Blood Products Advisory Committee Briefing Document

Exjade® (deferasirox; ICL670) for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis)

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List of abbreviations

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alaninine aminotransferase
AST	aspartate aminotransferase
AE	Adverse Event
CI	confidence interval
CYP	cytochrome P450
DBA	Diamond-Blackfan anemia
DFO	deferoxamine
FDA	Food and Drug Administration of the United States of America
GI	Gastrointestinal
IC_{50}	half-maximal inhibitory concentration
ITT	intent to treat
LIC	liver iron concentration
MDS	myelodysplastic syndromes
n	number of patients in study/treatment group
PD	pharmacodynamic
PK	pharmacokinetic
PP-1	per protocol-1
PP-2	per protocol-2
PRBC	packed red blood cells
SAE	Serious Adverse Event
s.c.	subcutaneous
SCD	sickle cell disease
SD	standard deviation
SQUID	magnetic susceptometry by superconducting quantum interference device
ULN	upper limit of normal

1 Executive Summary

Chronic iron overload is a serious complication of the potentially life-saving blood transfusions administered for a variety of congenital and acquired disorders. Regardless of the underlying disease state, progressive loading with excess iron leads to tissue damage, ultimately resulting in organ failure and death.

Currently, the only available iron chelation therapy in the United States is deferoxamine (DFO). The benefit of chelation therapy with DFO in reducing the morbidity and mortality from iron overload in patients with ß-thalassemia major is well-established. Convincing evidence also indicates that iron overload causes morbidity in patients with other types of anemia requiring transfusion therapy, and that in these conditions DFO is equally effective in preventing complications. Unfortunately, DFO can only be administered by prolonged subcutaneous or intravenous infusion (8 to 12 hours/day, 5 to 7 days/week), and therefore compliance is poor, leading to suboptimal efficacy of this therapy in preventing morbidity and mortality. As a result, complications of iron overload continue to develop in these patients, despite the availability of this otherwise effective drug.

ICL670 (Exjade®, deferasirox) is an N-substituted bis-hydroxyphenyl-triazole, which represents a new class of tridentate iron chelators with high affinity and selectivity for iron. Biopharmaceutical properties of ICL670 allow administration by the oral route and facilitate access to intracellular iron stores. ICL670 has been developed for the intended indication of the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderois) in adult and pediatric patients as young as two years of age.

In animal models, including the mouse, rat, and marmoset, daily oral doses of ICL670 produced dose dependent fecal iron excretion with a chelation efficiency of nearly 30% and a significant reduction of liver iron concentration (LIC). Toxicologic findings were attributed principally to excessive iron depletion with the higher doses, most notably a renal tubular nephropathy, which was decreased with iron supplementation.

Pharmacokinetics in humans show that ICL670 is rapidly and extensively absorbed after oral dosing and has a terminal elimination half-life of 8 to 16 hours, making it suitable for once-daily admimistration. Significant drug-drug interactions are not expected due to a lack of involvement of oxidative (cytochrome-mediated) metabolism.

Short-term data in ß-thalassemia patients from the pharmacodynamic (PD) Study 0104 showed dose-proportional net iron excretion exceeding the objective of 0.3 mg Fe/kg/day with daily doses of at least 20 mg/kg. Long-term effects of ICL670 in lowering LIC were observed in the one-year randomized, DFO-controlled PD Study 0105, where 20 mg/kg ICL670 had a similar effect to 40 mg/kg of DFO. A 10 mg/kg ICL670 dose maintained neutral iron balance on average.

Novartis planned the clinical development and registration strategy for ICL670 to reflect the intended use of ICL670 across pediatric and adult patients. ß-thalassemia was employed as a model disease for documentation of drug effectiveness, since morbidity and mortality from iron overload were well established in this population. Patients with sickle cell disease and

other less common types of congenital and acquired anemia served largely for the examination of safety of the compound, although efficacy data were also collected.

The efficacy of ICL670 in terms of its effect on LIC, an accepted marker of body iron burden, was examined as a primary or secondary objective in three large studies: a Phase III randomized, comparator controlled trial in 586 patients with ß-thalassemia (Study 0107), a large Phase II non-comparative study in 184 patients with various transfusion-dependent chronic anemias unable to be treated with DFO (Study 0108), and a Phase II randomized, comparator-controlled study in 195 patients with sickle cell disease (Study 0109). All three trials enrolled adult and pediatric patients and 46.7% of patients were <16 years of age. These registration studies for ICL670 represent the largest prospectively conducted clinical trial program of an iron chelator.

Based upon the baseline LIC group (2-3, > 3-7, > 7-14, > 14 mg Fe/g dw) as determined by liver biopsy or magnetic susceptometry by superconducting quantum interference device (SQUID), ICL670 doses of 5, 10, 20 and 30 mg/kg given daily and DFO doses of 20-30, 25-35, 35-50 and = 50 mg/kg given five nights per week were administered. Patients randomized to receive DFO with LIC values < 7 mg Fe/g dw were permitted to remain on their pre-study doses, even if these doses were higher than those specified by the protocol, since they were deemed to be on safe and effective doses of DFO at the time of study entry.

DFO doses of 20-30 and 25-35 mg/kg were compared to ICL670 doses of 5 and 10 mg/kg in the two groups of patients with lower body iron burden. These two lower ICL670 doses were selected for the patient groups with lower baseline iron burden in order to avoid the possibility of over-chelation (a potential toxicity of iron chelation noted in the literature and observed in preclinical studies of ICL670), even though they were below the optimal DFO:ICL670 dose ratio of 2:1 indicated by PD studies.

