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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-882

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-882

Letter Date: 4/29/05

Proposed Brand Name: Exjade®

Generic Name: Deferasirox

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ORM Division: Medical Imaging and Hematology Products

OCPB Division: Division of Pharmaceutical Evaluation 2

Sponsor: Novartis Pharmaceuticals

Submission Type: Original NDA (1 P)

Formulation, Strength(s): Tablets for Oral Suspension, 125, 250 & 500 mg

Proposed Indication : Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients aged 2 years and over.

Proposed Dosage Regimen:

Starting Dose:

Starting dose should be determined by the frequency of blood transfusions. The recommended initial daily dose of EXJADE for patients should be 20 mg/kg body weight for patients receiving blood transfusions (2 to 4 units per month or 7 to 14 mL/kg per month of packed red blood cells). An initial daily dose of 30 mg/kg should be considered for patients receiving more frequent blood transfusions. An initial daily dose of 10 mg/kg should be considered for patients receiving less frequent blood transfusions or exchange transfusions.

Maintenance Dose:

It is recommended that serum ferritin be monitored every month and the dose of EXJADE adjusted if necessary every 3 to 6 months based on serum ferritin trends. Dose adjustments should be made in steps of 5 or 10 mg/kg and should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). If the serum ferritin falls consistently below 500 µg/L, consideration should be given to temporarily interrupting therapy with EXJADE. Doses of EXJADE should not exceed 30 mg/kg per day since there is limited experience with doses above this level.
Doses (mg/kg) should be calculated to the nearest whole tablet. EXJADE should be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. Tablets should be completely dispersed by stirring in water or orange juice until a fine suspension is obtained. Doses of < 1 g should be dispersed in 3.5 ounces of liquid and doses of > 1 g in 7.0 ounces of liquid. After swallowing the suspension, any residue should be resuspended in a small volume of liquid and swallow.

1. Executive Summary

Deferasirox (ICL670) is an orally active iron chelator. ICL670 is representative of a new class of tridentate iron chelators, the N-substituted bishydroxyphenyl-triazoles. By forming a soluble complex with iron, ICL670 is able to promote excretion of iron primarily in the feces. The proposed indication for ICL670 is for the treatment of patients with chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients as young as two years of age. The only drug currently approved in the U.S. for the general therapy of chronic iron overload is deferoxamine (Desferal®, Novartis). Deferoxamine is most effective when treatment is given over 8 to 12 hours five to seven nights per week. However, adherence to prescribed regimens is poor as many patients find the mode of administration of deferoxamine or the associated local reactions, such as skin irritation, unacceptable.

ICL670 is formulated as an immediate release tablet for oral suspension at 125, 250 and 500 mg dose strengths and is recommended to be taken once daily after dispersing the tablet in water or orange juice. The proposed maintenance dose is to be adjusted from the starting dose every 3-6 months in steps of 5 or 10 mg/kg based on serum ferritin levels. Doses of ICL670 should not exceed 30 mg/kg per day as there is limited clinical experience beyond this dose.

Data was submitted from nine Clinical Pharmacology and Biopharmaceutics-related studies investigating among other things, relative bioavailability, mass balance, food-effect, dose proportionality, multiple dose Pharmacokinetics (PK) / Pharmacodynamics (PD), *in vitro* metabolism, drug-drug interaction with digoxin, and cardiac safety (thorough QT study).

Five Phase 2/3 clinical studies evaluated the safety and efficacy of patients with β-thalassemia and sickle cell disease. A total of 1076 patients have been enrolled in studies lasting at least 24 weeks in the clinical development program. Of these, 700 patients have received ICL670 for chronic periods of up to over three years.

1.1 Recommendation

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, NDA 21-882 is **acceptable** provided that a satisfactory agreement is reached between the Agency and the sponsor regarding the proposed phase 4 commitments and language in the package insert. See Appendix 3.2 for the package insert incorporating the Agency proposed changes to the labeling (See ***Detailed Labeling Recommendations*** on page 16).

1.2 Phase 4 Commitments

(1) Deferasirox is primarily eliminated by metabolism. As such, in hepatically impaired patients deferasirox is likely to accumulate with potential safety implications. Therefore, data should be obtained characterizing the pharmacokinetics of deferasirox in hepatically impaired subjects (subjects/patients with mild, moderate, and severe categories of impairment per Child-Pugh Classification) relative to otherwise healthy subjects/patients. If warranted, these data should be used to propose dosage adjustment in patients with hepatic impairment using this drug.

(2) Metabolism studies conducted *in vitro* have shown that deferasirox has the potential to inhibit CYP450 isozymes. The I/Ki ratios for CYP450 isozymes-2C8, 1A2, 2A6, 3A4/5, 2D6, and 2C19 were in the range of 0.4-1.2. Per the Agency's current practice, an estimated I/Ki ratio of greater than 0.1 is considered positive and a follow up *in vivo* evaluation is recommended. As such, conduct an *in vivo* interaction study investigating the potential of deferasirox to inhibit CYP450 3A4 isozyme. If results from this study are positive, additional *in vivo* studies should be conducted investigating the potential of deferasirox to inhibit other isozymes mentioned above.

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1.3 Summary of CPB Findings

Humans are unable to actively excrete excess iron. Hence, in conditions where repeated blood transfusions are required, the body iron burden can gradually increase, ultimately reaching levels that are toxic to organs such as the liver, heart and endocrine system. Complications of chronic iron overload are the major causes of death in patients with β-thalassemia major, if they receive repeated blood transfusions without sufficient chelation therapy. Patients with sickle cell disease, myelodysplastic syndrome, and a number of other rare hereditary and acquired anemias may also receive repeated blood transfusions; such patients are also susceptible to the adverse effects of iron loading.

The only drug currently approved in the U.S. for the general therapy of chronic iron overload is deferoxamine (Desferal®, Novartis). Because of its short half-life, deferoxamine is generally administered by slow S.C. or I.V. infusion. It is most effective when treatment is given over 8 to 12 hours five to seven nights per week. Sustained compliance with an adequate regimen of deferoxamine leads to near-normal organ function and patient survival. However, adherence to prescribed deferoxamine regimens is poor as many patients find the mode of administration of deferoxamine or the associated local reactions, such as skin irritation, unacceptable.

Deferasirox (referred to as ICL670 during drug development) is an orally active iron chelator that belongs to a new class of tridentate iron chelators. Approval of ICL670 for marketing in the U.S. is sought for the treatment of chronic iron overload due to blood transfusions in adult and pediatric patients as young as two years of age. The proposed starting dose of ICL670 is 10-30 mg/kg/day depending on the frequency of blood transfusions. The proposed maintenance dose is to be adjusted from the starting dose every 3-6 months in steps of 5 or 10 mg/kg based on serum ferritin levels. Doses of ICL670 should not exceed 30 mg/kg per day as there is limited clinical experience beyond this dose.

ICL670 is formulated as an immediate release tablet for oral suspension at 125, 250 and 500 mg dose strengths. ICL670 tablet is recommended to be taken once daily after dispersing the tablet in water or orange juice. The proposed maintenance dose is to be adjusted from the starting dose every 3-6 months in steps of 5 or 10 mg/kg based on serum ferritin levels. Doses of ICL670 should not exceed 30 mg/kg per day as there is limited clinical experience beyond this dose.

Data was submitted from nine Clinical Pharmacology and Biopharmaceutics-related studies investigating among others, relative bioavailability, mass balance, food-effect, dose proportionality, multiple dose Pharmacokinetics (PK) / Pharmacodynamics (PD), drug-drug interaction with digoxin, and cardiac safety (thorough QT study).

The mean %ICL670 chelated to iron in pharmacodynamic studies ranged from 15-32%. There was a dose-related negative iron balance for ICL670 in two pharmacodynamic studies. In addition, a correlation analysis between LIC and corresponding PK parameters in study 107 showed reasonable correlation between LIC (measured by liver biopsy) on one hand and Cmax and AUC of iron-complex ICL670 on the other. There was no clear relationship between systemic exposure to ICL670 and the incidence of adverse events.

The findings of *in vitro* and *in vivo* pre-clinical studies as well a definitive thorough QT study in healthy subjects indicate that ICL670 is not associated with QT prolongation effects on the cardiac system.

ICL670 is a poorly soluble, highly permeable drug (BCS Class II drug).

A significant food-effect was observed on the bioavailability of the ICL670 tablet, whereby the relative bioavailability of ICL670 is increased when administered within 5 minutes of a high-fat breakfast (1000 cal). Total exposure (AUC_{0-t}) was doubled while Cmax increased by 77% compared to administration of ICL670 under fasting conditions. Administration of ICL670 tablet 30 minutes before a high-fat breakfast (1000 cal) resulted in mean AUC_{0-t} and Cmax increases of 23% and 25%, respectively, relative to fasting conditions. Subsequently, ICL670 tablets were administered 30 min before a standard breakfast in the pivotal clinical trial (study 107).

Administration of ICL670 dispersed both in orange juice and in apple juice was studied as alternate administration options to dispersion in water. ICL670 tablets dispersed in orange juice and ICL670 tablets dispersed in water were bioequivalent. While ICL670 tablets dispersed in apple juice and ICL670 tablets dispersed in water were not bioequivalent, the observed PK differences are unlikely to be of clinical relevance.

The mean absolute bioavailability of ICL670 tablet for suspension was determined to be 73%. Peak plasma levels of ICL670 were achieved 1 to 4 hrs following oral administration, while the mean Cmax and AUC values of ICL670 and the iron complex increased in a dose-related manner in the dose range of 2.5 to 80 mg/kg. Steady-state of ICL670 was achieved after 3 days of multiple QD dosing of ICL670 tablets with an accumulation factor of 1.8.

ICL670 is highly bound to plasma proteins (99.5-99.7%) within a concentration range of 7-166 μg/mL. ICL670 is primarily bound to albumin in plasma.

In vitro metabolism studies in human liver microsomes as well as in human hepatocytes have shown that ICL670 is primarily metabolized by glucuronidation with the acyl-glucuronide (M3) being the major metabolite. Glucuronidation appears to be mediated predominantly by UGT1A1 and UGT1A3 isoforms. Up to 8% of an oral dose of ICL670 is metabolized by CYP450 enzymes, in particular, CYP1A1, CYP1A2 and CYP2D6.

In vitro metabolism studies have also shown that ICL670 is a weak inhibitor of CYP450 activities with IC_{50} values ranging from 100 to > 500 μM. Therefore, ICL670 can potentially inhibit the metabolism of CYP450 substrates.

A mass balance study using ^{14}C-radiolabeled ICL670 indicated that ICL670 was primarily excreted in feces (84% of the dose) with only 7.6% of the radioactivity excreted in the urine.

The terminal half-life of ICL670 following I.V. infusion was estimated at 4 hrs. However, following oral administration of ICL670, the apparent terminal half-life ranged from 12-18 hrs, likely due to enterohepatic recirculation.

As the renal excretion of ICL670 is limited (urinary excretion of ICL670 and its iron complex form account for < 0.1% of the administered ICL670 dose over 96 hrs post-dose), studies evaluating the PK of ICL670 in patients with renal impairment were not undertaken.

Data evaluating the PK of ICL670 in patients with hepatic impairment is not available. However, since patients with iron overload often have abnormal liver function tests due either to iron overload or concomitant viral hepatitis, patients with mild to moderate elevations in serum transaminase levels (up to 5 times the ULN) were enrolled in clinical studies and were treated with similar doses of ICL670 to patients without hepatic impairment. The general safety and efficacy profiles in these individuals were similar to the overall population. ICL670 is proposed to be used with caution in patients with hepatic impairment. Given the preponderance of hepatic impairment in patients with iron overload, the effect of hepatic impairment on the PK of ICL670 needs to be assessed.

Co-administration of ICL670 with digoxin did not result in a significant PK interaction.

Females exhibit lower apparent clearance (by 17.5%) for ICL670 compared to males. However, as ICL670 is dosed by weight, those gender-related differences in PK are unlikely to be of clinical relevance.

A total of 292 pediatric patients aged 2 to 16 years were treated with ICL670 during the clinical development program. Children and adolescents demonstrate a lower exposure to ICL60 following single and multiple doses. The exposure of children aged 2 to 6 years is around half that of adults. Drug exposure gradually increases between ages 2 to 18 years to reach adult levels. There was generally a trend toward reduced efficacy in children age 2 to 6 years, consistent with the lower drug exposure in these patients. However, since ICL670 dosing is based upon titration to the individual patient response, the pharmacokinetic differences may not have significant clinical implications.

A total of 30 geriatric patients > 65 years of age were treated with ICL670 during the clinical development program. Pharmacokinetic data in geriatric patients is not available to allow comparison to young adults with respect to total exposure.

An adequately validated dissolution method was developed, whereby the dissolution of ICL670 tablets is determined in — ml of USP phosphate buffer pH 6.8 with [ ] [ ] using USP test apparatus 2 (paddle) at 50 rpm and 37.0 ± 0.5°C. The proposed dissolution specification of Q = [ ] within 30 min is acceptable.

Three formulations of ICL670 tablet were utilized throughout the clinical development program. The formulations were adequately linked using *in vitro* dissolution.

