFO (0.3%). The percentage of patients who experienced ECG abnormalities and rhythm disorders in study 107 (during one year of therapy) was 4.7% in the deferasirox group vs. 4.1% in the DFO group. In study 109, ECG abnormalities and rhythm disorders were reported in 9.8% of patients in the deferasirox group *vs*. 3.2% in the DFO group. The time to onset was 220 days (70-359) in deferasirox treatment group and 212 days (81-340) in DFO treatment group. In most cases, confounding factors were found as pre-existing cardiac diseases (including arrhythmias). Negative rechallenge and resolution without interruption of treatment were observed.

Skin disorders: A total of 52 patients (12.4%) in the pooled thalassemia population experienced a rash, which resolved spontaneously without interruption or discontinuation in 33 cases (63.5%). These rashes were generally of mild severity and resolved, on average, in less than one week. Nineteen patients (36.5%) who developed a skin rash in the pooled β-thalassemia population discontinued or interrupted the treatment.

Digestive disorders: Gastrointestinal disturbances were reported in about 26% of patients (mainly nausea, vomiting, diarrhoea or abdominal pain) during chronic treatment with deferasirox in adult and paediatric patients. Diarrhoea was reported more commonly in paediatric patients aged 2 to 5 years than in older patients. A few cases of ulcer, pancreatitis, GI haemorrhage, hematemesis, dyspepsia, gastritis were reported in patients receiving deferasirox. No serious cases of gastritis were reported. These reactions were dose-dependent, mostly mild to moderate, generally transient and mostly resolved even if treatment was continued.

Ophthalmologic and audiometric examinations: Lens opacities and signs of deafness have been observed at a similar frequency in deferasirox and DFO groups.

- Laboratory findings

See section on "*Other significant events*".

- Safety in special populations

Safety data in paediatric patients are reported as part of study 0106 results.

- Safety related to drug-drug interactions and other interactions

No safety related to drug-drug interactions studies were conducted.

- Discontinuation due to adverse events

In the pivotal study, 13 patients (2.0%) permanently discontinued therapy due to AEs [9 (2.7%) in the deferasirox group and 4 (1.4%) in the DFO group]. Therapy discontinuations were mostly due to skin and liver disorders. Temporary dose interruptions or dose adjustments due to AEs occurred in 92/296 (31.1%) patients receiving deferasirox *vs*. 54/290 (18.6%) patients receiving DFO [most common

reasons were blood creatinine increases and 3 cases of blood creatinine abnormal (12.5% *vs*. 0%), infections (6.8% *vs*. 8.9%), GI disorders (5.1% *vs*. 3.4%), skin disorders (5.1%, *vs*. 0.3%)]. A possible dose response effect for dose interruptions/adjustments was apparent for serum creatinine, with 2.6%, 8.3% and 20.2% of patients affected at 10, 20 and 30 mg/kg, respectively. In study 0109, 5 patients (2.6%) permanently discontinued therapy due to adverse events [4 (3.0%) in the deferasirox group and 1 (1.6%) in the DFO group]. Temporary dose interruptions or dose adjustments due to AEs occurred in 33/132 (25%) patients receiving deferasirox *vs*. 14/63 (22.2%) patients receiving DFO [most common reason were GI disorders (8.3% *vs*. 3.2%), *s*kin disorders (2.3% *vs*. 0%), hepatic and renal disorders (ALT increased: 0.8% and creatinine increased: 2.3% vs. 0%)]. In study 0105, 3 patients (4.2%) permanently discontinued therapy due to adverse events [1 (4.2%) in the deferasirox group vs. 2 (8.7%) in the DFO group]. Temporary dose interruptions or adjustments were mainly due to GI and renal disorders and occurred in 13 (54.2%) patients receiving deferasirox 20mg/kg/day vs. 6 patients (25.0%) receiving deferasirox 10mg/kg/day and 25 (35.2%) patients receiving DFO. In the extension phase, 3 patients receiving deferasirox discontinued treatment due to a severe reactivation of hepatitis infection, QT prolongation, increase in β-2 M. Five patients receiving deferasirox interrupted treatment (including 3 cases of drug-related elevated β-2 M to > 10,000 µg/l) vs. 2 patients receiving DFO. In study 0108, 18 patients (4 in the group with β-thalassemia and 14 in the group with rare anemias) discontinued deferasirox due to renal disorders (5 cases), GI disorders, skin rash or atrial fibrillation. Dose interruptions or adjustments were mainly [32/184 (17.4%) patients] due to increases in creatinine by at least 33% at two consecutive visits compared to the average of the baseline values.