The primary endpoint for Studies 0107 and 0108 was ‘success rate’ based on the measure of LIC and was developed in conjunction with clinical experts and investigators. Maintenance of LIC was defined as success for patients with baseline LIC < 7 mg Fe/g dw, and reduction in LIC was defined as success for patients with higher baseline values. A non-inferiority margin of -15% for the lower limit of the 95% confidence interval (CI) for the difference in success rates was chosen for Study 0107. The sample size was based on the assumption of a 50% success rate for both ICL670 and DFO treatments (i.e., at maximal variance). The inclusion of several dosing cohorts in the pivotal trials, which was necessitated by the heterogeneity of the patient population in terms of baseline LIC, was acknowledged as potentially representing a challenge in terms of achievement of the primary efficacy endpoint. Therefore, the evaluation of non-inferiority in patients with baseline LIC = 7 mg Fe/g dw was added to the analysis plan for Study 0107 before closure of the study in order to support the primary analysis. Because there was no comparator in Study 0108, success was chosen to be declared if the lower limit of the 95% CI exceeded 50% in the overall population of patients treated.

The protocol-specified, preplanned analysis of secondary endpoints included change in LIC in patients with baseline LIC = 7 mg Fe/g dw, change in serum ferritin, and iron balance as defined as the ratio of iron excretion to iron intake. Since determination of LIC by biopsy is invasive and access to LIC measurement by SQUID is limited, serum ferritin measurement

was investigated for the establishment of a correlation with LIC in order to facilitate patient management in routine clinical practice.

In the cohort of patients with baseline LIC values = 7 mg Fe/g dw (those treated with ICL670 doses of 20 or 30 mg/kg) in Study 0107, ICL670 was non-inferior to DFO (Table 1-1). In addition, in Study 0108 the success criteria were met in the population of patients with baseline LIC values = 7 mg Fe/g dw that could be evaluated for efficacy (58.5%, 95% CI 50.3-66.6). However, ICL670 did not achieve the protocol-specified primary criteria for declaring success in either Study 0107 or Study 0108 for the overall population. This result was mainly due to the under-dosing of ICL670 relative to DFO, particularly in patients with baseline LIC values < 7 mg Fe/g dw, who received insufficient ICL670 doses (5 and 10 mg/kg). Indeed, in Study 0107 the ratio of the average DFO:ICL670 doses was 5.5:1 and 3.6:1 in the two lowest dose groups as compared to 2.2:1 and 1.9:1 in the two higher dose groups. Thus, the effective dose ratio established by the PD studies was only achieved in the two higher dose groups.

Table 1-1 Study 0107: Success rates (PP-1 population)

	ICL670	DFO
	n=276	**n=277**
Average daily dose (mg/kg/day)	20.0 ± 8.3	43.5 ± 9.5
Success rate (n (%))	146 (52.9)	184 (66.4)
95% CI	47.0, 58.8	60.9, 72.0
Difference [95% CI]	-13.5 [-21.6, -5.4]	
LIC < 7 mg Fe/g dw	**n=85**	**n=87**
Average daily dose (mg/kg/day)	9.5 ± 1.9	35.7 ± 8.1
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**
Average daily dose (mg/kg/day)	24.7 ± 5.2	47.1 ± 7.8
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]**	

Analyses of secondary endpoints (change in LIC in patients with LIC = 7 mg Fe/g dw, change in serum ferritin, and iron balance) were consistently positive and supportive of the clinical effect of ICL670 20 and 30 mg/kg doses. In addition, a dose-effect relationship was demonstrated in these parameters across the full range of ICL670 doses administered.

Serial serum ferritin measurements were analyzed and correlated with changes in LIC. The correlation coefficient between the change in serum ferritin and the change in LIC over one year was 0.63 ($p<0.001$) in patients treated with ICL670 and evaluated by liver biopsy in Studies 0107 and 0108. This correlation supports the utility of regularly monthly measurements of serum ferritin in the monitoring of chelation therapy.

ICL670 demonstrated acceptable safety and tolerability in adult and pediatric patients. Overall, the most common adverse events reported were diarrhea, vomiting, nausea, headache, abdominal pain, pyrexia, and cough. In the comparative Study 0107, abdominal

pain, diarrhea, nausea and skin rash were reported more frequently in patients receiving ICL670, whereas pyrexia, headache, cough, pharyngeal pain and back pain were reported more frequently in patients receiving DFO. In this same study, serious adverse events (SAEs) were reported in 9.1% and 8.6% and discontinuations were reported in 5.7% and 4.1% of those receiving ICL670 and DFO, respectively.

Increases in serum creatinine that were generally within the normal range and which never exceeded twice the upper limit of normal were the most common laboratory abnormality observed in 36% of patients overall. Dose reductions as specified in the clinical protocols resulted in normalization or stabilization of the serum creatinine value in about 25% and 60% of patients, respectively. The remaining patients had values that fluctuated between baseline and the maximal increase observed prior to dose reduction, and no patient discontinued study because of progressive increases in serum creatinine. In two patients an increase in serum alaninine aminotransferase (ALT) levels occurred during ICL670 treatment that resolved with drug discontinuation and recurred with rechallenge, suggesting drug-induced change. In both cases the ALT values returned to baseline after subsequent drug discontinuation.

ICL670 did not have an effect on hematologic parameters or on the bone marrow. Drug-related agranulocytosis, thrombocytopenia, growth failure or bone changes have not been observed in clinical studies, in contrast to published information on other iron chelators.