Table 1. Summary of the PK changes for ICL670 in the Clinical Pharmacology studies and observations in clinical trials

	Change in Cmax	Change in AUC	Sponsor's Proposed Labeling Recommendations	Agency Perspective on Proposed Labeling Recommendations
Renal Impairment	NS	NS	Use with caution in patients with serum creatinine above the age adjusted upper limit of normal	Acceptable
Hepatic Impairment	NS	NS	Use with caution in patients with hepatic impairment	Recommend Phase 4 commitment to study PK in hepatic impairment
Food High fat meal Standard breakfast 30 min before high fat breakfast	 + 77% + 49% + 23%	 + 100% + 47% + 25%	Take once daily on an empty stomach at least 30 min before food	Acceptable
Obese	---	---	Weight-based dosing employed	Acceptable
Co-administration with Digoxin (PgP substrate)	NC	NC	---	Acceptable
Elderly >65	NS	NS	Weight-based dosing employed	Acceptable
Gender	NC	CL in females is 17.5% lower than in males	Weight-based dosing employed	Acceptable

* NS denotes not studied, while NC denotes no change.

2. Question-Based Review

2.1 General Attributes

Deferasirox (ICL670) is an orally active iron chelator. ICL670 is representative of a new class of tridentate iron chelators, the N-substituted bishydroxyphenyl- triazoles. Two molecules of ICL670 are needed to form a complete complex with one Fe^{+3} ion. By forming a soluble complex with iron, ICL670 is able to promote excretion of iron primarily in the feces. It has low affinity for zinc and copper and does not cause a measurable change in excretion of these metals.

The proposed clinical indication for ICL670 is for the treatment of patients with chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients as young as two years of age. Patients with β-thalassemia, sickle cell disease, myelodysplastic syndrome, and a number of other rare hereditary and acquired anemias may also receive repeated blood transfusions.

ICL670 is available as a tablet for oral suspension at 125, 250 and 500 mg dose strengths. The proposed maintenance dose is to be adjusted from the starting dose every 3-6 months in steps of 5 or 10 mg/kg based on serum ferritin levels. Doses of ICL670 should not exceed 30 mg/kg per day as there is limited clinical experience beyond this dose. ICL670 tablet is recommended to be taken once daily after dispersing the tablet in water or orange juice.

Nine Clinical Pharmacology and Biopharmaceutics studies were submitted in support of this NDA, characterizing the relative bioavailability (study 2101) and food effect (studies 2120 and 2121) as well as a definitive QT study in healthy subjects (study 2122). In addition, the following studies were conducted in β-thalassemia patients; single dose pharmacokinetics (study 101), food effect (study 105F), multiple dose pharmacokinetics/pharmacodynamics (studies 101 and 104) and mass balance (study 115).

Five Phase 2/3 clinical studies evaluated the safety and efficacy of patients with β-thalassemia and sickle cell disease (studies 105, 106, 107, 108 and 109). A total of 1076 patients have been enrolled in studies lasting at least 24 weeks in the clinical development program. Of these, 700 patients have received ICL670 for chronic periods of up to over three years.

ICL670 is currently not marketed anywhere in the world and as such no post marketing experience is available.

2.2 General Clinical Pharmacology

1. Is there an Exposure/Response (E/R) relationship on safety or efficacy for ICL670?

There was a dose-related negative iron balance for ICL670 in two pharmacodynamic studies. A reasonable correlation was demonstrated between LIC (measured by liver biopsy) on one hand and Cmax and AUC of iron-complex ICL670 on the other. No such correlation was demonstrated for ICL670. There was no clear relationship between systemic exposure to ICL670 and the incidence of adverse events.

A key PD parameter believed to be of direct clinical relevance in β-thalassemia patients is the overall iron balance, which is defined as the difference between total iron intake (iron in consumed diet, blood transfusions and medication) and iron excreted in urine and feces. As the most serious complications in β-thalassemia patients are associated with chronic iron overload, a negative iron balance is a desirable outcome of iron chelation therapy.

The clinical development program for ICL670 evaluated both the short-term (12 days) and long-term (48 weeks) iron balance at daily doses up to 40 mg/kg. Three studies evaluated the PK/PD relationship of ICL670 in β-thalassemia patients including; study 101 (PK/PD study of six single oral doses of ICL670), study 104 (PK/PD study of ICL670 following 12-day multiple dose administration), and a population PD analysis of studies 105, 106, 107 and 108.

The PK/PD relationship, PD being iron balance in transfusion-dependent β-thalassemia patients, was explored in study 101, a study evaluating the safety, tolerability and PK/PD of six single oral doses of ICL670 (ranging from 2.5 to 80 mg/kg) in a randomized, double-blind, placebo-controlled, sequential, parallel group design in β-thalassemia patients ($n = 24$, age ≥ 18 yrs; previously treated with deferoxamine).

The results of the study indicate that the mean %ICL670 chelated to iron relative to the free ICL670 in plasma ranged from 15-31% with a tendency towards lower %ICL670 chelated with higher doses (Fig. 1). Urinary iron excretion (UIE) was low up to a dose of 20 mg/kg, beyond which markedly higher excretion was observed, which might possibly be related to the iron-chelating effect of ICL670. Large inter- and intra- individual variability was observed in the excretion of iron in urine within the study. It should be noted that the urinary excretion of ICL670 and its iron complex form account for $< 0.1\%$ of the administered ICL670 dose over the first 96 hrs post-dose. Therefore, while UIE is a useful efficacy marker for deferoxamine which is primarily excreted via the kidneys, it is not of much value with respect to the efficacy of ICL670.

No consistent effects were observed on other secondary markers of iron disposition such as transferrin and serum iron concentrations.

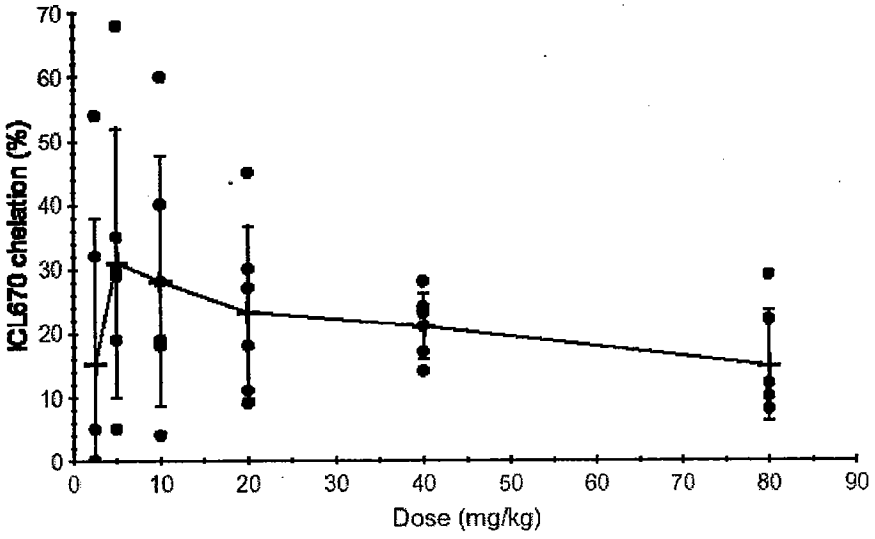


Fig 1. ICL670 chelation to iron versus dose

Table 1. Urinary iron excretion (median and range; mg/kg) after single dose administration of six ICL670 escalating doses (2.5 to 80 mg/kg)

Dose (mg/kg)	N	0-24 h	N	24-48 h	N	48-72 h	N	72-96 h
Placebo	12	0.017 (0.006, 0.629)	12	0.015 (0.003, 0.142)	12	0.013 (0.003, 0.742)	12	0.006 (0.002, 0.072)
2.5	6	0.009 (0.005, 0.031)	6	0.009 (0.005, 0.163)	5	0.039 (0.007, 0.055)	4	0.006 (0.004, 0.008)
5	6	0.010 (0.006, 0.028)	6	0.010 (0.009, 1.795*)	6	0.007 (0.004, 0.021)	6	0.006 (0.005, 0.011)
10	6	0.010 (0.004, 0.014)	6	0.005 (0.002, 0.006)	6	0.006 (0.003, 0.009)	6	0.005 (0.002, 0.007)
20	6	0.016 (0.006, 0.119)	6	0.009 (0.004, 0.013)	6	0.007 (0.004, 0.009)	6	0.005 (0.002, 0.008)
40	6	0.193 (0.053, 0.508)	6	0.031 (0.007, 0.211)	6	0.108 (0.004, 0.334)	6	0.080 (0.006, 1.894)
80	6	0.391 (0.121, 0.842)	6	0.032 (0.009, 0.277)	6	0.014 (0.003, 0.249)	6	0.040 (0.002, 0.150)

In study 104, the PK/PD of three oral doses of ICL670 (10, 20 and 40 mg/kg) were evaluated in a randomized, double-blind, placebo-controlled, sequential, parallel group design in β-thalassemia patients (n = 24, age ≥ 16 yrs; previously treated with deferoxamine). The patients were allocated to one of 3 study groups, each group consisting of 7 patients (5 patients on ICL670 and 2 on placebo). In the study, patients received single oral daily doses of ICL670 (or placebo) for 12 days. Plasma samples were collected for quantitation of free ICL670 and the iron complex form up to 24 hrs post-dose on study day 1 and up to 96-hrs post-dose on study day 12. Trough samples were collected on days 4, 6, 8, 1 and 12. In addition, urine samples were collected for

quantitation of free ICL670 and the iron complex form up to 24 hrs post-dose on study day 1 and up to 48-hrs post-dose on study day 12. Fecal samples were collected for iron output from study day -5 to 13 in 24-hr intervals.

The study results indicated that negative iron balance was achieved at all three ICL670 doses, averaging 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. Also, consistent with the findings of study 101, the urinary excretion of ICL670 and its iron complex was very low (0.05-0.15% of administered ICL670 dose). Elimination of ICL670 occurred mainly in feces.

A linear correlation (r^2=0.732) was demonstrated between both total exposure (AUC) of ICL670 and trough concentrations of ICL670 versus the iron excretion.

Study 105 was a randomized clinical trial in which 71 adult β-thalassemia patients receiving frequent blood transfusions with moderate iron overload were randomized to receive once daily oral ICL670 at doses of 10 or 20 mg/kg/day or S.C. infusions of deferoxamine 40 mg/kg/day for five days each week (n = 24, 24 and 23, respectively). The core period of the study was 3 months. However, there was an additional comparative extension phase lasting for a total of at least 48 weeks. The primary efficacy measure was liver iron concentration (LIC), which was assessed non-invasively using superconducting quantum interference device (SQUID), as this technology allowed repeated LIC measurements every three months.

Unlike the findings of study 104, study 105 failed to show any PK/PD correlations with the changes in LIC. Moreover, SQUID has proven to be unreliable for accurate measurement of LIC.

Using PD data from studies 105, 106, 107 and 108, a model was developed that characterizes the time course of change in LIC and serum ferritin as a function of iron input from blood transfusions and iron excretion due to chelation therapy. The main aim of the study was to assess the agreement between observed changes from baseline for serum ferritin compared to the change in LIC at different time points since the start of ICL670 treatment. The changes from baseline for serum ferritin were thought to be a more practical surrogate of LIC than direct methods such as SQUID and liver biopsy which present numerous limitations in clinical practice. In conclusion, a 20 mg/kg dose of ICL670 was deemed an appropriate starting dose in most β-thalassemia patients receiving frequent blood transfusions. In addition, using six months serum ferritin data and baseline LIC as compared to using 12 months of serum ferritin and baseline LIC, did not result in a large drop in quality of the LIC predictions but did result in a deterioration of the serum ferritin parameter estimates and prediction of future serum ferritin data.

For long-term studies, liver iron concentration (LIC) was selected as the method for determination of iron balance, as it has been shown to correlate with total body iron burden more accurately and directly than single measures of serum ferritin. In addition, LIC has been correlated with morbidity and mortality from iron overload. Liver biopsy is the reference method for determination of LIC, for practical purposes it cannot be performed more than annually except under exceptional circumstances because it is surgical procedure associated with discomfort and risk of complications. For some

individuals (e.g., those with thrombocytopenia) it is also contraindicated. For this reason SQUID, an investigational non-invasive method for the biomagnetic estimation of LIC available only at four centers world-wide, was used in the dose finding study (study 0105), as it could be employed at more frequent intervals relative to liver biopsy. Studies to validate the SQUID methodology demonstrated that SQUID underestimated LIC by approximately half when compared to biopsy. Given the discrepancy demonstrated between liver biopsy and SQUID measurements, the sponsor resorted to adding a correction factor of 2.34 on SQUID data so that biopsy and SQUID are on similar scales in the pharmacodynamic studies.

Study 0107, the only adequate and comparator-controlled clinical safety and efficacy trial in the submission, was intended to investigate the hypothesis that ICL670 was non-inferior to deferoxamine.

Study 107 was a randomized, comparative, open-label phase 3 trial comparing the efficacy and safety of ICL670 and deferoxamine in frequently transfused β-thalassemia patients ≥ 2 years of age with chronic iron overload from blood transfusions (n = 541). LIC, the primary outcome variable in the study, was assessed at baseline by liver biopsy or, in some pediatric patients (16% of patients), non-invasively by SQUID. LIC was reassessed after 12 months of therapy in each patient using the same methodology as that used at baseline. Patients enrolled in the study were dosed according to preset scheme depending on their baseline LIC levels (Table 3).