- Post marketing experience

At the time of the submission, post-marketing experience on deferasirox was not available. Deferasirox was authorised in the US on 02 November 2005.

- User testing

The readability test of the package leaflet of Exjade (deferasirox) 125, 250 and 500 mg dispersible tablets was performed in English, in 20 subjects. The respondents were healthy volunteers or patients with sickle cell disease or thalassemia, aged between 18 and 63 years. Age, gender, socio-professional profiles and reading ability were taken into account; some respondents had English as a second language. The test received globally good results and the enlightened difficulties have conducted the applicant to perform several changes at each round of the evaluation to improve the readability. There were no question on the risks regarding the renal function but the test was performed before the SPC was modified. Overall, the test conformed to EMEA guidance and the results were considered satisfactory.

- Discussion on clinical safety

Serum creatinine increases of > 30% to > 90% occurred early, in general within the first month of treatement with deferasirox. There was a correlation between the increase of serum creatinine and the decrease of the creatinine clearance, which occured during the first four weeks of treatement.
Creatinine clearance decreases confirmed that deferasirox may cause renal dysfunction. In the pivotal study, 9.7% of patients (*vs.* 3.1% in the DFO group) experienced abnormal creatinin clearance (< 90 ml/min). Two of the three patients who had abnormal creatinine clearance at baseline experienced a worsening of their renal function test while receiving deferasirox. From week 52 to week 84 there was a further decrease in median levels of about - 7.5 ml/min.
No risk factors were identified regarding the age. The time course in creatinine clearance from the long-term study 108-108E showed similar effects across various underlying diseases. Only scarce information was provided in patients with renal impairment before initiation of deferasirox treatment. However, according to the US post marketing reports, which showed a worsening of the renal function in patients treated with deferasirox, the responsibility of deferasirox as a contributing factor could not be ruled out based on the chronology.
Serum creatinine values may decrease after dose reduction. However, in 50% of patients, the serum creatinine values only stabilized after dose reduction. This stabilisation may be transient, since further increases were observed. The outcome after dose discontinuation were difficult to assess as the duration of the interruption was often short (a few days). In a few cases, the duration was longer. The serum creatinine decreased slowly after drug interruption. However, the serum creatinine values remained > ULN in some cases.

Since deferasirox was resumed while serum creatinine was still > ULN in some patients, it was difficult to conclude regarding the reversibility of the renal events. However, in two patients, a decrease of serum creatinine with a value similar to the baseline value was observed.
Therefore, the data observed did do not allow to affirm the reversibility of the renal events associated with deferasirox after interruption of the treatment. A dose reduction did not systematically correspond to a decrease in serum creatinine.
Two fatal cases were spontaneously reported in the US. Both patients had an underlying disease: the first case of fatal renal failure occurred in a patient with acute lymphocytic leukaemia but had no history of renal disease and no concomitant nephrotoxic drugs. The second one developed sepsis with multi-organ dysfunction. Both cases occurred shortly after the initiation of the treatment with deferasirox and the fatal outcome occurred rapidly after the symptoms began;. Thus, a possible causal relationship to desferasirox cannot be excluded. Therefore it is recommended that serum creatinine be assessed in duplicate before initiating therapy. Serum creatinine, creatinine clearance (estimated with the Cockcroft-Gault or MDRD formula in adults and with the Schwartz formula in children) and/or plasma cystatin C levels should be monitored weekly during the first month after initiation or modification of the therapy, and monitored monthly thereafter (see SPC section 4.4). Guidance on dose reduction is provided in section 4.4 of the SPC for adult and paediatric patients. The applicant's hypothesis of overchelation, as a possible mechanism to explain the renal findings, was considered interesting but not sufficient to explain the renal disorders associated with deferasirox. Particular attention should therefore be paid to monitoring of serum creatinine in patients who are receiving high doses of deferasirox and/or low rates of transfusion (<7 ml/kg/month of packed red blood cells or <2 units/month for an adult). Particular attention should also be paid to monitoring of serum creatinine in patients who are concomitantly receiving medicinal products that depress renal function.