In summary, in Study 0107 ICL670 was shown to be non-inferior to DFO when the proper dose ratio was achieved (i.e., a DFO:ICL670 ratio of about 2:1). This result is supported by the success rate in the 20 and 30 mg/kg dose groups evaluable in Study 0108 as well as by secondary endpoints analyzed in these studies. Safety and efficacy were demonstrated in both pediatric and adult patients and in various underlying diseases affected by iron overload.

Overall, ICL670 has a favorable benefit to risk profile when administered at starting doses of 20 and 30 mg/kg. At these doses, ICL670 has similar efficacy to DFO but is not associated with the complications and burden of subcutaneous or intravenous infusion. In fact, the greatest risk of DFO therapy may be non-compliance which leads to potential morbidity and mortality due to iron overload. Although gastrointestinal events are more common with ICL670 therapy compared to DFO, these were mostly mild to moderate in severity and resulted in few discontinuations of therapy. The monthly monitoring of serum ferritin and safety markers (serum creatinine, liver function tests) allows effective dose titration in which the benefit/risk ratio is optimized for the individual, regardless of their underlying age, iron burden or anemic condition. Therefore, the availability of ICL670 would fulfill an unmet medical need for an effective oral chelation therapy that can be instituted early in childhood and be continued through adolescence into adulthood, thus preventing the development of complications of iron overload.

2 Background information

Chronic iron overload represents a serious complication of potentially life-saving regular blood transfusions administered for a variety of congenital and acquired types of anemia. Iron from frequent blood transfusions deposits mainly in the liver, endocrine organs, and heart. The pathologic changes and clinical manifestations associated with progressive iron overload have been best documented in patients with ß-thalassemia major where they are already apparent within the first 5 years of life (Iancu et al, 1977; Jean et al, 1984). A convincing body of evidence also shows that morbidity and mortality from iron overload affects patients with other disorders requiring long-term blood transfusion (Schafer et al, 1981; Ballas, 2001; Olivieri, 2001). Regardless of the underlying disease state, without intervention excess iron leads to tissue damage, ultimately culminating in organ failure and early death (Olivieri and Brittenham, 1997).

2.1 Pathophysiology of iron overload

Iron is an essential element in the body, playing a critical role in electron transfer reactions and in transporting oxygen. Iron absorbed through the diet is bound to transferrin and is transported to tissues, where it is normally stored as soluble ferritin, or in some cases, as insoluble hemosiderin. A small amount of ferritin is normally found in plasma, and this usually correlates with total body iron stores (Andrews, 1999). Red blood cells normally contain the majority of the body's iron. The remaining iron that is not utilized for metabolic reactions is stored in the liver and reticuloendothelial system.

There is no biological mechanism for the active elimination of excess iron from the body. This has critical clinical relevance in humans when iron accumulates due to blood transfusion or when there is an excessive uptake of dietary iron. The toxicity of iron results from two related events: 1) excess iron deposits in various tissues of the body, particularly the liver, heart, and endocrine organs, and 2) free iron catalyzes the formation of highly reactive hydroxyl radicals that lead to membrane damage and denaturation of proteins. Once iron in the body exceeds a certain level, these effects lead to significant morbidity and mortality.

Although morbidity and mortality from iron overload has been most clearly documented in patients with ß-thalassemia major requiring lifelong blood transfusions in order to survive, patients with a variety of other congenital and acquired conditions requiring long-term blood transfusions are also similarly affected once they have received a sufficient iron load (Jensen et al, 1996; Kwiatkowski and Cohen, 2004). Because of disease-dependent differences in the frequency of transfusions and the rate of iron loading, there is some variability in the amount of time taken for toxic levels to accumulate (Olivieri, 1999). Notwithstanding these variations, the toxic effects of iron loading appear to be similar.

In patients with ß-thalassemia major who are regularly transfused (defined for an adult as receiving about 2 to 4 units of packed red blood cells (PRBC) per month), evidence of iron overload is generally present by two years of age as evidenced by increased LIC or serum ferritin (Olivieri and Brittenham, 1997). If chelation therapy is not instituted, serious clinical manifestations of iron overload soon become apparent. Similarly, although the time course may vary, serious clinical manifestations of transfusional iron overload eventually also occur

in other congenital and acquired disorders if treatment with chelation therapy is not instituted after evidence of iron overload is appreciated.

2.2 Beta-thalassemia major: a model disease for iron overload

2.2.1 Clinical course of iron overload without adequate chelation therapy

PRBC contain approximately one milligram of elemental iron per milliliter. Evidence of iron overload is generally apparent after about 100 to 120 mL/kg of PRBC have been administered, equivalent to 20 to 30 adult units (Olivieri, 1999; Porter, 2001a; National Institutes of Health, 2002). In frequently transfused thalassemic patients, the total body iron burden is estimated to increase at a rate of 2 to 5 g of iron per year (Olivieri, 1999). The accumulation of iron in the body is reflected by a measurable increase in LIC as well as by an increase in serum ferritin (Table 2-1). Increased morbidity and mortality are observed in patients with serum ferritin values above 2500 µg/dL or with LIC values above 7 mg Fe/g dw (Olivieri and Brittenham, 1997).