The primary analysis of the study results failed to meet the prospectively defined criterion (lower bound of 95% CI of -15%) to establish non-inferiority based on the comparison of success rates between ICL670 and deferoxamine treatment groups (Table 4).

A correlation analysis between LIC and corresponding PK parameters in study 107 showed reasonable correlation between LIC (measured by liver biopsy) on one hand and Cmax and AUC of iron-complex ICL670 on the other (see Table 4). No such correlation was observed for ICL670 (Table 4). Similarly, while there was little correlation between transferrin saturation on one hand and Cmax and AUC of ICL670 on the other, there was good correlation with iron-complex ICL670.

Table 2. Average daily dose by LIC category in study 107

	Baseline LIC in mg Fe/g dw (regardless of method)			
	<=3	>3-7	>7-14	>14
ICL670 (N = 296)	**N=15**	**N=78**	**N=84**	**N=119**
Protocol 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
Average ICL670 dose: DFO dose	**1 : 5.47**	**1 : 3.60**	**1 : 2.18**	**1 : 1.69**

Table 3. Success rates for study 107 on the primary outcome (LIC)

	ICL670	DFO
Biopsy & SQUID	**n=276**	**n=277**
Success rate (n (%))	146 (52.9)	184 (66.4)
95% CI	[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=85**	**n=87**
Success rate (n (%))	34 (40.0)	72 (82.8)
95% CI	[29.6, 50.4]	[74.8, 90.7]
Difference [95% CI]	-42.8 [-55.9, -29.7]	
LIC ≥ 7 mg Fe/g dw	**n=191**	**n=190**
Success rate (n (%))	112 (58.6)	112 (58.9)
95% CI	[51.7, 65.6]	[52.0, 65.9]
Difference [95% CI]	**-0.3 [-10.2, 9.6]**	
Biopsy	**n=229**	**n=234**
Success rate (n (%))	117 (51.1)	147 (62.8)
95% CI	[44.6, 57.6]	[56.6, 69.0]
Difference [95% CI]	-11.7 [-20.7, -2.8]	
LIC < 7 mg Fe/g dw	**n=53**	**n=55**
Success rate (n (%))	12 (22.6)	42 (76.4)
95% CI	[11.4, 33.9]	[65.1, 87.6]
Difference [95% CI]	-53.7 [-69.6, -37.8]	
LIC ≥ 7 mg Fe/g dw	**n=176**	**n=179**
Success rate (n (%))	105 (59.7)	105 (58.7)
95% CI	[52.4, 66.9]	[51.4, 65.9]
Difference [95% CI]	**1.0 [-9.2, 11.2]**	
SQUID	**n=47**	**n=43**
Success rate (n (%))	29 (61.7)	37 (86.0)
95% CI	[47.8, 75.6]	[75.7, 96.4]
LIC < 7 mg Fe/g dw	**n=32**	**n=32**
Success rate (n (%))	22 (68.8)	30 (93.8)
95% CI	[52.7, 84.8]	[85.4, 100]
LIC ≥ 7 mg Fe/g dw	**n=15**	**n=10**
Success rate (n (%))	7 (46.7)	7 (63.6)
95% CI	[21.3, 73.4]	[30.8, 89.1]

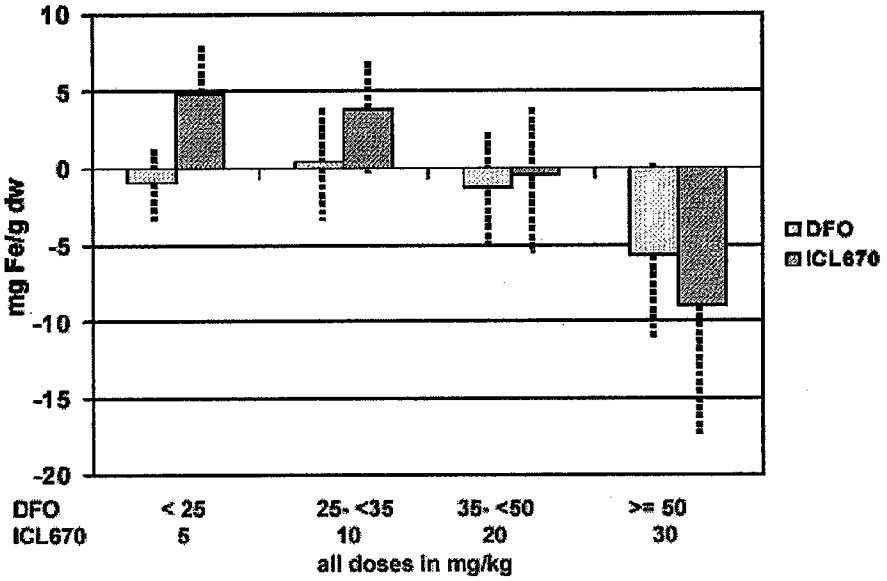


Fig 2. Absolute change in LIC in study 107

Table 4. Results of a correlation analysis between LIC and corresponding PK parameters and trough levels of ICL670 and iron complex ICL670

			Variable									
			AUCall			Cmax			Trough			
Laboratory parameter	Analyte	Visit	N. Obs.	Correlation coefficient	p-Value	N. Obs.	Correlation coefficient	p-Value	N. Obs.	Correlation coefficient	p-Value	
LIC (SQUID)	Fe-[ICL670]2	16							26	-0.21	0.293	
	ICL670	16							26	-0.50	0.010	
LIC (biopsy)	Fe-[ICL670]2	16	14	0.57	0.035	14	0.48	0.081	138	-0.12	0.159	
	ICL670	16	14	0.17	0.573	14	0.28	0.333	138	-0.29	0.001	

2. Have the single and multiple dose pharmacokinetics of ICL670 been adequately characterized?

The mean Cmax and AUC values of ICL670 and the iron complex form increase in a dose-related manner. The accumulation factor of ICL670 was 1.78 with multiple dosing. In addition, the AUCss of the iron-complexed ICL670 accounted for 10% of that of ^{14}C-ICL670 and 11% of that of ICL670.

The single dose PK of ICL670 were characterized in three studies in healthy subjects (a relative bioavailability study and two food-effect studies) and three studies in β-thalassemia patients (a mass balance study, a food-effect study and a dose ranging study).

The multiple dose PK of ICL670 were characterized in two studies in β-thalassemia patients (a mass balance study; 115, and a PD study; 104). In addition, trough plasma concentrations were determined following multiple dose administration of ICL670 in study 107 at visits 4 (week 4), 6 (week 12), 9 (week 24) and 16 (week 52). Additional plasma samples were collected in a subgroup of adult patients in study 107 on visits 9 and 16 at 0 (pre-dose), 1, 2, 4 and 8 hrs post-dose. For a detailed description of those studies, refer to the related sections in the review.

In study 101, the safety, tolerability and PK/PD of six single oral doses of ICL670 (ranging from 2.5 to 80 mg/kg) were evaluated in a randomized, double-blind, placebo-controlled, sequential, parallel group design in β-thalassemia patients (n = 24, age ≥ 18 yrs; previously treated with deferoxamine). The patients were allocated to one of 3 study groups, each group consisting of 8 patients. Each group was given 2 single administrations at an interval of at least 7 weeks, first a lower dose of ICL670A (or placebo) and later a higher dose (or placebo). In each treatment period, 6 of the 8 patients per group received ICL670A and 2 patients received placebo in such a way that no patients received placebo more than once.

Plasma and urine samples were collected up to 96 hrs post-dose for quantitation of free ICL670 and the iron complex form. In addition, serum iron, transferrin and the total urinary iron excretion were determined. A 7-day washout period separated successive treatments.

The study results indicated that tmax for ICL670 ranged from 1 to 3 hrs at the 6 dose levels studied while Cmax and AUC_{0-24} of ICL670 increased in a roughly dose-proportional manner. Also, $t_{1/2}$ of ICL670 tended to be longer at higher doses (ranging from 11.9 hrs at 2.5 mg/kg dose to 18.2 hrs at 80 mg/kg dose), which might be due to a greater extent of enterohepatic recirculation with higher doses of ICL670 (see Table 5).

As for the iron-complex ICL670, while mean AUC_{0-24} values increased in a dose-proportional manner, Cmax increased in a less than dose-proportional manner. There was also large interindividual variability in AUC_{0-24} values, particularly at lower ICL670 doses (up to 20 mg/kg). Mean systemic clearance (CL/f) values for the iron complex were 3.3-5.7-fold higher than for ICL670, suggesting that the iron complex form is eliminated from the body more rapidly than ICL670.

The findings of study 115, a mass balance study in male and female β-thalassemia patients (n = 5, age 20-38 years) who received oral ICL670 at a dose of 1000 mg/day (~ 20 mg/kg) for 8 days, demonstrated that the accumulation factor of ICL670 was 1.78 with multiple dosing. In addition, the AUCss of the iron-complexed ICL670 accounted for 10% of that of ^{14}C-ICL670 and 11% of that of ICL670. In another study (study 104), a 12-day PK/PD study of three multiple oral doses of ICL670 (10, 20 and 40 mg/kg) in β-thalassemia patients, steady-state was achieved after 3 days of treatment. Also, the total exposure to the iron complex form did not correlate well with the ICL670 dose and was 10-20 times lower than that of ICL670 (See Table 6).

In study 107, which was a randomized, comparative, open-label, 52-week phase 3 trial, there generally was a dose-related increase in Cmax and AUC of both ICL670 and the iron complex form up to an ICL670 dose of 30 mg/kg/day. The %chelation of ICL670 to iron ranged between 12-32% and was in line with the findings of study 101. Overall,

there was high variability observed in estimates of Cmax and AUC of ICL670 and the iron complex form (see Table 7).

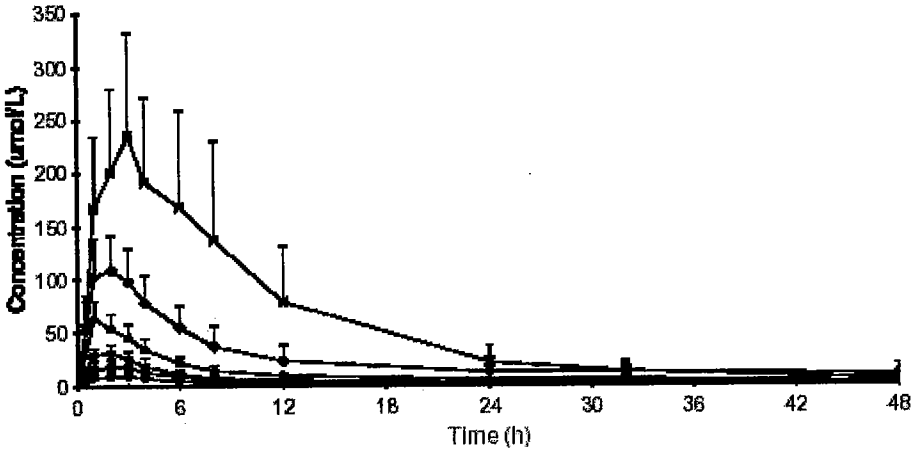


Fig 3. Mean concentration-time profiles of ICL670 following oral administration of ICL670 single doses of 2.5 mg/kg to 80 mg/kg (study 101)

Table 5. Mean PK parameters of ICL670 and its iron complex in plasma following oral administration of ICL670 single doses of 2.5 mg/kg to 80 mg/kg (study 101)

Dose (mg/kg)	ICL670A				[ICL670A]$_2$-Fe			
	T_{max} (h) median min; max	C_{max} (µmol/L) mean ± SD	AUC_{0-24h} (h•µmol/L) mean ± SD	$t_{1/2}$ (h) mean ± SD	T_{max} (h) median min; max	C_{max} (µmol/L) mean ± SD	AUC_{0-24h} (h•µmol/L) mean ± SD	$t_{1/2}$ (h) mean ± SD
2.5	2.50 1.0; 3.0	9.40 ±3.66	70 ±20	11.87 ±9.46	2.00 2.0; 4.0	0.70 ±1.09	5 ±7	7.72 ±6.45
5	2.00 1.0; 3.0	19.25 ±5.23	139 ±50	11.34 ±4.52	2.50 1.0; 3.0	3.05 ±1.17	20 ±12	6.73 ±4.35
10	1.50 1.0; 2.0	32.33 ±6.89	200 ±53	14.18 ±10.65	2.00 1.0; 3.0	4.91 ±3.09	30 ±26	7.23 5.77
20	1.00 1.0, 2.0	64.28 ±17.20	388 ±73	18.48 6.70	2.50 1.0; 6.0	6.11 ±1.93	46 ±32	17.20 ±7.82
40	1.50 1.0; 3.0	119.35 ±27.39	889 ±329	19.48 ±6.42	5.00 4.0; 8.0	6.43 ±1.47	89 ±24	17.69 ±5.14
80	3.00 2.0; 6.0	240.67 ±96.43	2364 ±1175	18.23 ±7.56	5.00 3.0, 24.2	10.95 ±5.30	154 ±66	15.47 ±5.32

Table 6. Summary of the PK parameters of ICL670 and its iron complex in plasma following single and multiple dose administration of ICL670 doses of 10, 20 and 40 mg/kg (study 104)