Important increases of ß2M observed during clinical trials suggested a tubular toxicity due to deferasirox. Markers of tubular function (such as uricemia, kalemia, phosphoremia, glycosuria) and glycemia were measured in all studies. These results showed no clinically relevant abnormalities except a minimal (on average, a 5% reduction from baseline) in uric acid.

Tests for proteinuria should be performed monthly. As needed, additional markers of renal tubular function may also be monitored. Dose reduction or interruption may be considered if there are abnormalities in levels of tubular markers and/or if clinically indicated. If, despite dose reduction and interruption, the serum creatinine remains significantly elevated and there is also persistent abnormality in another marker of renal function (e.g. proteinuria, Fanconi's Syndrome), the patient should be referred to a renal specialist, and further specialised investigations, such as renal biopsy, may be considered (see SPC section 4.4).
The long term consequences of the renal toxicity of deferasirox are unknown. PSURs will be submitted every 6 months during the first two years and will contain a section on renal safety. Annual Safety Reports (ASRs) will be provided every 12 months for ongoing clinical trials with deferasirox and will include summaries on outcomes in patients whose dose was decreased due to creatinine increases. Reports to be provided every 18 months will contain full renal safety updates on the long-term studies (0105E2, 0106E, 0107E, 0108E and 0109E). Deferasirox is contra-indicated in patients with estimated creatinine clearance < 60ml/min.

Hepatobiliary disorders and liver function tests changes were more frequently observed in patients treated with deferasirox than DFO. These adverse effects occurred within a few months after therapy initiation and led in some cases to dose reduction, treatment interruption or study medication withdrawal. The elevation in transaminases was reported in patients treated with low doses of deferasirox and was intermittent or fluctuated. Cholelithiasis is a known complication in patients with thalassemia and sickle cell disease but the responsibility of deferasirox in the occurrence of cholelithiasis occurring in the patients treated was not excluded. It is recommended that that liver function tests be performed every month. Guidance on posology adaptation or interruption are provided in the SPC (see SPC, section 4.4 and 4.8).
Cardiac dysfunction is a known complication of severe iron overload. Cardiac function should be monitored in patients with severe iron overload during long-term treatment with deferasirox (see SPC section 4.4).
Skin rash occurred in about 7% of adult and paediatric patients during chronic treatment with deferasirox. The rashes resolved spontaneously in most cases. When interruption of treatment may be

necessary, treatment may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation. In severe cases this reintroduction could be conducted in combination with a short period of oral steroid administration (see SPC section 4.4 and 4.8).
Deferasirox were not associated with growth disorders compared to DFO in paediatric patients. No differences between the treatment groups have been observed regarding sexual development as well. These results should be interpreted with caution given the small number of patients involved and the duration of treatment. As a precautionary measure in the management of paediatric patients with transfusional iron overload, body weight, height and sexual development should be monitored at regular intervals (every 12 months). No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses (see non-clinical assessment and SPC section 5.3). As a precaution, it is recommended that deferasirox not be used during pregnancy unless clearly necessary (see SPC section 4.6). As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with deferasirox. Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of treatment and at regular intervals thereafter (every 12 months). If disturbances are noted during the treatment, dose reduction or interruption may be considered (see SPC section 4.4 and 4.8). As the tablets contain lactose, deferasirox is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption (see SPC section 4.4). Exjade is contra-indicated in patients with hypersensitivity to deferasirox or any of the excipients (see SPC section 4.3). No case of overdose has been reported during the clinical trials. Single doses of 80 mg/kg in iron-overloaded thalassaemic patients caused mild nausea and diarrhoea. Acute signs of overdose may include nausea, vomiting, headache and diarrhoea. Overdose may be treated by induction of emesis or by gastric lavage, and by symptomatic treatment (see SPC section 4.9). No studies on the effects of deferasirox on the ability to drive and use machines have been performed. Caution when driving or operating machinery are recommended (see SPC section 4.7).