Table 2-1 Development of complications of iron overload in transfused patients with beta-thalassemia major who do not receive chelation therapy

LIC (mg Fe/g dw)	Average age at onset (years)	Description
3.2 to 7	3	Optimal level for maintenance in ß-thalassemia
7 to 15	9	Increased risk of complications
>15	18	Threshold for cardiac disease and early death

Adapted from Olivieri and Brittenham, 1997; Porter, 2001a

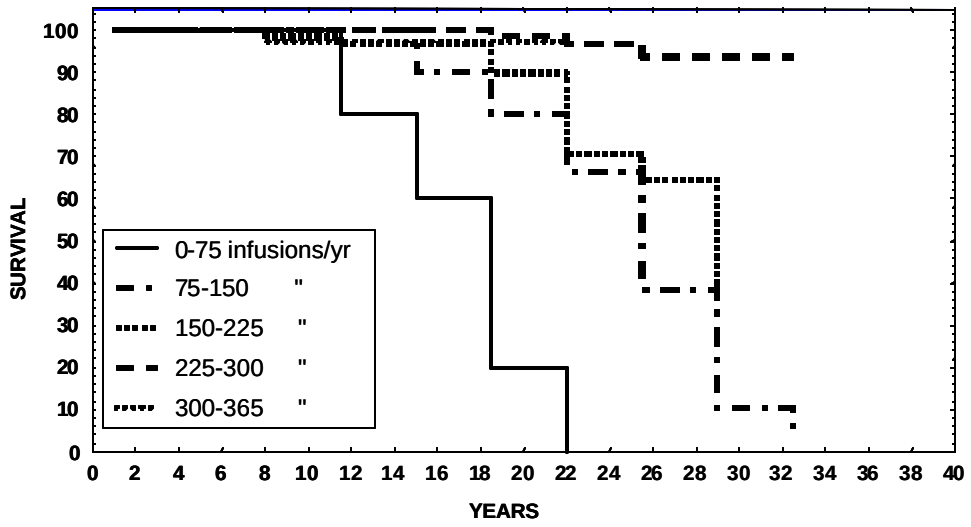
In the absence of chelation therapy, iron overload leads to the development of multi-system organ dysfunction, ultimately culminating in death in all patients (McLaren et al, 1983). Organs including the heart, liver, and endocrine organs appear to be preferentially affected by iron overload. This occurs either because the organ serves as a normal storage site for iron that becomes overwhelmed (e.g., the liver) or because of sensitivity of the organ to disruption by iron overload (e.g., endocrine organs). Medical histories of transfused thalassemic patients published before deferoxamine (DFO) became generally available suggest that the liver damage may be detectable as early as 2 years of age (Iancu et al, 1977; Jean et al, 1984). Without chelation therapy, patients generally develop cirrhosis between the ages of 10 to 15 years, but mild cirrhosis has been observed as early as 8 or 9 years of age (Prati et al, 2004). Endocrine complications including pituitary and gonadal failure are common even early in life leading to growth failure and delayed development of secondary sexual characteristics. The development of diabetes mellitus by early in the second decade of life is frequent. Cardiac complications, often manifest as congestive heart failure, have a peak incidence between age 10 and 15 years (Engle 1963, Olivieri 1999).

Consequently, regularly transfused patients with ß-thalassemia major who do not receive or who do not comply with chelation therapy to remove excess iron do not survive past the third decade of life due to the cumulative toxic effects of iron resulting in organ failure. A variety of epidemiologic data are consistent and indicate that in the absence of good compliance with an adequate regimen of chelation therapy, cardiomyopathy attributable to iron overload is the

most frequent cause of death in patients with ß-thalassemia major (Olivieri, 1999; Schrier and Angelucci, 2005).

A direct relationship between compliance with the prescribed chelation regimen over time and survival has been clearly documented (Olivieri and Brittenham, 1997). For example, in one series of 257 patients, 90% of the population of thalassemic patients who were administered more than 225 DFO infusions per year survived to age 30. In contrast, none who received fewer than 75 infusions survived to that age (Gabutti and Piga, 1996, Figure 2-1). Importantly, the survival curves start to diverge early, at around 10 years of age.

Figure 2-1 Relationship of survival to deferoxamine infusions in thalassemia



2.2.2 Iron chelation therapy

In patients with ß-thalassemia, iron chelation therapy is generally initiated very early in life when the body iron burden is clearly increased, as evidenced by a serum ferritin level of greater than 1000 µg/L or after the cumulative administration of 10 to 20 blood transfusions (Gabutti and Piga, 1996; Porter, 2001a).

Deferoxamine mesylate (Desferal®, DFO) was introduced about forty years ago and remains the standard chelation therapy, and the only approved drug in the United States for the removal of excess iron due to blood transfusions. Doses of DFO are commonly in the range from 30 to 50 mg/kg given as subcutaneous infusions over a period of 8 to 12 hours five to seven nights per week (Porter, 2001a). There is clear and consistent evidence in the literature of the clinical benefits of DFO therapy on both morbidity and mortality.

Early studies performed shortly after the introduction of DFO demonstrated an improvement in liver pathology and liver function (Barry et al, 1974; Hoffbrand et al, 1979; Cohen et al, 1984). Beneficial effects of DFO on growth, development, and gonadal function have been described with normalization of growth and sexual development in children and adolescents

(Maurer et al, 1988; Bronspiegel-Weintrob et al, 1990, Brittenham et al, 1994). DFO therapy also prevents and reverses cardiac insufficiency, the major cause of mortality in patients with ß-thalassemia major (Wolfe et al, 1985; Freeman et al, 1989; Richardson et al, 1993; Aessopos et al, 2004; Anderson et al, 2004; Davis et al, 2004). For example, in one study patients treated with DFO had an mean improvement in left ventricular ejection fraction from 36 to 49% (Davis and Porter, 2000).