		ICL670				Fe-[ICL670]$_2$			
Day	Dose (mg/kg) (n of subjects)	t_{max} (h) median (range)	C_{max} (µmol/L) mean ± SD	AUC_{0-24h} (h•µmol/L) mean ± SD	$t_{1/2}$ (h) mean ± SD	t_{max} (h) median (range)	C_{max} (µmol/L) mean ± SD	AUC_{0-24h} (h•µmol/L) mean ± SD	$t_{1/2}$ (h) mean ± SD
1 (Single Dose PK)	10 (n=5)	1.50 1.00-2.08	54.86 ± 18.15	364 ± 95	7.09* ± 2.14	4.03 3.00-24.1	4.29 ± 3.25	51 ± 39	10.22* ± 4.46
	20 (n=6)	1.50 1.00-3.00	87.98 ± 23.55	605 ± 171	7.26* ± 1.21	4.00 3.00-8.00	8.71 ± 5.14	109 ± 83	10.14* ± 2.13
	40 (n=7)	1.50 1.00-3.02	199 ± 41	1925 ± 460	10.44 ± 3.83	4.00 1.00-12.0	6.41 ± 4.44	107 ± 73	29.50[a]
12 (Multiple Dose PK)	10 (n=5)	1.50 1.00-2.00	73.52 ± 34.45	720 ± 252	13.40* ± 1.04	4.00 1.50-6.00	4.46 ± 3.24	73 ± 53	21.22[a] ± 47.2
	20 (n=4)	2.25 1.50-8.00	120.5 ± 20.6	1404 ± 521	12.63‡ ± 0.68	4.00 3.00-8.00	5.66 ± 2.24	81 ± 48	12.14‡ ± 2.42
	40 (n=3)	2.00 1.00-2.00	254 ±107	3065 ± 1131	11.88 ± 3.30	3.00 2.00-6.00	9.03 ± 5.91	149 ± 109	19.34 ± 4.66

Table 7. Mean PK parameters of ICL670 and its iron complex at steady-state following oral administration of ICL670 doses of 5 mg/kg to 30 mg/kg/day (study 107)

		ICL670			Fe-[ICL670]$_2$		
Dose (mg/kg/day)	Visit*	C_{max} mean (µmol/L) ± SD	AUC_τ mean (h•µmol/L) ± SD	$t_{1/2}$ mean (h) ± SD	C_{max} mean (µmol/L) ± SD	AUC_τ mean (h•µmol/L) ± SD	$t_{1/2}$ mean (h) ± SD
5	9 (n=2)	25.05 ± 1.48	262.92 ± 98.60	8.09 ± 0.40	1.37 ± 0.30	18.44 ± 0.96	12.77 ± 1.96
	16 (n=1)	2.96	50.61	Missing	0.42	5.53	Missing
10	9 (n=8)	50.34 ± 35.35	610.11 ± 527.74	14.88 ± 7.75	2.56 ± 1.98	35.03 ± 31.27	12.10 ± 4.22
	16 (n=4)	55.40 ± 30.47	690.71 ± 300.03	14.34 ± 3.72	4.20 ± 1.02	53.47 ± 28.25	Missing
15	9 (n=0)	Missing	Missing	Missing	Missing	Missing	Missing
	16 (n=1)	88.50	1174.42	10.94	1.50	21.05	16.99
20	9 (n=6)	155.97 ± 141.40	2248.55 ± 2706.40	15.28 ± 8.95	6.13 ± 6.83	105.08 ± 129.61	11.60 ± 2.25
	16 (n=6)	97.17 ± 50.41	1162.38 ± 632.96	9.94 ± 3.83	5.68 ± 3.60	79.45 ± 65.34	13.84 ± 4.03
30	9 (n=5)	163.88 ± 94.11	2132.20 ± 1505.78	10.45 ± 2.61	15.51 ± 20.63	271.18 ± 388.34	20.47 ± 8.69
	16 (n=3)	92.93 ± 33.16	1153.76 ± 421.66	13.11 ± 3.74	10.37 ± 1.23	159.71 ± 21.32	16.31

3. Does ICL670 cause QT/QTc prolongation?

The findings of in vitro and in vivo pre-clinical studies as well a definitive QT study in healthy subjects indicate that ICL670 is not associated with effects on the cardiac system.

No findings considered to be related to ICL670 were observed in the following *in vitro* cardiovascular safety studies conducted: HR and force of contraction in the isolated atrium of the guinea pig, action potential duration in sheep Purkinje fibers, and, the Langendorff perfused isolated rabbit heart. Additionally, a cardiac telemetry study was performed in dogs. Although there were effects of ICL670 on HR at the highest doses tested (300 mg/kg), no effect was noted on the QTc interval. ICL670 was also tested in the HERG channel assay. No inhibition of the tail current was seen at concentrations of up to 250 μM, the highest soluble concentration.

In order to evaluate the cardiac safety of ICL670 in a conclusive manner, a definitive QT study (study 2122) was conducted per the ICH; E14 guidance. In study 2122, the effect of a single dose of ICL670 on QT interval in healthy subjects (n = 182; 44-46/treatment arm, age 18-65 years) were assessed in a randomized, single-blind, single center, active (moxifloxacin) and placebo-controlled, four treatment, parallel-group study. Subjects were randomly allocated to receive one of four treatments:

- ICL670, 20 mg administered 5 min after a high-fat breakfast
- ICL670, 40 mg administered 5 min after a high-fat breakfast
- Placebo, administered 5 min after a high-fat breakfast
- Moxifloxacin 400 mg, administered 30 min before a standard breakfast

In the study, ICL670 was administered under fed conditions to maximize systemic exposure as there is a significant food-effect on the bioavailability of ICL670.

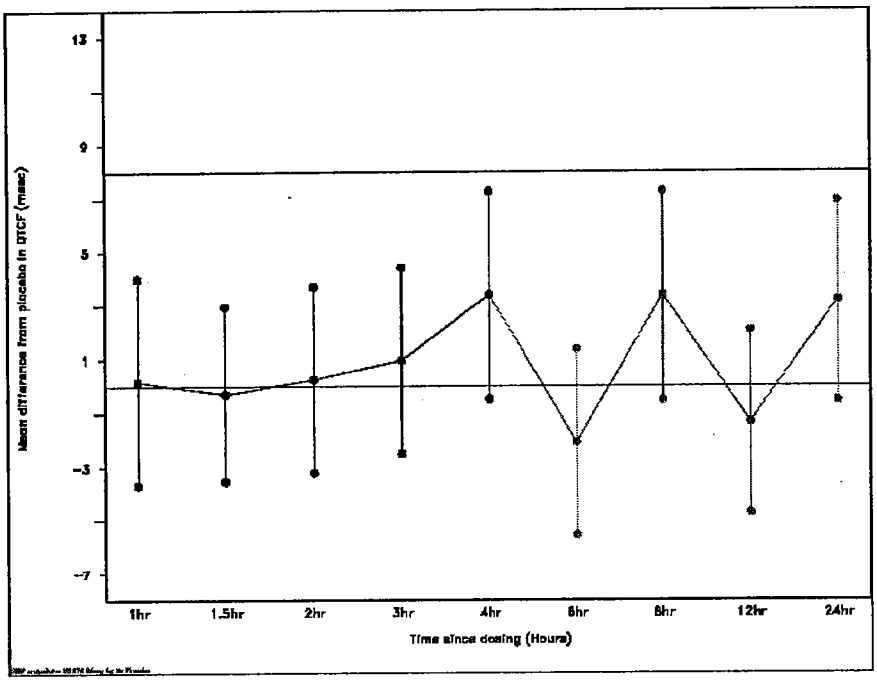
Assuming within-treatment variability equal to 8.4 ms and an expected difference between ICL670 and placebo of 3.5 ms, a sample size of 45 subjects per arm would have provided 80% power to obtain a 90% confidence interval for the difference between ICL670 and placebo entirely below 8 ms.

Plasma concentrations of ICL670 were determined up to 24 hrs post-dose. The primary PD variable was the mean treatment differences and their corresponding 95% confidence intervals were obtained from the model for the pair-wise comparisons of interest (ICL670 20 mg/kg versus ICL670 placebo, ICL670 40 mg/kg versus ICL670 placebo, and moxifloxacin 400 mg versus ICL670 placebo).

The study results indicated that ICL670 treatment did not result in a significant increase of QT intervals (QT, QTcF, QTcB) at single doses of 20 and 40 mg/kg (Table 8). ICL670 treatment also did not result in a significant increase of QT, QTcF, or QTcB at single doses of 20 and 40 mg/kg when analyzed at peak plasma exposure. In addition, moxifloxacin, a positive control, statistically significantly prolonged the QT and QTcF intervals by 5.32 and 8.96 ms, respectively, which is consistent with previous observations (Table 8).

Table 8. Mean change from baseline in QT/QTc over the 24-hr treatment period

	Treatment compared to ICL670 Placebo		
	ICL670 20 mg/kg	ICL670 40 mg/kg	Moxifloxacin 400 mg
	Mean difference*, ms (95% CI)		
QT	-2.56 (-5.31, 0.18)	-3.29 (-6.08, -0.51)	5.32 (1.96, 8.69)
QTcB	2.61 (0.47, 4.76)	1.13 (-1.05, 3.30)	10.89 (8.02, 13.76)
QTcF	0.85 (-0.83, 2.54)	-0.48 (-2.18, 1.22)	8.96 (6.68, 11.24)
QTcI	1.23 (-0.67, 3.13)	0.11 (-1.81, 2.04)	10.45 (7.80, 13.09)



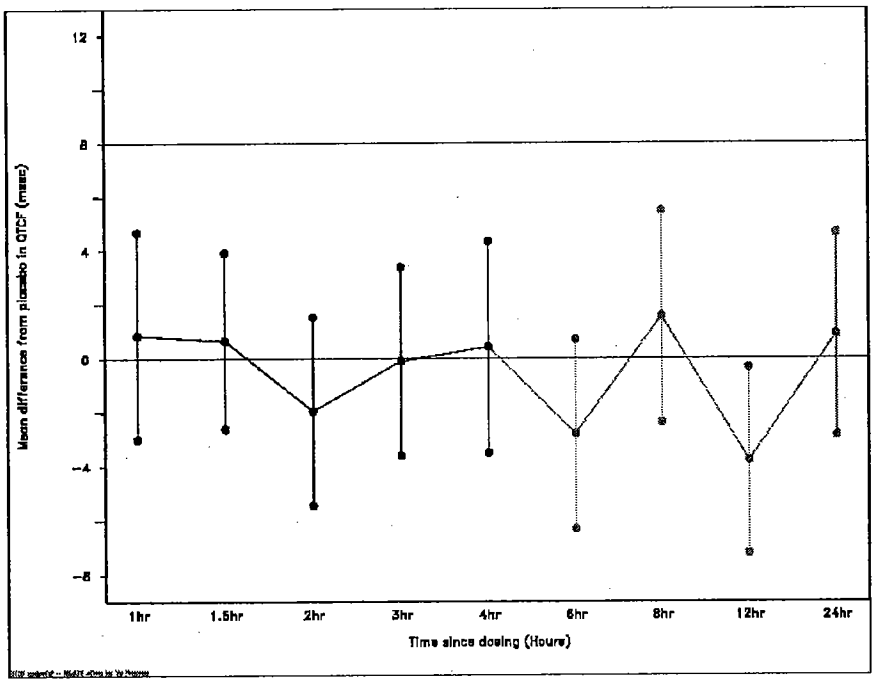


Fig 4 & 5. Mean difference between ICL670 (upper 20 mg and lower 40 mg) and placebo for the change from baseline in QTcF (ms) over 24-hrs post-dose

Table 9. Number of patients with at least one QT/QTc > 450, 480 and 500 ms post-baseline

	N	>450 ms	>480 ms	>500 ms
Uncorrected QT				
ICL670 20 mg/kg	46	1 (2.2)	0 (0.0)	0 (0.0)
ICL670 40 mg/kg	44	0 (0.0)	0 (0.0)	0 (0.0)
ICL670 placebo	46	0 (0.0)	0 (0.0)	0 (0.0)
Moxifloxacin 400 mg	44	1 (2.3)	0 (0.0)	0 (0.0)
QTcB				
ICL670 20 mg/kg	46	3 (6.5)	0 (0.0)	0 (0.0)
ICL670 40 mg/kg	44	8 (18.2)	0 (0.0)	0 (0.0)
ICL670 placebo	46	7 (15.2)	0 (0.0)	0 (0.0)
Moxifloxacin 400 mg	44	8 (18.2)	1 (2.3)	0 (0.0)
QTcF				
ICL670 20 mg/kg	46	0 (0.0)	0 (0.0)	0 (0.0)
ICL670 40 mg/kg	44	1 (2.3)	0 (0.0)	0 (0.0)
ICL670 placebo	46	0 (0.0)	0 (0.0)	0 (0.0)
Moxifloxacin 400 mg	44	2 (4.5)	0 (0.0)	0 (0.0)
QTcI				
ICL670 20 mg/kg	46	3 (6.5)	1 (2.2)	1 (2.2)
ICL670 40 mg/kg	43	4 (9.3)	0 (0.0)	0 (0.0)
ICL670 placebo	46	3 (6.5)	0 (0.0)	0 (0.0)
Moxifloxacin 400 mg	42	4 (9.5)	1 (2.4)	1 (2.4)

Table 10. Number of patients with at least one measurement ≥ 30 and 60 ms increase in QT/QTc post-baseline

	N	>=30 ms	>=60 ms
Uncorrected QT			
ICL670 20 mg/kg	46	3 (6.5)	0 (0.0)
ICL670 40 mg/kg	43	4 (9.3)	0 (0.0)
ICL670 placebo	46	3 (6.5)	0 (0.0)
Moxifloxacin 400 mg	42	8 (19.0)	0 (0.0)
QTcB			
ICL670 20 mg/kg	46	1 (2.2)	0 (0.0)
ICL670 40 mg/kg	43	1 (2.3)	0 (0.0)
ICL670 placebo	46	4 (8.7)	0 (0.0)
Moxifloxacin 400 mg	42	9 (21.4)	0 (0.0)
QTCF			
ICL670 20 mg/kg	46	0 (0.0)	0 (0.0)
ICL670 40 mg/kg	43	1 (2.3)	0 (0.0)
ICL670 placebo	46	0 (0.0)	0 (0.0)
Moxifloxacin 400 mg	42	5 (11.9)	0 (0.0)
QTcI			
ICL670 20 mg/kg	46	0 (0.0)	0 (0.0)
ICL670 40 mg/kg	43	1 (2.3)	0 (0.0)
ICL670 placebo	46	1 (2.2)	0 (0.0)
Moxifloxacin 400 mg	42	6 (14.3)	0 (0.0)

4. What are the ADME characteristics of ICL670 following oral administration?

4.1 Absorption

The mean absolute bioavailability of ICL670 tablets for oral suspension is 73%.