1.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table 19- Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Serum creatinine increases	- Sentinel site monitoring. - Renal mechanistic study 2123. - Inclusion of patients with baseline serum creatinine >ULN in study US03. - Renal monitoring in ongoing studies (including long-term studies 0105E2, 0106E1, 0107E1, 0108E1, 0109E1) and in planned clinical study 2204. - Collection in a database of all available data on renal biopsies - Nonclinical renal mechanistic study. - Routine PhV, use of targeted questionnaires, follow-up in PSUR.	- SPC: contraindication for renal impairment in section 4.3; extensive monitoring and dose adjustment recommendations in section 4.4;adverse effect information in section 4.8. - Physician education. - Patient booklet for monitoring laboratory test results. - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).
Elevations of liver transaminases	- Sentinel site monitoring. - Monitoring of hepatic function in ongoing studies (including long-term studies 0105E2, 0106E1, 0107E1, 0108E1, 0109E1) and in future clinical studies. - Routine PhV, use of targeted questionnaires, follow-up in PSUR.	- SPC: monitoring and dose adjustment recommendations in section 4.4; adverse effect information in section 4.8; product not recommended in severe hepatic impairment (section 4.4). - Physician education. - Patient booklet for monitoring laboratory test results. - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).
High-frequency hearing loss	- Annual auditory monitoring in ongoing and planned clinical studies. - Routine PhV, use of targeted questionnaires, follow-up in PSUR.	- SPC: annual monitoring recommendation in section 4.4; adverse effect information in section 4.8. - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).
Lenticular opacities and cataracts	- Ophthalmologic monitoring and annual ocular examination in ongoing and planned clinical studies including study 2204. - Routine PhV, use of targeted questionnaires, follow-up in PSUR.	- SPC: annual monitoring recommendation in section 4.4; adverse effect information in section 4.8. - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).
Cardiac monitoring in cardiac iron overload	- Sentinel site monitoring. - Clinical studies (cardiac monitoring in extension studies and in study 2204). - Routine PhV, follow-up in PSUR.	- SPC, section 4.4: “Cardiac dysfunction is a known complication of severe iron overload. Cardiac function should be monitored in patients with severe iron overload during long-term treatment with EXJADE”. - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).

Limited experience in pediatric patients age 2 to <6 years	- Pediatric registry. - Inclusion of pediatric patients in ongoing and planned clinical studies. - Routine PhV, use of targeted questionnaires, follow-up in PSUR.	- SPC: specific comments on monitoring of development in section 4.4; adverse event information in section 4.8; information on patient numbers in section 5.1; lower PK exposure and dosing recommendations mentioned in sections 4.2 & 5.2. - Pediatric patient booklet. - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).
Limited experience in patients with renal impairment	- Clinical study US03 (inclusion of patients with baseline serum creatinine values up to 2xULN).	- SPC, sections 4.2 and 4.3: "EXJADE has not been studied in patients with renal impairment".
Limited experience in patients with hepatic impairment	- Clinical study 2125 (pharmacokinetic study in subjects with hepatic impairment).	- SPC, section 4.4: "EXJADE is not recommended in patients with severe hepatic impairment as it has not been studied in such patients".

The CHMP, having considered the data submitted in the application is of the opinion that the following pharmacovigilance activities are necessary for the safe and effective use of the medicinal product:

The MAH shall set up a surveillance programme to collect information on the demographics of patients prescribed Exjade, any adverse reactions and reasons for discontinuation of Exjade. The formal protocols for the sentinel monitoring surveillance should be reviewed by the CHMP.
- Active sentinel site surveillance will be used in order to monitor renal, hepatic and cardiac function in long-term actual practice settings. The intended exposure will be of approximately 500 patient years for each of the three strata which will be studied: beta-thalassemia, sickle cell disease and other anemias (including myelodysplastic syndromes). Active drug surveillance through networks of sentinel sites in institutional and primary care settings will be conducted throughout the Europe Union and potentially in parts of Africa and Asia. Sentinel site monitoring will allow for surveillance of a geographically diverse sample of patients found in actual practice settings.
- A voluntary patient registry (study 2411) will be implemented in approximately 200 pediatric patients aged 2 to < 6 years. The registry will include the monitoring of renal function using serum creatinine, estimated creatinine clearance and proteinuria. The observation period in the registry will be 5 years.
- The total number of patients with beta-thalassemia entered in ongoing extensions is 679, of all ages. The majority of them is being studied in centres specialized for the treatment of beta-thalassemia in the EU member states. For these patients, prospectively planned monitoring of parameters of renal function includes serum creatinine, calculated creatinine clearance and proteinuria, since the beginning of the core trial. This monitoring will continue until the completion of the extension studies, which will last up to 4 years following the completion of the 1-year core studies.
- The monitoring of patients of all ages with beta-thalassemia included in ongoing extensions, will continue until the completion of the extension studies, which will last up to 4 years following the completion of the 1-year core studies. The prospectively planned monitoring of parameters of renal function includes serum creatinine, calculated creatinine clearance and proteinuria.
- The same centers that are involved in the ongoing study extensions are also participating in the phase IV study 2409, in which beta-thalassemia patients will also be studied for one year, as well as in the planned confirmatory study 2204, in patients with beta-thalassemia will be evaluated for two years.