Good compliance to therapy is critical to the efficacy of the chelation therapy. In a study examining 97 ß-thalassemia major patients treated with chelation therapy, survival free of cardiac disease was correlated with the number of serum ferritin measurements that did not exceed 2500 µg/L (Olivieri et al, 1994). Other studies have documented similar results on morbidity and mortality (Ehlers et al 1991; Brittenham et al, 1994; Olivieri et al, 1994; Gabutti and Piga 1996; Borgna-Pignatti et al, 2004). Unfortunately, due to the challenges of administering DFO by prolonged subcutaneous infusion, compliance with therapy is often poor. Therefore, many patients experience morbidity and mortality related to non-compliance, despite the availability of a drug that is otherwise effective in preventing complications (Cohen, 1987; Arboretti et al, 2001). This has driven the search for safe and effective oral iron chelators which are easy to administer and thus may enhance compliance.

2.3 Sickle cell disease

2.3.1 Transfusion practice

The goal of blood transfusion in sickle cell disease is different from that in ß-thalassemia major. Regular transfusions are used to decrease the proportion of circulating red cells containing abnormal sickle hemoglobin (HbS and others) and thereby to decrease the risk of developing severe complications such as stroke and acute chest syndrome (Stuart and Nagel, 2004). Types of transfusions administered to patients with sickle cell disease include intermittent or regular transfusions and exchange transfusions.

Because of a peak incidence of stroke in the first 3 to 5 years of life, regular blood transfusions are more common in the pediatric population than in adults. A large multicenter trial (STOP) demonstrated a clear benefit in reduction in incidence of stroke. Therefore, it is recommended that pediatric patients with abnormal transcranial Doppler evaluations (a measure of cerebral blood flow) receive regular blood transfusion therapy, either by simple or exchange transfusion (Adams et al, 1999). Subsequently, data have become available from a follow-up trial (STOP II) indicating that continued long-term transfusion therapy is necessary in high-risk pediatric patients to prevent stroke (National Institutes of Health, 2004).

2.3.2 Complications from iron overload

With the increased use of prophylactic transfusion therapy in the pediatric SCD population, iron overload prevalence is expected to increase rapidly, requiring intervention with chelation therapy in order to prevent morbidity and mortality (Kwiatkowski and Cohen, 2004). Adults with SCD also become iron overloaded. One prospective study performed over 11 years in 247 adult patients with SCD revealed that 62% of patients received an average of 10 units of PRBC per year, and that one-third had iron overload, as defined by a transferrin saturation of >50% (Ballas, 2001). Similar complications of iron overload develop over time in SCD as in

ß-thalassemia; for example, the development of hepatic fibrosis and cirrhosis (Olivieri, 2001). The above data are supported by the emerging findings from an ongoing registry of transfused sickle cell disease patients sponsored by the National Institutes of Health (Fung et al, 2004).

2.3.3 Iron chelation therapy

As transfusions to prevent complications often start later in life in patients with sickle cell disease than in patients with ß-thalassemia major, therapy with DFO is often initiated later in childhood or adolescence. In practice, doses of between 30 and 40 mg/kg at least five nights a week are used, with one guideline recommending 175 mg/kg/week (National Institutes of Health, 2002). Although large clinical trials have not been performed examining the effect of DFO on morbidity and mortality in patients with sickle cell disease, it is well accepted that chelation therapy is important in this population to prevent complications of iron overload (National Institutes of Health, 2002; Kwiatkowski and Cohen, 2004). Small case series examining DFO for the treatment of iron overload in patients with sickle cell disease have been published in the literature (Cohen and Schwartz 1978; Sillman et al, 1993; Porter, 2001b). These studies confirm the efficacy of DFO in facilitating iron excretion.

2.4 Myelodysplastic syndromes and other anemias

2.4.1 Transfusion practice and complications from iron overload

The myelodysplastic syndromes (MDS) are a spectrum of disorders that share ineffective hematopoiesis affecting one or more hematopoietic lineages and have the potential for transformation into acute myelogenous leukemia (AML). Clinically, they manifest with anemia, thrombocytopenia, and neutropenia. Based on the number of blasts in the bone marrow, the karyotype, and the number of cytopenias present, the International Prognostic Scoring System (IPSS) for MDS has been developed for use in predicting the progression of disease. The IPSS is predictive of both the median survival and the evolution to AML, and allows patients to be categorized into low, intermediate-1, intermediate-2, and high risk groups for disease progression (Greenberg et al, 1997). Low risk patients have a median survival of 5.7 years; however, some individuals survive for more than a decade.

Although there have been recent advances in the management of MDS, supportive care including regular blood transfusions remains a mainstay of therapy. Low risk patients with MDS who receive frequent blood transfusions on an ongoing basis gradually become iron overloaded in a manner similar to individuals with hereditary types of anemia requiring blood transfusions. Evidence indicates that these individuals develop similar complications of iron overload such as cardiac and liver disease (Schafer et al, 1981; Jensen et al, 1996; Jensen et al, 2003).

A variety of other congenital and acquired types of anemia, such as Diamond-Blackfan anemia (DBA) and aplastic anemia, require regular blood transfusions. There is currently no curative therapy for DBA (a genetic inability to produce red blood cells) other than bone marrow transplantation, so frequent transfusion from infancy is required for survival in the majority of patients. Although a large clinical study of the effects of iron overload in this disease is not available, case reports of complications in patients who have not received adequate chelation therapy indicate the development of complications typical of those seen in

ß-thalassemia major, including iron overload cardiomyopathy (Schafer et al, 1981). For patients with aplastic anemia who do not respond to bone marrow transplantation or to immunosuppressive therapy, regular blood transfusions are required which ensures long-term survival in some patients. Though no large clinical study is available, case reports in the literature clearly document that typical complications of iron overload can develop after a few years of regular blood transfusion (Himoto et al, 1995; Porter, 2001a), so institution of effective chelation therapy is important.