In study 2101, the absolute bioavailability of a single 375 mg oral tablet of ICL670 was determined as it compares to 130 mg I.V. infusion of ICL670 (administered over 90 min) in an open label, randomized, two treatment, two-period crossover study in healthy male subjects (n = 18, wt = 70-90 kg, age = 18-45 years). A washout period of 5 days separated the treatment periods. The results of the study show that the mean absolute bioavailability of ICL670 tablet is 73%, while half-life of ICL670 following I.V. infusion was estimated at 4 hrs (see Table 11).

Table 11. Summary of the mean PK parameters of ICl670 following administration of a single 375 mg oral tablet of ICL670 and a 130 mg I.V. infusion of ICL670

Parameter (arithmetic mean ± SD)	375 mg ICL670 FMI tablets	130 mg ICL670 90-min i.v. infusion
C_{max} (µmol/L)	26.32 ± 8.54	25.76 ± 5.08
t_{max} (h)	2.50 [ ]	1.50 [ ]
AUC_{0-t} (h•µmol/L)	208.03 ± 76.80	100.14 ± 29.07
$AUC_{0-\infty}$ (h•µmol/L)	223.68 ± 82.28	104.33 ± 25.60#
$t_{1/2}$ (h)	8.42 ± 2.76	4.05 ± 1.46#
CL (L/h)	-	3.53 ± 0.87#
V_{ss} (L)	-	14.37 ± 2.69#
F (%)	73.49 ± 19.58#	
	range (min, max): 44.06, 108.95	

* median (min, max); # n=16 since the terminal elimination rate constant λ_z could not be estimated in one subject

• 375 mg ICL670 FMI tablets; ▲ 130 mg ICL670 90 min i.v. infusion

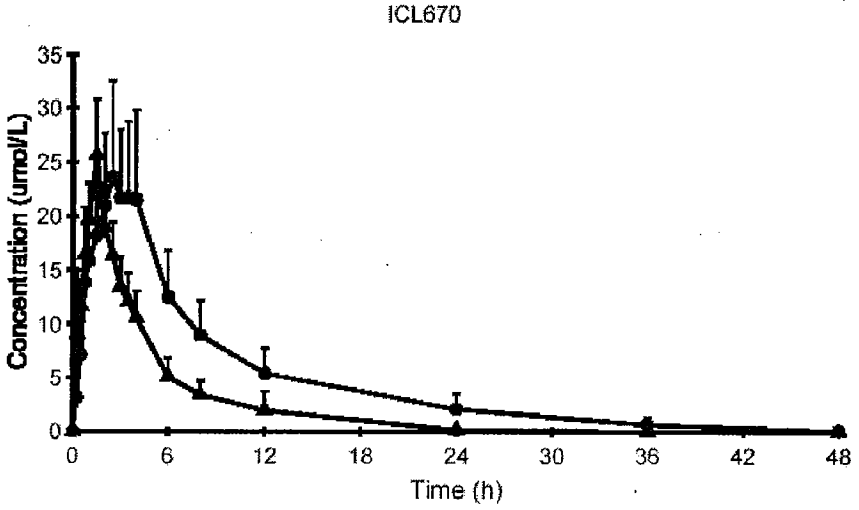


Fig. 6. Mean plasma concentrations of ICL670 following administration of a single 375 mg oral tablet of ICL670

4.2 Distribution

The mean steady state volume of distribution of ICL670 after intravenous infusion is 14.4 L. ICL670 is 99.5-99.7% bound to plasma proteins at a concentration range of 7-166 μg/mL. It is primarily bound to albumin in plasma.

The extent of protein binding of ICL670 was determined *in vitro* using ultrafiltration at nominal concentrations ranging from 7 to 166 μg/mL, using blood from 3 subjects (study 1998/039). The protein bound fraction of ICL670 in plasma was 99.7% at the lowest conc. studied (7 μg/mL), decreasing to 99.5% at the highest conc. studied (166 μg/mL). In addition, the mean fraction of drug in erythrocytes was 12.9% ± 4.4% at ICL670 concentrations ranging from 5 to 100 μg/mL. Altogether, the binding data indicate that ICL670 is highly bound to plasma proteins and a small fraction of the drug distributes into erythrocytes.

The specific nature of plasma protein binding of ICL670 was explored in study R98-083 using ultrafiltration. The results indicate that ICL670 is primarily bound to albumin (98-99%), while the binding to α1-acid glycoprotein decreased from 85 to 8% with ICL670 concentration increasing from 0.5 to 105 μg/mL (corresponding to 1.3-263 μM) indicating saturable binding of this protein. However, the impact of the saturation of α1-acid glycoprotein at higher ICL670 concentrations is unlikely to be of clinical relevance. Binding of ICL670 to γ-globulins was negligible.

Plasma samples from patients after ICL670 dosing were not analyzed to assess the free fraction of ICL670 as the unbound fraction (0.01-0.05 μM) was projected to be well below the limit of quantitation.

4.3 Metabolism and Excretion

In vitro metabolism studies in human liver microsomes and hepatocytes have shown that ICL670 is primarily metabolized by glucuronidation with the acyl- glucuronide (M3) being the major metabolite. Glucuronidation appears to be mediated predominantly by UGT1A1 and UGT1A3. Additionally, ICL670 is a weak inhibitor of CYP450 activities with IC_{50} values ranging from 100 to > 500 μM. Given its I/Ki ratio however, it is conceivable that ICL670 might inhibit the activity of several CYP450 isozymes (in particular, CYPs 2C8 and 1A2). The sponsor needs to assess the potential for inhibition of CYP450 isozymes by ICL670.

In vitro metabolism studies in human liver microsomes and human hepatocytes have shown that ICL670 is primarily metabolized by glucuronidation with the acyl-glucuronide (M3) being the major metabolite. Glucuronidation appears to be mediated predominantly by UGT1A1 and UGT1A3 (accounting altogether for 95% of the glucuronide formation) with minor contributions from UGT1A7 and UGT1A9. (Studies R0201160 and R0201162).

Another study in human liver microsomes showed that the major metabolic pathways ICL670 involve the formation of four mono-hydroxylated metabolites (M1-M4). The

enzymes mediating the metabolism were determined to be CYP1A1, CYP1A2 and CYP2D6 (Study R99-078). Of those enzymes, CYP1A2 appears to be the major enzyme responsible for the oxidative metabolism of ICL670 around 6-8-fold higher than CYP2D6).

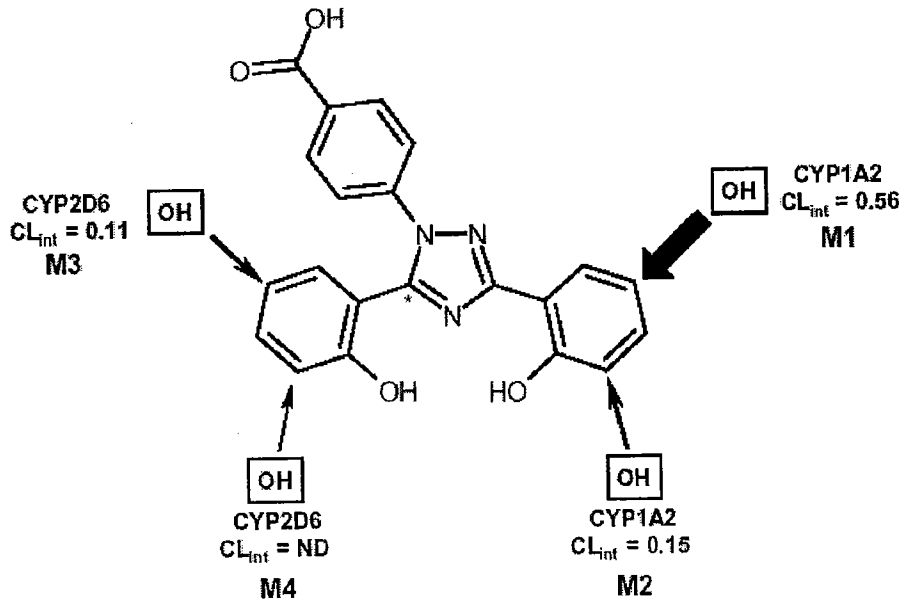


Fig. 7. Oxidative metabolic scheme of ICL670 in human liver microsomes.

Potential for CYP inhibition by ICL670:

In vitro metabolism studies have shown that ICL670 is a weak inhibitor of CYP450 activities with IC_{50} values ranging from 100 to > 500 μM (see Table 12). ICL670 inhibited CYP2C8 with the lowest IC_{50} value of 100 μM followed by inhibition of CYP1A2 at an IC_{50} value of 175 μM. In addition, the iron complex-ICL670 also exhibited weak inhibitory activity of CYP 450 enzymes (referred to in the Table as CGP82813A). Maximal plasma concentrations of ICL670 observed in the clinical studies were 120 μM at doses of 40 mg/kg. It is therefore conceivable that ICL670 could exhibit inhibitory effects on CYP 450 enzymes.

ICL670 inhibits acetaminophen glucuronidation in human liver microsomes in a non-competitive manner with a ki value of 204.8 ± 28.7 μM. However, given the high protein binding of ICL670 and the minimal free fraction of ICL670, such an interaction is unlikely.

Table 12. Inhibitory effects of ICL670 on human CYP 450 activity

Enzyme activity	Responsible human P-450	ICL670A IC_{50}	CGP82813A IC_{50}
phenacetin O-deethylation	CYP1A2	175 μM	100 μM
coumarin 7-hydroxylation	CYP2A6	200 μM	100 μM
paclitaxel 6α-hydroxylation	CYP2C8	100 μM	160 μM
diclofenac 4'-hydroxylation	CYP2C9	210 μM	n.d.[c]
S-mephenytoin 4-hydroxylation	CYP2C19	330 μM	250 μM
bufuralol 1'-hydroxylation	CYP2D6	200 μM	320 μM
dextromethorphan O-demethylation	CYP2D6	340 μM	> 500 μM
chlorzoxazone 6- hydroxylation	CYP2E1	> 500 μM	470 μM
cyclosporine A metabolism	CYP3A4/5	200 μM	> 500 μM

[c] not determined

In an *in vivo* open-label, mass balance study (study 0115), male and female β-thalassemia patients (n = 5, age 20-38 years) received oral ICL670 at a dose of 1000 mg/day (~ 20 mg/kg) for 6 days, followed by a single oral dose of ^{14}C-ICL670 1000 mg on day 7. Patients were continued on daily doses of ICL670 from day 8 to the end of the study. Blood, urine and feces samples were collected on day 7 up to 168 hours post-dose.

The study findings indicate the following:

- Following administration of ^{14}C-ICL670, tmax of ICL670 and radioactivity was 4-6 hrs post-dose. In some subjects, a secondary peak was observed at 24 hrs post-dose, which is suggestive of enterohepatic recirculation.
- Most of the plasma radioactivity was due to unchanged ICL670 (around 91%), which indicates that ICL670 is not extensively metabolized. Similarly, the AUCss of ICL670 accounted for 87% of the AUCss of ^{14}C-ICL670 (see Fig. 8).
- ^{14}C-radioactivity was primarily excreted in feces (84% of the dose) with only 7.6% of the dose excreted in urine.

- The AUCss of the iron-complexed ICL670 accounted for 10% of that of ^{14}C-ICL670 and 11% of that of ICL670.
- The accumulation factor of ICL670 was 1.78 with multiple dosing.
- Radioactivity was mainly present in plasma with only 5% of the radioactivity associated with RBCs.
- Several metabolites and conjugates of ICL670 were isolated from urine and feces. The extent of all metabolites was not determined as access to human bile was not possible (See Table 14).