- The protocols of extension studies will be amended to integrate special high-risk populations [patients with renal impairment (studies US03 and 2204) and hepatic impairment patients (study 2125)].

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

The MAH must ensure that, at launch, all physicians who are expected to prescribe Exjade are provided with a physician information pack containing the following: Product information; physician information about Exjade (including brochure and pocket card); patient information pack.
The physician information about Exjade should contain the following key elements:

- The need to monitor serum ferritin monthly
- That Exjade causes rises in serum creatinine in some patients
  - The need to monitor serum creatinine
    - On two occasions prior to initiation of treatment
    - Every week during the first month of initiation of treatment or after therapy modification
    - Monthly thereafter
  - The need to reduce by 10mg/kgthe dose if serum creatinine rises:
    - Adults: >33% above baseline and creatinine clearance <LLN (90ml/min)
    - Paediatrics: either > ULN or creatinine clearance falls to <LLN at two consecutive visits.
  - The need to interrupt treatment after a dose reduction if serum creatinine rises:
    - Adults and Paediatrics: remain >33% above baseline or creatinine clearance <LLN (90ml/min)
  - The need to consider renal biopsy:
    - When serum creatinine is elevated and if another abnormality has been detected (e.g. proteinuria, signs of Fanconi's Syndrome).
- The importance of measuring creatinine clearance
- Brief overview of methods of measuring creatinine clearance
- That rises in serum transaminases occur in patients treated with Exjade
  - The need for liver function tests prior to prescription, then at monthly intervals or more often if clinically indicated
  - Not to prescribe to patients with pre-existing severe hepatic disease
  - The need to interrupt treatment if persistent and progressive increase in liver enzyme were noted.
- The need for annual auditory and ophthalmic testing
- The need for a guidance table highlighting pre-treatment measurements of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin
- That the safety database of Exjade is limited and physicians are encouraged to enrol patients in a surveillance programme (sentinel site monitoring and pediatric registry) to increase knowledge about the incidence of important ADRs.

The information collected should include:

- Anonymised patient details – age, sex, weight
- Transfusion history and requirements
- Initial dose of Exjade and subsequent changes in dose
- Concomitant medications
- Record of measurements of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin
- Renal histology, if available
- Reason for discontinuation
- ADRs

- The educational programme should prompt doctors to report serious ADRs and certain selected ADRs as below:
  - All serious ADRs
  - Persistent and progressive increase in hepatic enzymes
  - Increase in serum creatinine levels (>33% above baseline) or clearance creatinine decrease (<90ml/min)
  - Significant changes found in auditory or ophthalmological testing
  - Gallstones
  - Unexpected ADRs according to the SPC.

The Patient information pack should include the following information

- Patient information leaflet
- Information on the need for regular monitoring, and when it should be carried out, of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin
- Information that renal biopsy may be considered if significant renal abnormalities occur
- Patient booklet where the physician can record the results of the above along with the dose of Exjade
- Reminder card for dates of tests

Other conditions

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

Risk Management plan

The MAH commits to perform the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

The MAH must inform the EMEA and the CHMP of the status and results of the surveillance programme in each Member State within 6 months of the Decision and at each update of the EU Risk Management Plan. This report shall also provide the details of the ADRs as specified above.

As well as the requirements in the legislation, the following serious ADRs should be forwarded on an expedited basis to the appropriate competent authority as well as summarised in the above reports:

- Increase in hepatic enzymes > 10xULN
- Serious rise in creatinine
- Results of renal biopsies, if available
- Cataracts
- Hearing loss
- Gallstones

An updated Risk Management Plan should be provided as per the CHMP Guideline on Risk Management Systems for medicinal products for human use.