2.4.2 Iron chelation therapy

Although evidence for the efficacy of chelation therapy with DFO to reduce complications related to iron overload in MDS and other anemias is limited mainly to case reports, a few small case series have been published. Summarizing the individual case reports regarding patients with various congenital anemias, such as Diamond-Blackfan anemia and congenital dyserythropoietic anemia, DFO appears able to prevent typical complications of iron overload that would otherwise be encountered in these individuals (Janka et al 1981; Ambruso et al 1982; Smithson and Perrault, 1982).

On the basis of the experience with ß-thalassemia, without adequate chelation therapy clinically relevant consequences of iron overload in the liver or other organs may develop in MDS patients within 2 to 5 years of initiation of regular transfusions. In comparison to ß-thalassemia, patients with MDS are older and likely to have other co-morbid conditions, notably cardiovascular disease. Accordingly, it is reasonable to speculate that these patients may eventually become more sensitive to the organ toxicity of iron overload. For this population of low risk MDS patients who develop chronic iron overload due to blood transfusion, the timely institution of effective chelation therapy is therefore an important part of overall disease management (National Comprehensive Cancer Network, 2004).

2.5 Clinical assessment of iron overload

2.5.1 Serum ferritin

Serum ferritin determination is the most commonly used method in clinical practice to monitor iron chelation therapy, even though factors independent from iron stores affect serum ferritin levels (e.g., infection and inflammation). Although isolated serum ferritin measurements may not adequately reflect body iron status, repeated measurement of serum ferritin levels over time have been reported to provide useful information pertaining to body iron burden (Gabutti and Piga, 1996; Porter and Davis, 2002).

2.5.2 Liver biopsy

Determination of LIC from a biopsy specimen remains the reference method for the assessment of iron overload in patients with transfusional iron overload. It involves an invasive procedure that is occasionally associated with serious complications including death (Bravo et al, 2001). This parameter reflects total body iron stores and is known to correlate well with morbidity and mortality from iron overload (Angelucci et al 2000; Olivieri, 1999).

2.5.3 Biomagnetic susceptometry (SQUID)

Because liver biopsy is an invasive procedure, non-invasive methods for measurement of LIC have been under development. A biomagnetic susceptometer includes a Superconducting QUantum Interference Device (SQUID) which consists of superconducting material and is able to measure the very small magnetic field differences caused by the presence of iron. Magnetic susceptometry, commonly referred to as 'SQUID' represents a non-invasive technique that has been developed in order to repeatedly measure LIC. The method has been calibrated, validated by means of liver biopsies and other biological models, and clinically evaluated (Brittenham 1982, Fischer 1992). However, it is not widely available as there are only four clinical machines in the world.

3 Preclinical background information on ICL670

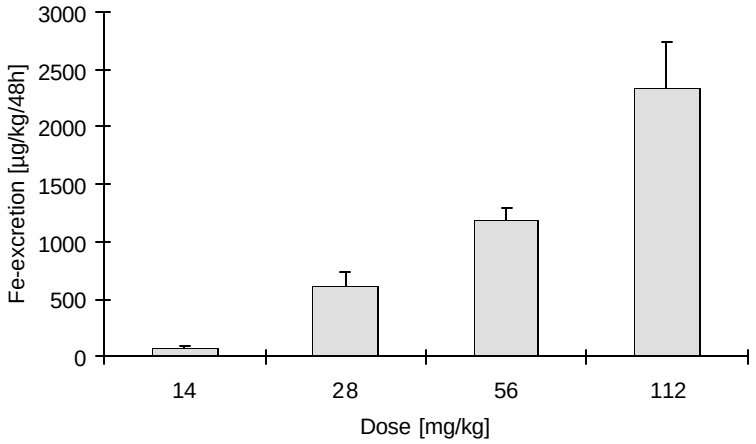
ICL670 is a synthetic, tridentate iron-selective compound that represents a novel class of iron chelators. ICL670 was designed by computer-assisted molecular modeling and was identified from over 700 chelating compounds.

3.1 Pharmacodynamics

The affinity of ICL670 for metal ions is: Fe(III) >Al(III) >>Cu(II) >>Zn(II) >Fe(II) >Mg(II) >Ca(II). It is a poor chelator for divalent metal ions and has a low affinity for Fe(II). In marmoset monkeys treated with ICL670 there was no increased excretion of copper and zinc above background.

In both rat and marmoset models, iron excretion was largely proportional to the ICL670 dose, and occurred primarily in bile, while urinary excretion was consistently low (<15%). In a single-dose study in iron-overloaded marmosets, the chelation efficiency was 29%. The daily dose of ICL670 corresponding to a therapeutic objective of excreting up to 0.5 mg/kg of iron was calculated to be approximately 22 mg/kg (Figure 3-1).

Figure 3-1 Dose-dependent iron excretion induced by ICL670 in iron-overloaded marmosets



Daily administration of up to 80 mg/kg ICL670 to non iron-loaded marmoset monkeys for 39 weeks (toxicity study) resulted in an average reduction of liver iron of up to approximately 85%. This high degree of liver iron depletion in a non-iron loaded model further confirms the high potency of this compound *in vivo*.

Safety pharmacology studies (primarily single dose studies) were conducted to assess the safety of ICL670 in particular organ systems. ICL670 has no significant effects on the uptake of dietary iron, central nervous system, renal, or respiratory function. A variety of *in vitro* and *in vivo* studies were conducted to explore possible cardiovascular effects of ICL670. While divergent data were generated in some of these *in vitro* systems, dog telemetry evaluations noted only an increase in mean heart rate (at concentrations six fold above the C_{max} observed in humans and twice that utilized in *in vitro* studies). Neither the hERG assay nor the telemetry study showed evidence for QTc prolongation.