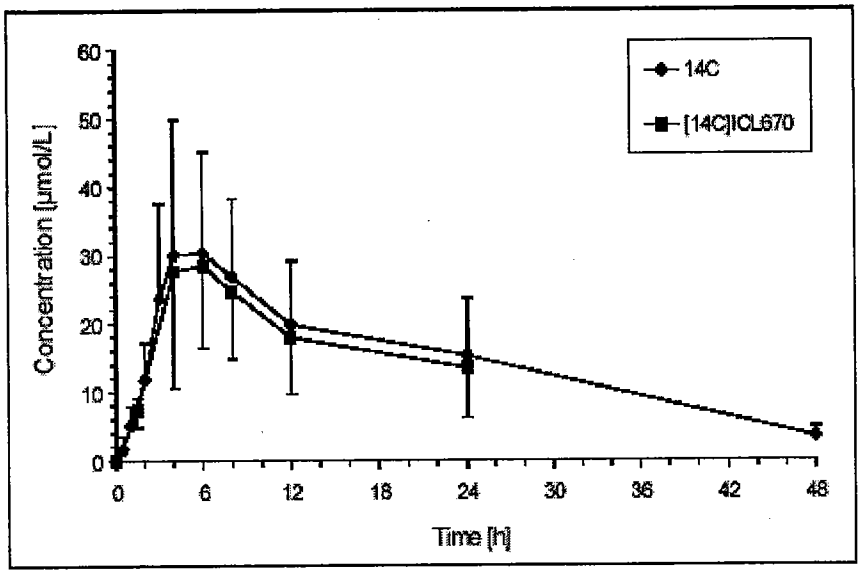


Fig. 8. Mean ICL670 and ^{14}C-ICL670 plasma concentration-time profiles following administration of a multiple oral doses

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Table 13. Summary of the PK parameters of ICL670 and ^{14}C-ICL670 following multiple dose administration.

PK Parameter	Blood	Plasma			
	total ^{14}C	total ^{14}C	[^{14}C]ICL670 [a]	ICL670 (SS, cold analysis)	Complex (SS, cold analysis)
t_{max} [h] (median)	6	4	6	6	6
C_{max} [µmol/L]	20.2 ± 10.6	32.7 ± 18.4	30.6 ± 15.7	46.5 ± 22.7	4.7 ± 3.0
AUC_{24h} [µmol•h/L] [b, c]	292 ± 138	477 ± 229	434 ± 196	688 ± 307	79 ± 50
[% of ^{14}C-$AUC_{24h\ plasma}$]	61 ± 2	(100)	91 ± 6		
[% of ^{14}C-AUC_{plasma}]		60 ± 9		87 ± 21	9.8 ± 5.2
AUC_t [µmol•h/L] [b]	434 ± 217	753 ± 351			
t [h] (median)	48	72	(24)	(24)	(24)
AUC [µmol•h/L] [b]	459 ± 207	785 ± 355	710 ± 291 [e]		
[% of ^{14}C-AUC_{plasma}]	59 ± 4	(100)	91 ± 6		
$t_{½}$ [h]	12.2 ± 2.8	12.4 ± 1.6	11.0 ± 5.3	9.4 ± 3.6	[d]
time interval (typical) [h]	12-48	12-48	8-24	8-24	
Extrapolation factor F_{∞}		1.70			
Accumulation factor R [f]				1.78 ± 0.47 [f]	

Table 14. Identified metabolites in urine and feces (expressed as % administered dose)

	Metabolite		% of dose
feces	M1	5-hydroxy metabolite of ICL670	4
	M4	5'-hydroxy metabolite of ICL670	2
	M7	O-sulfate conjugate of M1	2
		total of hydroxylated, CYP-catalysed metabolites	8
urine	M3	acyl glucuronide metabolite of ICL670	« 1
	M6	phenol-O-glucuronide	6
		total of glucuronides	6
	M7	O-sulfate conjugate of M1	« 1

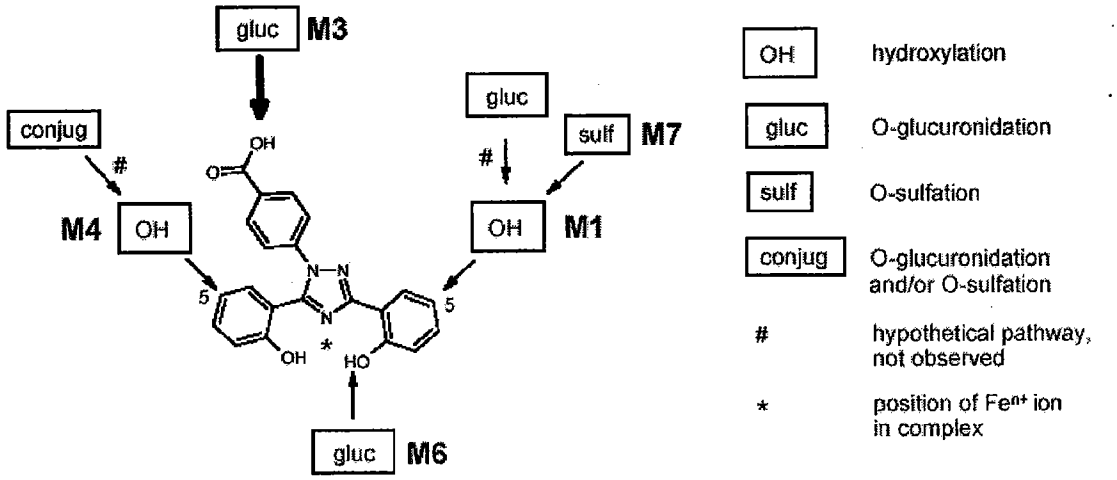

Fig. 9. The known metabolic pathways of ICL670

2.3 Intrinsic Factors

1. Is there a need for dosage adjustment in special populations?

1.1 Elderly

The pharmacokinetics of ICL670 have not been evaluated in elderly patients. Only 30 patients >65 years of age were treated with ICL670 during the drug development program. Package insert will reflect the lack of PK information in the elderly.

A total of 30 geriatric patients > 65 years of age were treated with ICL670 during the clinical development program. Pharmacokinetic data in geriatric patients is not available to allow comparison to young adults with respect to total exposure. Novartis proposal to add the statement 'The pharmacokinetics of deferasirox have not been studied in geriatric patients (aged 65 or older)' in the Clinical Pharmacology section of the package insert is acceptable.

1.2 Gender

There is no need for dosage adjustment in female patients.

Females exhibit lower apparent clearance (by 17.5%) for ICL670 compared to males. However, as ICL670 is dosed by weight, those gender-related differences in PK are unlikely to be of clinical relevance.

1.3 Pediatrics

In general, exposure is lower in children relative to adults. Exposure in the age group of 2 to 6 years is half that of adults. Exposure increases gradually to reach adult levels. Consistent with lower drug exposure, there is a general trend toward reduced efficacy. Since ICL670 dosing is based upon titration to individual patients response, there is no need for dosage adjustment in pediatric patients based on the observed PK differences.

A total of 292 pediatric patients aged 2 to 16 years were treated with ICL670 during the clinical development program. Children and adolescents demonstrate a lower exposure to ICL60 following single and multiple doses. The exposure of children aged 2 to 6 years is around half that of adults. Drug exposure gradually increases between ages 2 to 18 years to reach adult levels. There was generally a trend toward reduced efficacy in children age 2 to 6 years, consistent with the lower drug exposure in these patients. However, since ICL670 dosing is based upon titration to the individual patient response, the pharmacokinetic differences may not have significant clinical implications. Patients younger than two years old were not included in clinical trials, as they have received an insufficient number of blood transfusions to justify the treatment of iron overload. Therefore, no safety data are available for this population as well, and the indication will be limited to patients of 2 years of age and over. Novartis proposal to add the statement 'The overall exposure of adolescents and children to deferasirox after single or multiple doses was less than in adult patients. In children < 6 years of age, exposure was about 50% lower than adults. Since dosing is individually adjusted according to response this difference in exposure is not expected to have clinical consequences' in the Clinical Pharmacology section of the package insert is acceptable.

1.4 Hepatic Impairment

The pharmacokinetics of ICL670 have not been evaluated in patients with hepatic impairment. The sponsor's proposed labeling states that ICL670 should be used with caution in patients with hepatic impairment. Given the preponderance of hepatic impairment in patients with iron overload, the effect of hepatic impairment on the PK of ICL670 needs to be assessed.

Data evaluating the PK of ICL670 in patients with hepatic impairment is not available. However, since patients with iron overload often have abnormal liver function tests due either to iron overload or concomitant viral hepatitis, patients with mild to moderate elevations in serum transaminase levels (up to 5 times the ULN) were enrolled in clinical studies and were treated with similar doses of ICL670 to patients without hepatic impairment. The general safety and efficacy profiles in these individuals were similar to the overall population. ICL670 is proposed to be used with caution in patients with hepatic impairment.

1.5 Renal Impairment

No dosage adjustment is needed in patients with renal impairment as renal excretion of intact ICL670 is negligible (< 1% of administered dose of ICL670).

As the renal excretion of intact ICL670 is limited (urinary excretion of ICL670 and its iron complex form account for < 0.1% of the administered ICL670 dose over 96 hrs post-dose), studies evaluating the PK of ICL670 in patients with renal impairment were not undertaken.

2.4 Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence systemic exposure and/or response and what is the impact of any differences in exposure on response?

Drug interaction of ICL670 with digoxin:

Co-administration of ICL670 with digoxin did not result in a significant PK interaction

Digoxin is commonly used to treat cardiac failure secondary to transfusional iron overload in patients with thalassemia major. It is also known to be a narrow index drug and its absorption is mediated in part by PgP and OATP transporters. Therefore, the sponsor conducted a study to evaluate the drug-drug interaction potential when co-administering digoxin and ICL670 in healthy subjects.

In a randomized, open-label, two-period study of 14 healthy male subjects (aged 18-45 years; Study 2102), subjects received a digoxin loading dose of 0.5 mg on day 1 of each treatment period followed by a digoxin daily dose of 0.25 mg on days 2-8. On day 8, subjects received a single oral dose of 20 mg/kg ICL670 immediately following the digoxin dose. A washout period of 14 days separated the two treatment periods.

The results of the study indicate that no significant drug interaction with co-administration of digoxin and ICL670 (see Table 15).

Table 15. Summary of digoxin PK parameters in study 2102

Parameter (arithmetic mean ± SD)	Digoxin and ICL670	Digoxin alone
$C_{max,ss}$ (ng/mL)	1.55 ± 0.31	1.73 ± 0.60
t_{max}* (h)	1.50 [ ]	1.00 [ ]
AUC_τ (h•ng/mL)	15.21 ± 4.45	16.52 ± 4.57
$C_{min,ss}$ (ng/mL)	0.46 ± 0.17	0.46 ± 0.13
$C_{avg,ss}$ (ng/mL)	0.63 ± 0.18	0.69 ± 0.19
Fluctuation Index (%)	189.76 ± 84.94	182.2 ± 36.43
Ae (%)	38.64 ± 12.00	44.37 ± 9.96
CL/F (L/h)	18.74 ± 9.57	16.59 ± 6.04
CL_R/F (L/h)	6.73 ± 2.35	7.12 ±2.14
CL_{NR}/F (L/h)	12.01 ± 7.98	9.47 ±4.86

* median (min, max)

a) Is ICL670 a substrate and/or an inhibitor of any transport processes?

ICL670 is a substrate for an unknown efflux system other than PgP and MRP, which is thought to play an important role in the absorption of ICL670.

Employing the human intestinal Caco-2 cell line, ICL670 was determined to be a highly permeable compound (intrinsic permeability [ ]). ICL670 is transported in a concentration-dependent manner across Caco-2 cells and it appears to be a substrate for an unknown efflux system which is predicted to play a significant role in the absorption of ICL670. The addition of cyclosporin A (PgP/MRP1/MRP2 inhibitor) or verapamil (PgP/MRP1 inhibitor) did not influence ICL670 permeability, indicating that neither PgP nor MRP efflux system was involved in the transport of ICL670 (Studies R0201161 and R0200436). In addition, ICL670 was shown to have a low competitive inhibitor potential (Km ≥ 5 μM).

2.5 General Biopharmaceutics

1. What is the BCS classification of ICL670?

ICL670 is a poorly soluble, highly permeable drug (Class II BCS drug).

ICL670 is poorly soluble at low pH. At a pH of 6.8, the solubility of ICL670 is [ ] mg/mL.

Mass balance study findings indicate that around 90% of an orally administered dose of ICL670 is absorbed. In addition, ICL670 was shown to be highly permeable (intrinsic permeability [ ] using human intestinal Caco-2 cell line.

2. Are the proposed dissolution test method and specifications for ICL670 tablets acceptable?

A dissolution method was developed, whereby dissolution of tablets is determined in [ ] ml of USP phosphate buffer pH 6.8 with [ ] using USP test apparatus 2 (paddle) at 50 rpm and 37.0 ± 0.5°C. The proposed dissolution method specifications are Q=[ ] in 30 min for 125 mg and 250 mg tablets, and Q=[ ] in 30 min for 500 mg tablets.

The apparatus, agitation rate and dissolution medium were selected by the sponsor based on the US guidance for industry on "Dissolution testing of immediate release solid oral dosage forms".