1.6 Overall conclusions, risk/benefit assessment and recommendation

Quality, Non-clinical pharmacology and toxicology

The quality of Exjade was considered acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and were controlled in a satisfactory way.

There were no issues concerning the quality, the non-clinical pharmacology or the toxicology of deferasirox that negatively affected the overall benefit-risk assessment. Some issues required further clarification, to be provided post-authorisation.

Efficacy

The pivotal study was an open-label randomised comparative study conducted in 586 patients, aged 2 years and older, suffering from beta-thalassaemia and transfusional iron overload. The primary efficacy objective was to show that deferasirox is non-inferior to deferoxamine for the efficacy variable defined as binary outcome, indicating a successful or failed treatment effect on hepatic iron stores, assessed by liver biopsy and SQUID at baseline and at the end of a 12 month treatment period. Deferasirox was to be declared non-inferior to deferoxamine if the lower limit of the 95% CI (two sided) for the difference in the percentage of treatment successes on deferasirox and deferoxamine was above a delta of -15% in the per protocol population (all patients who had LIC at end of study or discontinued due to safety). The principal analysis of the total patient population did not demonstrate non-inferiority of deferasirox to deferoxamine.

It appeared from a post-hoc analysis of this study that, in the subgroup of patients with liver iron concentration ≥7 mg Fe/g dw treated with deferasirox (20 and 30 mg/kg) or deferoxamine (35 to ≥50 mg/kg), the non-inferiority criteria were achieved. However, in patients with liver iron

concentration <7 mg Fe/g dw treated with deferasirox (5 and 10 mg/kg) or deferoxamine (20 to 35 mg/kg), non-inferiority was not established; this difference could be due to an imbalance in the dosing of the two chelators. This imbalance occurred because patients on deferoxamine were allowed to remain on their pre-study dose even if it was higher than the protocol specified dose.
Supportive studies were conducted to allow extrapolation of non-inferiority in other forms of transfusional iron overload (i.e., sickle cell disease, myelodysplastic syndromes, rare forms of congenital anaemia). The same non-parametric success criterion was used to assess the efficacy of deferasirox in maintaining or reducing LIC. In the absence of comparator arm, success was to be declared if the lower limit of the 95% confidence interval exceeded 50% in the ITT population. The efficacy was not demonstrated in the ITT population. The success rate was significantly higher than 50% in patients whose LIC was ≥7 mg Fe/g dw (biopsy + SQUID) at baseline. Positive results was also observed in the ITT population with a baseline LIC ≥7 mg Fe/g dw measured by biopsy.

Safety

The most frequent reactions reported during chronic treatment with deferasirox in adult and paediatric patients included gastrointestinal disturbances in about 26% of patients and skin rash in about 7% of patients. These reactions were dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued. During clinical trials, increases in serum creatinine of >33% on ≥2 consecutive occasions, sometimes above the upper limit of the normal range, occurred in about 36% of patients. These were dose-dependent. About two-thirds of the patients showing serum creatinine increase returned below the 33% level without dose adjustment. In the remaining third the serum creatinine increase did not always respond to a dose reduction or a dose interruption. Complete recovery was exceptional (2/68 patients). The preventability, reversibility and long-term consequences of the modification of the renal function were questioned. The mechanism of these renal alterations could not be explained. Over-chelation and/or haemodynamic changes leading to functional clearance alterations are possible explanations (pure haemodynamic moderate drug-induced modifications of the renal function, e.g. observed during angiotensin converting enzyme inhibitors treatments, are rapidly and completely reversible). There was no demonstration of risk prevention by progressively and slowly increasing the dose. There was no effective measure identified to reverse the impaired renal function; interruption of the treatment is not always completely efficient.
Gallstones and related biliary disorders were reported in about 2% of patients. Elevations of liver transaminases occurred in 2% of patients and were not dependent on dose. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%).
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. The CHMP considered that the proposed activities described in section 3.5 adequately addressed the safety concerns listed in the risk management plan.

Risk-benefit assessment

The principal analysis of the pivotal study conducted in patients with beta-thalassemia and transfusional iron overload did not demonstrate the non-inferiority of deferasirox to deferoxamine.