3.2 Toxicity

Repeat-dose toxicity studies were conducted in rodents and non-rodents up to nine months in duration. The rat and marmoset were selected as the rodent and non-rodent species for toxicity testing. Both were also used as pharmacological models for ICL670 pharmacodynamics, as both species displayed metabolic profiles similar to humans. Exposure to ICL670 in animals at no-observed-adverse-effect levels (NOAEL) was generally less than that in humans at 20 mg/kg. As the animal models used in toxicology studies were not iron-overloaded, exposure was limited by toxic effects resulting from iron depletion in these animals. In rats fed a diet enriched in iron, the dose level for a NOAEL was increased, but exposure was still generally less than human exposure. At the highest doses tested in the shorter term toxicity studies, low multiples of human exposure to ICL670 could be obtained in the rat, with the marmoset exposure approaching the human exposure based on a clinical dose of 20 mg/kg/day. In the maximum doses tested in rat and mouse carcinogenicity studies, plasma exposures were 28 to 39% and 122 to 210% of human exposure, respectively. The limitation on obtaining high multiples of human exposure presented by using non iron-overloaded animals in the toxicology studies does not diminish the usefulness of these models for the identification of potential targets of toxicity in humans.

A nephropathy consisting of renal tubular degeneration was observed in all species tested. In the rat, renal tubular degeneration was observed at doses of 100 mg/kg (4 week study; normal diet) and 180 mg/kg (26 week study; iron supplemented diet). The exposure (area under the curve, AUC) at these doses was approximately 1.4 to 2.6 fold the human exposure. In rats, iron supplementation decreased the nephrotoxicity of ICL670, suggesting that the renal findings are a consequence of the pharmacological action of iron chelators under conditions of normal tissue iron levels. Similarly, in a marmoset study using iron-overloaded animals, no renal effects were observed. In an *in vitro* study, the addition of iron to cultures of human or porcine proximal tubular cells also reduced ICL670 cytotoxicity. While no conclusive statement can be made as to the specific mechanism responsible for the reduction in toxicity observed with iron supplementation, iron supplementation appeared to offer some protection. Based on a review across the rat toxicity studies, stable increases in creatinine levels were observed frequently at doses that produced histological evidence of renal tubular damage. Creatinine increases were less frequently observed in marmosets. In both species, creatinine

levels returned to baseline upon cessation of treatment. There was no evidence of ICL670-mediated glomerular damage, based on histological review, in any of the toxicity test species.

Cataracts were observed in the 26-week rat toxicity study with increased incidence as treatment progressed. The ocular changes, most of which were bilateral, varied in morphology from early cortical striations or vacuoles to mature cataracts. Cataracts were also observed in the rat neonatal/juvenile toxicity study and in the 26-week transgenic mouse carcinogenicity study. In contrast, in the 2-year rat carcinogenicity study, in which the doses and exposures overlapped with those in the 26-week study, no lenticular lesions were observed at any dose level. Cataracts were also not observed in any marmoset toxicity study.

Inflammatory and degenerative changes in the gallbladder and bile ducts were seen in some marmosets at high doses (400 mg/kg in studies = 4 weeks and at 80 mg/kg in chronic studies) and at doses that resulted in morbidity/mortality. When gall bladder inflammation was reviewed across all marmoset studies, the background incidence (control animals) was similar to that observed in all ICL670-treated animals. While the severity of these observations was greater in individual animals treated with high doses of ICL670, the increased severity may represent an effect on a pre-existing condition of the marmoset gall bladder.

There was no indication of genotoxicity *in vitro*, except for a weakly positive result in the V79 micronucleus screening test. A slight but statistically significant increase in the number of micronuclei was observed at the highest dose (50% mortality) in a rat *in vivo* bone marrow micronucleus assay; this was not considered an indication of direct genotoxicity but rather an alteration of hematopoiesis due to iron chelation. This result was not reproduced when iron overloaded animals were used. In addition, no carcinogenic potential was detected in rats treated for with ICL670 for 104 weeks or in transgenic (p53 heterozygous) mice treated for 26 weeks. ICL670 is not teratogenic. Reproductive and fertility studies in rats and rabbits showed an increase in skeletal variations in rat fetus and in the number of still-born animals only when lethal doses of ICL670 were administered to the maternal animals. As a precaution, ICL670 should be used during pregnancy only if benefits far outweigh risks.

The spectrum of ICL670-related effects noted in juvenile animal studies was generally similar to those seen in the repeated dose toxicity studies in adult animals without an apparent increase in tissue sensitivity.

4 Clinical pharmacology and dose-finding trials

ICL670 is formulated as a dispersible tablet (125, 250, and 500 mg tablets for oral suspension), which facilitates administration of the appropriate quantity of drug substance based on body weight to both pediatric and adult patients. The key pharmacology studies are listed in Table 4-1.