A pH of 6.8 was selected based on the pH-dependent solubility of ICL670 (see Table 16). However, even at a pH of 6.8, ICL670 is still practically insoluble. [ ] was added to the dissolution medium. [ ] concentration of

[redacted] was selected as it allows for optimal discriminatory power of the dissolution medium relative to other [redacted] concentrations (see Fig. 11).

Table 16. Solubility of ICL670 as a function of pH

Medium	Solubility (mg/ml) at 25 °C	Solubility (mg/ml) at 37 °C
Water		
HCl 0.1 N (pH 1.2)		
USP acetate or phthalate buffer pH 4.5		
USP phosphate buffer pH 6.8		
HCl 0.1 N (pH 1.2) + [redacted]		
USP acetate buffer pH 4.5 + [redacted]		
USP phosphate buffer pH 6.8 + [redacted]		

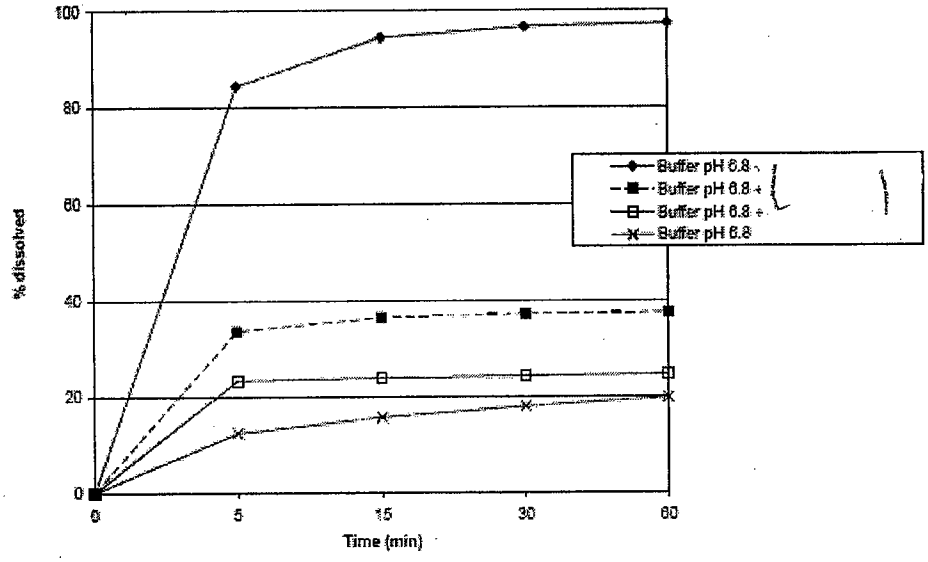

Fig. 11. Comparative dissolution profiles of ICL670 250 mg tablet as a function [redacted] concentration at pH 6.8

3. Are the various formulations of ICL670 used throughout the clinical development adequately linked?

Three formulations of ICL670 tablet were utilized throughout the clinical development program. The formulations were adequately linked using in vitro dissolution.

The initial clinical formulation (CSF) was a quadri-divisible dispersible tablet of 250 mg dosage strength. The initial clinical formulation was utilized in studies 115, 101, 104 and 105. The CSF formulation was then modified to reduce the disintegration time. The resulting formulation (Market Form, or MF) was again a quadri-divisible 250 mg dispersible tablet, contained only minor qualitative and quantitative modifications compared to the CSF. The MF formulation was utilized in studies 105F and 106. The

CSF and MF formulations were considered similar, based on similar *in vitro* dissolution profiles (see Fig. 10).

The MF was further modified to produce lower and higher dosage strength tablets of 125 mg and 500 mg, and to further reduce the disintegration time to less than 3 minutes. Only very minor quantitative modifications were made relative to the MF. The three FMI (Final Market Image) tablet strengths 125, 250 and 500mg are formed from the same blend and so contain the same ingredients in the same proportions (see Table 17). The FMI formulation was utilized in studies 2101, 2102, 2120, 2121, 2122 and 107 (Phase 3 pivotal clinical trial). With the development of the lower dosage strength tablets, the tablets were no longer made to be divisible. The dissolution profiles of the FMI 250 mg tablets and MF were compared and found to be similar (see Fig. 11). A side-by-side comparison of the composition of the various ICL670 tablet formulations used during clinical development is shown in table 18.

Table 17. Composition of the ICL670 dispersible to-be-marketed tablet formulation

	Amount per tablet (mg)				
Ingredient	**125mg tablet**	**250mg tablet**	**500mg tablet**	**Function**	**Reference to standards**
ICL670	125.0	250.0	500.0	Drug substance	Novartis monograph***
Crospovidone					
Lactose monohydrate					
Microcrystalline cellulose (NF)					
Povidone (K30)					
Sodium lauryl sulphate					
silicon dioxide (NF)					
Magnesium stearate*					
Total tablet weight	425.0	850.0	1700.0		

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Table 18. Side-by-side comparison of the composition of the various ICL670 tablet formulations used during clinical development

Dosage strength	250 mg	250 mg	125 mg	250 mg	500 mg
Development stage	CSF	MF	FMI	FMI	FMI
Formulation identification number(s)	3753852.001 3753852.002 3753852.005	3753852.007	3766078.003	3753852.008	3756087.003
Deferasirox, drug substance	250	250.00	125.00	250.00	500.00
Crospovidone Lactose monohydrate Microcrystalline cellulose (NF) Povidone (K30) Hydroxypropyl cellulose Sodium lauryl sulfate silicon dioxide Magnesium stearate	[redacted]				
Tablet weight	1000	850.0	425.0	850.0	1700.0

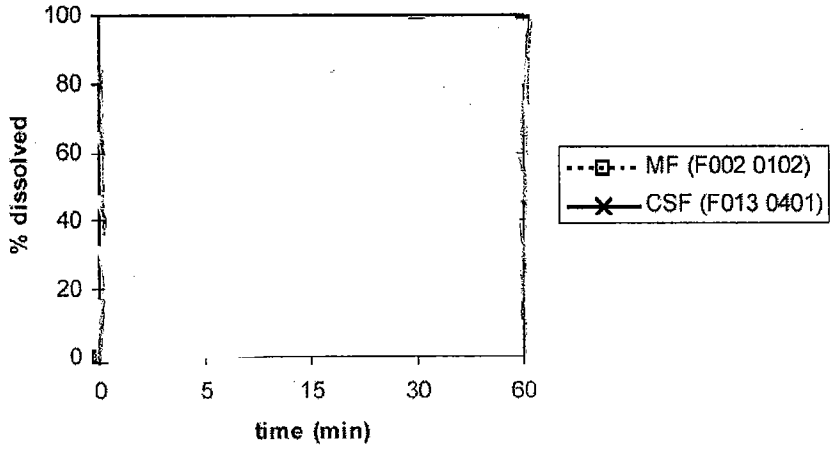

Fig. 11. Dissolution profiles of ICL670 CSF and MF 250 mg tablets

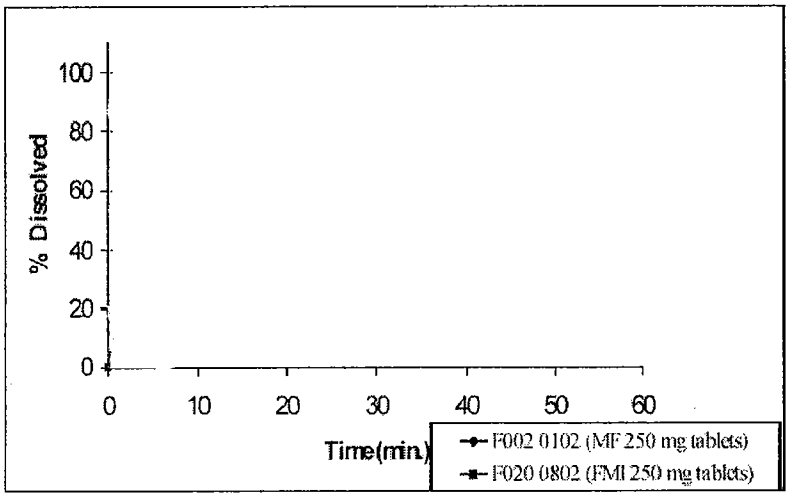

Fig. 11. Dissolution profiles of ICL670 FMI and MF 250 mg tablets

4. What is the effect of food on the bioavailability of ICL670?

There is a significant food-effect on the PK of ICL670, whereby AUC_{0-t} was doubled while Cmax increased by 77% with high fat meal compared to administration of ICL670 under fasting conditions. Administration with standard breakfast (450 cal) resulted in a increase for AUC_{0-t} and Cmax of 47% and 49%, respectively. Administration of ICL670 tablet 30 minutes before a high-fat breakfast (1000 cal) and standard breakfast (450 cal) resulted in mean AUC_{0-t} and Cmax increases of 23% and 25%, and 21% and 19%, respectively, relative to fasting conditions. ICL670 tablets were administered 30 min before a standard breakfast in the pivotal clinical trial (study 107). ICL670 tablets are proposed to be dispersed in water and administered. They may alternately be administered intact or dispersed in apple juice or orange juice.

Three studies were conducted to evaluate the effect of food on the bioavailability of ICL670 ; namely studies 2120, 2121 and 105F.

Study 105F was an open-label, randomized, single-dose, two-treatment, two period, two-sequence crossover design in β-thalassemia patients (n =12). In each of the two periods, patients received a single 20 mg/kg oral dose of ICL670 either under fasting conditions or within 5 min of consuming a high-fat breakfast. The results indicated that administration of ICL670 following a high-fat breakfast resulted in doubling of the total exposure (AUC_{0-t}) while Cmax increased by 77% relative to the corresponding values after administration of ICL670 under fasting conditions (see Table 19).

Table 19. PK parameters of ICL670 after single oral dose of 20 mg/kg under fasting and fed conditions

Treatment	t_{max} (h) median (min, max)	C_{max} (µmol/L) mean ± SD (CV%)	AUC_{0-t} (h•µmol/L) mean ± SD (CV%)	$AUC_{0-\infty}$ (h•µmol/L) mean ± SD (CV%)	$t_{1/2}$ (h) mean; median ± SD (CV%)
A (fasted)	2.59 (1.00, 3.58)	47 ± 12 (26)	458 ± 162 (35)	570[1)] ± 203 (36)	20.96[1,2)]; 14.44[1)] ± 22.20 (106)
B (fed)	3.71 (2.50, 8.00)	84 ± 23 (27)	892 ± 226 (25)	924[3)] ± 282 (31)	10.13[3)]; 10.90[3)] ± 4.31 (43)

[1)] Determined in 9 evaluable subjects; [2)] One patient had slowly declining and low concentrations (probably related to enterohepatic recirculation) and therefore had a $t_{1/2}$ of 78 h; [3)] Determined in 8 evaluable subjects

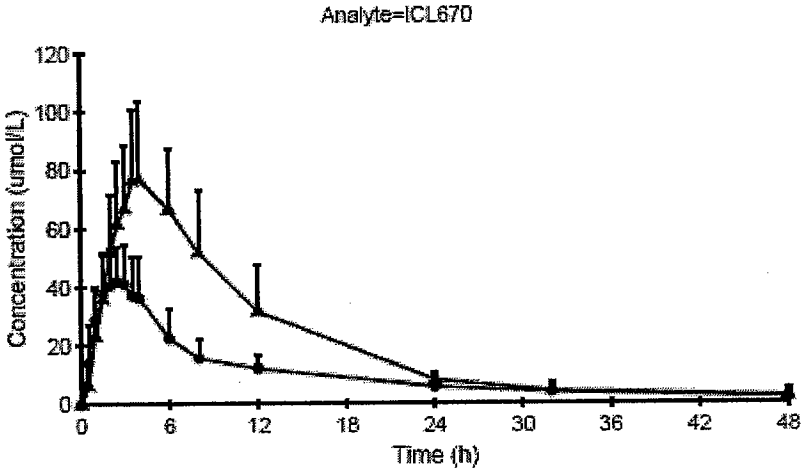

Figure 12. Mean plasma concentration (SD) of ICL670 after administration of single doses of 20 mg/kg of ICL670 under fasting and fed conditions.

Study 2121 was an open-label, randomized, four-period, four-treatment crossover study in healthy volunteers to evaluate the bioequivalence of ICL670 (20 mg/kg) administered either 0.5 hour before a high-fat 1000 cal breakfast, 0.5 hour before a standard 450 cal breakfast, or with a standard 450 cal breakfast compared to fasting condition. The results indicated that PK profiles for ICL670 were comparable when administering ICL670 0.5 hr before either a standard breakfast or a high-fat breakfast, with mean Cmax and AUC_{0-t} values increasing by 21-23% and 19-25%, respectively, relative to that under fasting conditions. Administration of ICL670 with a standard 450 cal standard breakfast resulted in mean Cmax and AUC_{0-t} values that were 49% and 47% higher, respectively, relative to administration under fasting conditions (see Tables 20 & 21).