From a subgroup post-hoc analysis including patients with liver iron concentration ≥7 mg Fe/g dw, the non-inferiority criteria were achieved. Therefore, the efficacy of deferasirox was considered established in patients with moderate to severe iron overload, receiving high dose of blood transfusions. As LIC cannot be assessed to decide treatment dosage in clinical practice, the most heavily overloaded patients were subsequently defined as those receiving high amounts of packed red blood cells (≥7 ml/kg/month of packed red blood cells). Secondary endpoints confirmed the likelihood of an acceptable efficacy of deferasirox, which offers the advantage of its oral availability.
In patients with beta thalassemia with less severe iron overload, receiving relatively low doses of blood transfusions, the non inferiority of deferasirox as compared to deferoxamine was not established and it cannot be excluded that the use of deferasirox results in a less efficient overload control. In these patients, the potential benefit of deferasirox, an orally available compound, is overweighed by the availability of deferoxamine, a recognized therapy.

In patients with beta thalassemia, the risk of a moderate decrease in glomerular filtration rate, as observed in the clinical trials, was considered acceptable as long as patients do not suffer from other renal disease. The risk of renal toxicity was considered probably higher in patients treated with high doses of deferasirox.

In patients with other anaemias (e.g. sickle cell disease or myelodysplastic syndromes) the efficacy of deferasirox could not be robustly extrapolated from the weak evidence obtained from the pivotal study, even if an activity was observed in a non comparative trial. Moreover, the risk of renal toxicity was of special concern [22]. Therefore, in these patients, deferasirox was considered a valid second line treatment option when deferoxamine is contraindicated or inadequate. This same indication (when deferoxamine is contraindicated or inadequate) was also recommended in patients aged 2 to 5 years, due to the low number of paediatric patients exposed to the treatement in the clinical studies, and the importance of a long term preservation of the nephronic capital in this population.

Based on this assessment, the CHMP recommended that deferasirox is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. In the other subgroups, such as patients with other anaemias, patients aged 2 to 5 years and patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells), the CHMP recommended the use of deferasirox for the treatment of chronic iron overload, due to blood transfusions, when deferoxamine therapy is contraindicated or inadequate.

Cardiologic consequences of iron overload being a major prognostic factor, the effect of deferasirox on cardiac iron overload and cardiac function will be further investigate post-authorisation.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance studies and activities (i.e. extension clinical studies including high-risk populations and surveillance programme, respectively) in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

The following additional risk minimisation activities were required:

Safety issue	Proposed risk minimisation activities
Serum creatinine increases	- SPC: contraindication for renal impairment in section 4.3; extensive monitoring and dose adjustment recommendations in section 4.4; adverse effect information in section 4.8. - Physician education. - Patient booklet for monitoring laboratory test results. - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).
Elevations of liver transaminases	- SPC: monitoring and dose adjustment recommendations in section 4.4; adverse effect information in section 4.8; product not recommended in severe hepatic impairment (section 4.4). - Physician education. - Patient booklet for monitoring laboratory test results. - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).
High-frequency hearing loss	- SPC: annual monitoring recommendation in section 4.4; adverse effect information in section 4.8. - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).
Lenticular opacities and cataracts	- SPC: annual monitoring recommendation in section 4.4; adverse effect information in section 4.8. - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).
Cardiac monitoring in cardiac iron overload	- SPC, section 4.4: "Cardiac dysfunction is a known complication of severe iron overload. Cardiac function should be monitored in patients with severe iron overload during long-term treatment with EXJADE". - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).
Limited experience in pediatric patients age 2 to <6 years	- SPC: specific comments on monitoring of development in section 4.4; adverse event information in section 4.8; information on patient numbers in section 5.1; lower PK exposure and dosing recommendations mentioned in sections 4.2 & 5.2. - Pediatric patient booklet. - Legal status (restricted medical prescription to experienced physicians in the treatment of chronic iron overload due to blood transfusions).
Limited experience in patients with renal impairment	- SPC, sections 4.2 and 4.3: "EXJADE has not been studied in patients with renal impairment".
Limited experience in patients with hepatic impairment	- SPC, section 4.4: "EXJADE is not recommended in patients with severe hepatic impairment as it has not been studied in such patients".

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus, that the risk-benefit balance of Exjade in:
- the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.
- the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups: patients with other anaemias, patients aged 2 to 5 years, patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells)
was favourable, and therefore recommended the granting of the marketing authorisation.

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