Table 20. PK parameters of ICL670 after single oral dose of 20 mg/kg under fasting and fed conditions (study 2121)

Treatment	A (before high-fat breakfast)	B (before standard breakfast)	C (with standard breakfast)	D (fasted)
N of subjects	N = 28	N=28	N=28	N=28
t_{max} (h)*	2.0 [ ]	2.25 [ ]	3.5 [ ]	3.0 [ ]
C_{max} (µmol/L)	102±26.7	98.2±29.0	118±23.7	82.2±24.0
AUC_{0-4h} (h•µmol/L)	293±71.2	286±86.9	339±67.7	240±71.0
AUC_{0-24h} (h•µmol/L)	1080±393	1040±351	1300±366	812±250
AUC_{0-t} (h•µmol/L)	1340±523	1320±479	1580±492	1060±332
N of subjects#	N = 22	N = 24	N = 20	N = 20

Table 21. Statistical comparison of ICL670 PK data: ICL670 given 0.5 hour before a high fat breakfast, 0.5 hour before, and together with a standard breakfast vs. administration under fasting conditions

Treatment compared to ICL670 under fasting condition	Parameters (unit)	Geometric mean ratio*	Lower 90% confidence limit*	Upper 90% confidence limit*
ICL670 0.5 hour before high fat breakfast (A vs D)	$AUC_{0-\infty}$ (h•µmol/L)	1.13	1.02	1.25
	AUC_{0-t} (h•µmol/L)	1.23	1.13	1.33
	C_{max} (µmol/L)	1.25	1.14	1.37
ICL670 0.5 hour before standard breakfast (B vs D)	$AUC_{0-\infty}$ (h•µmol/L)	1.25	1.13	1.38
	AUC_{0-t} (h•µmol/L)	1.21	1.12	1.32
	C_{max} (µmol/L)	1.19	1.09	1.31
ICL670 together with standard breakfast (C vs D)	$AUC_{0-\infty}$ (h•µmol/L)	1.41	1.27	1.56
	AUC_{0-t} (h•µmol/L)	1.49	1.37	1.62
	C_{max} (µmol/L)	1.47	1.34	1.61

*means and confidence limits are back transformed from log-scale; a value greater than 1 indicates a smaller value when ICL670 was administered under fasting condition.

Study 2120 was an open label, randomized, four-way crossover study in 28 male healthy individuals (age 18-45 years). Subjects received a total of four treatments of ICL670 – each treatment consisted of a single oral dose of 20 mg/kg ICL670 tablets in water without dispersion or dispersed in one of the three liquids; orange juice, apple juice, and water. The results indicated that ICL670 tablets dispersed in orange juice and ICL670 tablets dispersed in water were bioequivalent. While ICL670 tablets dispersed in apple juice and ICL670 tablets dispersed in water were not bioequivalent, the observed PK differences are unlikely to be of clinical relevance (see Table 22).

Novartis proposed statement in the package insert, "EXJADE should be taken on an empty stomach at least 30 minutes prior to food preferably at the same time every day",

is acceptable. In addition, language related to dispersion of the tablets should be changed as follows to allow dispersion in apple juice; "EXJADE tablets for oral suspension can be dispersed in water, orange juice or apple juice".

Table 22. Mean PK parameters of ICL670 in healthy volunteers following a single oral dose of 20 mg/kg non-dispersed in water (A), dispersed in orange juice (B), dispersed in apple juice (C) and dispersed in water (D)

Parameter	Arithmetic mean ± SD* (CV%) [Geometric mean]			
	A: 20 mg/kg non-dispersed in water (N=28)	B: 20 mg/kg dispersed in orange juice (N=28)	C: 20 mg/kg dispersed in apple juice (N=28)	D: 20 mg/kg dispersed in water (N=28)
t_{max} (h)	3.50 (1.50-6.00)	3.00 (2.00-6.00)	3.50 (2.50-6.00)	3.00 (1.50-4.00)
C_{max} (µmol/L)	70.3 ± 28.0 (40) [66.3]	75.2 ± 17.9 (24) [73.1]	61.9 ± 17.1 (28) [59.6]	71.0 ± 24.7 (35) [67.7]
$AUC_{(0-4h)}$ (h•µmol/L)	184 ± 71.3 (39) [173]	192 ± 44.6 (23) [187]	132 ± 45.9 (35) [123]	201 ± 62.4 (31) [193]
$AUC_{(0-24h)}$ (h•µmol/L)	763 ± 415 (54) [697]	762 ± 193 (25) [738]	619 ± 182 (30) [595]	728 ± 263 (36) [686]
$AUC_{(0-t)}$ (h•µmol/L)	1040 ± 530 (51) [953]	1010 ± 278 (28) [969]	882 ± 252 (29) [848]	996 ± 352 (35) [939]

Table 23. Statistical comparison of ICL670 PK data: ICL670 tablet administered dispersed in orange juice, apple juice or water, and as non-dispersed in water

Comparison	Parameters (unit)	Geometric mean ratio*	Lower 90% confidence limit*	Upper 90% confidence limit*
ICL670 dispersed in apple juice/ICL670 dispersed in water	$AUC_{(0-t)}$ (h•µmol/L)	0.90	0.83	0.98
	C_{max} (µmol/L)	0.88	0.79	0.98
ICL670 dispersed in orange juice/ICL670 dispersed in water	$AUC_{(0-t)}$ (h•µmol/L)	1.03	0.95	1.12
	C_{max} (µmol/L)	1.08	0.96	1.21
ICL670 non-dispersed in water/ICL670 dispersed in water	$AUC_{(0-t)}$ (h•µmol/L)	1.01	0.93	1.10
	Cmax (µmol/L)	0.98	0.87	1.10

2.6 Analytical Section

1. Have the analytical methods been adequately validated?

Validated HPLC/UV and [redacted] analytical assay methods were developed and used to quantify ICL670 and the iron complex in biological fluids throughout the clinical development program.

An HPLC method with UV detection was developed for the determination of ICL670 and its iron complex in plasma. The limit of quantification (LOQ) was [redacted] µmol/L for ICL670 and [redacted] µmol/L for the iron complex. Another HPLC-UV method was used for the determination of the total concentration of ICL670 present as the free ligand and the iron complex in urine and the limit of quantification was [redacted] µmol/L. The HPLC-UV methods were used for the analysis of the plasma and urine samples of the first clinical trials. Subsequently, an HPLC method with [redacted] detection with a higher throughput and selectivity was used for the analysis of the plasma samples of the clinical trials performed during the full development phase of the clinical program. Both HPLC-UV and [redacted] methods were fully validated, including a cross-validation between the two methods. The two methods, HPLC-UV and [redacted] were found to be entirely compatible. The performance of the HPLC-UV and the [redacted] methods for the determination of either ICL670 and its iron complex or total ICL670 were validated against each other in human plasma.

The [redacted] method developed to assay ICL670 and its iron complex in plasma and urine was found to be precise and accurate over a concentration range of [redacted] µmol/L for ICL670 and [redacted] µmol/L for the iron complex. The limit of quantification was [redacted] µmol/L for ICL670 and [redacted] µmol/L for the iron complex.

With respect to intra-day accuracy and precision for ICL670, accuracy at LLOQ was [redacted] while precision was [redacted]. Above LLOQ, accuracy was within the range of [redacted] while precision was within the range of [redacted]. For the iron complex, accuracy at LLOQ was [redacted] while precision was [redacted]. Above LLOQ, accuracy was within the range of [redacted] while precision was within the range of [redacted]

With respect to inter-day accuracy and precision for ICL670, accuracy at LLOQ was [redacted] while precision was [redacted]. Above LLOQ, accuracy was within the range of [redacted] while precision was within the range of [redacted]. For the iron complex, accuracy was [redacted] while precision was [redacted]. Above LLOQ, accuracy was within the range of [redacted] while precision was within the range of [redacted] to [redacted]

Table 24. Summary of the analytical methods used for ICL670 and the its iron complex in biological fluids

Analyte	Method	Matrix	LOQ [µmol/L]	Report	Date
ICL670	HPLC-UV	Plasma		[R97-0009]	14.04.1997
ICL670	HPLC-UV	Plasma		[R98-0020]	25.09.1998
Fe-[ICL670]$_2$	HPLC-UV	Plasma		[R98-0020]	25.09.1998
ICL670	HPLC-UV	Plasma		[R99-0043]	04.06.1999
ICL670	HPLC-UV	Urine		[R99-0011]	06.09.1999
ICL670	HPLC-UV	Plasma		[R99-0014]	31.01.2000
Fe-[ICL670]$_2$	HPLC-UV	Plasma		[R99-0014]	31.01.2000
ICL670	/	Plasma		[R02-1713]	23.09.2003
Fe-[ICL670]$_2$	/	Plasma		[R02-1713]	23.09.2003
ICL670	/	Plasma		[R03-0421]	10.11.2004
[^{14}C]ICL670	/	Plasma	quantitative*	[R97-0522]	11.08.1998

* For radioactivity determination, a limit of detection (LOD) was defined. The LOD depends on specific radioactivity, sample size and counting time. Generally, the LOD was 1-70-fold lower than the analytical method for non-radiolabeled ICL670.

3. *Detailed Labeling Recommendations*

The key CPB labeling recommendations are summarized as follows:

- Under **Pharmacokinetics** subsection of the **CLINICAL PHARMACOLOGY** section, the following statement was revised to include the reported elimination half-life for ICL670 following I.V. administration:

"Deferasirox and metabolites are primarily (84% of the dose) excreted in the feces. Renal excretion of deferasirox [ ] The mean elimination half-life ($t_{1/2}$) ranged from 8 to 16 hours following oral administration. [ ]

- Under **Food/Drug Interaction** subsection of the **PRECAUTIONS** section, the following statement was revised to include apple juice as an additional alternate administration option for ICL670 tablet:

"EXJADE tablets for oral suspension can be dispersed in water, orange juice or apple juice. "

Additional labeling changes may be forthcoming after discussions with the Clinical Review Team.

4. Appendices

4.1 Proposed labeling (original and Agency proposed)

4.2 Division Director's Concurrence

4.3 OCPB Filing and Review Form

Appendix 4.1

Proposed Package Insert

12 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Appendix 4.2

Division Director's Concurrence

-----Original Message-----
From: Doddapaneni, Suresh
Sent: Thursday, October 06, 2005 9:20 AM
To: Malinowski, Henry J
Cc: Al-Fayoumi, Suliman I
Subject: Phase IV commitments for Deferasirox (NDA 21-882)

Suresh,
I made some small changes which allows for patients with hepatic impairment to be used, perhaps as part of a clinical study...Hank

Hank

Following are the two Clin Pharm Phase IV commitments for Deferasirox. Briefing attendees agreed with the hepatic impairment study while Shiew-Mei gave input into the in vitro metabolism study.

(1) Deferasirox is primarily eliminated by metabolism. As such, in hepatically impaired patients deferasirox is likely to accumulate with potential safety implications. Therefore, data should be obtained characterizing the pharmacokinetics of deferasirox in hepatically impaired subjects (subjects/patients with mild, moderate, and severe categories of impairment per Child-Pugh Classification) relative to otherwise healthy subjects/patients. If warranted, these data should be used to propose dosage adjustment in patients with hepatic impairment using this drug.

(2) Metabolism studies conducted *in vitro* have shown that deferasirox has the potential to inhibit CYP450 isozymes. The I/Ki ratios for CYP450 isozymes-2C8, 1A2, 2A6, 3A4/5, 2D6, and 2C19 were in the range of 0.4 - 1.2. Per the Agency's current practice, an estimated I/Ki ratio of greater than 0.1 is considered postive and a follow up *in vivo* evaluation is recommended. As such, conduct an *in vivo* interaction study investigating the potential of deferasirox to inhibit CYP4503A4 isozyme. If results from this study are positive, additional *in vivo* studies should be conducted investigating the potential of deferasirox to inhibit other isozymes mentioned above.

Please provide your feedback.

Thanks, Suresh

Appendix 4.3

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-882	Proposed Brand Name	Exjade
OCPB Division (I, II, III)	II	Generic Name	Deferasirox
Medical Division	GI & Coagulation	Drug Class	Metal chelator
OCPB Reviewer	Suliman Al-Fayoumi Christy John	Indication(s)	Treatment of chronic iron overload
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	IR tablet for suspension
		Dosing Regimen	20-30 mg/kg/day
Date of Submission	5/2/05	Route of Administration	Oral
Estimated Due Date of OCPB Review	9/15/05	Sponsor	Novartis
PDUFA Due Date	11/2/05	Priority Classification	Priority
Estimated Division Due Date	10/2/04		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1	1	
Isozyme characterization:	X	1	1	
Blood/plasma ratio:	X	1	1	
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:				
Patients-				
single dose:	X	1	1	
multiple dose:	X	2	2	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	
In-vivo effects of primary drug:				
In-vitro:	X	2	2	
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	2	2	
Phase 3:	X	1	1	
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	

Phase 3 clinical trial:				
Population Analyses –				
Data rich:	X	1	1	
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1	1	
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	3	3	
Dissolution:	X	2	2	
(IVIVC):				
Bio-waiver request based on BCS				
BCS class	X	1	1	
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	X	9	9	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	Not needed at this time	
QBR questions (key issues to be considered)	• **Is there a need for a PK study in hepatic impairment?** • **Is there a need for *in vivo* drug-drug interaction studies?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suliman Alfayoumi
10/7/2005 10:21:42 AM
BIOPHARMACEUTICS

Christy John
10/11/2005 01:24:54 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
10/11/2005 02:04:27 PM
BIOPHARMACEUTICS