Table 4-1 Summary of pharmacology studies

Study No.	Study objectives, population	No. of subjects	Treatment duration	Medication dose/day
Healthy volunteers				
2101	Absolute bioavailability	21	1 day	IV: 130 mg, PO: 375 mg
2102	Digoxin drug interaction	16	1 day-ICL670 8 days-digoxin	ICL670 20 mg/kg, digoxin 0.25 mg
2120	Drink effect on ICL670	28	1 day each of 4 periods	20 mg/kg
2121	Food effect on ICL670	29	1 day each of 4 periods	20 mg/kg
2122	QT study	182	1 day each of 4 periods	Placebo, ICL670 20 mg/kg, ICL670 40 mg/kg, moxifloxacin 400 mg
Patients				
0101	Dose ranging in transfused ß-thalassemia patients	25	1 day	2.5, 5, 10, 20, 40, 80 mg/kg
0104	Iron balance in transfused ß-thalassemia patients	23	12 days	Placebo, ICL670 10, 20, 40 mg/kg
0115	ADME using radiolabeled ICL670 in transfused ß-thalassemia patients	5	14 days (radiolabeled given 1 day)	1000 mg
0105F	Food effect on ICL670 in transfused ß-thalassemia patients	12	1 day	20 mg/kg

4.1 Absorption, Distribution, Metabolism, Excretion

Following oral administration in ß-thalassemia patients peak plasma concentrations of ICL670 are achieved between 1 and 4 hours. The bioavailability of ICL670 is dose-proportional. The mean terminal elimination half-life of ICL670 is in the range of 8 to 16 hours after multiple-dose administration. The absolute bioavailability of ICL670 is 70% as determined by oral versus intravenous dosing in healthy volunteers. The high oral bioavailability of the drug and long half-life support a once-daily dosing regimen.

Phase I oxidative metabolism by CYP enzymes (primarily hydroxylation by CYP1A2 and CYP2D6) appears to be minimal, affecting about 8% of the administered dose. Phase II conjugation of ICL670 to glucuronic acid is the main route of metabolism, yielding both acyl- and phenol-glucuronides.

ICL670 and its iron complex Fe-$[ICL670]_2$ are eliminated primarily by hepatobiliary excretion into the feces. Renal excretion is minimal representing less than 8% of the dose administered.

4.2 Drug interactions

The potential for interactions between ICL670 and co-medications via CYP enzymes, and via hepatic anion transporters is low. ICL670 is a weak CYP enzyme inhibitor with IC_{50} values ranging from 100 to 500 µM. *In vitro* studies demonstrated a low glucuronidation interaction potential with paracetamol (acetaminophen). In the population pharmacokinetic (PK) analysis of the pivotal clinical studies, no significant drug interaction with concomitant acetaminophen was identified. No inhibition on the metabolism of ICL670 by hydroxyurea is expected based

upon the results of an *in vitro* study. A clinical study was performed to examine the potential for drug-drug interaction with digoxin, which is often used in patients with iron overload and impaired cardiac function. ICL670 had no impact on steady-state digoxin levels.

4.3 Pharmacokinetics in special patient populations

Hepatic or renal dysfunction

Renal excretion of ICL670 is minimal, representing about 8% of the dose. Studies of ICL670 did not enroll patients with serum creatinine values above the upper limit of normal. Therefore, specific studies assessing ICL670 pharmacokinetics in renal impairment were not done.

Thalassemia 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 the clinical studies and were treated with doses of ICL670 similar to patients without hepatic impairment. Safety, efficacy, and trough PK parameters were similar in these two groups of patients.

Demographic or baseline features

No major differences in exposure to ICL670 were seen when the PK of ICL670 was evaluated in healthy volunteers or in patients with ß-thalassemia, although healthy subjects showed lower concentrations in plasma of the iron complex of ICL670, which was likely due to the absence of iron overload in this population.

Population PK analysis based on data from 369 patients in four studies (0104, 0105, 0106, 0107) indicated that ethnic origin does not appear to affect the PK of ICL670. Female patients have an apparent clearance of ICL670 and the ICL670 iron complex which is moderately lower compared to males by 17.5% and 9.4%, respectively. These differences are not considered clinically relevant and do not warrant implementing separate dosing schemes in female and male patients, considering that the maintenance dose will be individually titrated.

The population analysis identified an age effect on PK, with pediatric patients showing a lower systemic exposure to drug compared to adults. For both ICL670 and the iron complex, the area under the plasma concentration versus time curve increased with age, approximately doubling between ages 2 and 18, but without further changes over the age range 18 to 50 years. The small number of elderly patients in the studies do not allow projections beyond 50 years, and the PK of ICL670 in patients = 65 years have not been investigated. In the pivotal Study 0107 there was a somewhat lower clinical success rate in achievement of the primary end point in the 2 to < 6 year-old age group of 42.9% compared to 65.1% and 63.2% in the 6 to 11 year-old and 12 to 16 year-old age groups, respectively. However, the success rates in children ages 6 to 11 years and adolescents ages 12 to 16 years were similar to those in adults. Therefore, the same doses calculated on the same body weight basis as adults and as administered in clinical trials are appropriate for children at least 6 years of age. Although there was a reduced exposure in the youngest patients, higher dosing recommendations are not appropriate for the age group 2 to < 6 years considering the high variability in their PK data.

In any case, this age group also showed a positive success rate associated with acceptable safety when receiving the same mg/kg dose as the older children and adolescents.

4.4 Pharmacodynamic studies

A key measure for assessing drug effect of an iron chelator is to study iron balance, which is calculated as the amount of iron excreted versus the amount of iron intake. The desirable ratio is = 1. Study 0104 studied short-term iron balance after the administration of ICL670.

Direct measurement of iron balance over a prolonged time interval is impractical. However, in patients receiving blood transfusions, the iron balance over a given interval may be calculated by determining the amount of iron administered in the form of blood transfusions and estimating the total iron excretion from the body through serial measurement of LIC using the formula of Angelucci et al (2000) and calculation of total body iron excretion (Table 4-2). An iron balance ratio less than 1 indicates that iron is accumulating in the body, whereas a value greater than 1 indicates iron removal from the body in excess of intake. The efficiency of chelation represents the proportion of the dose of ICL670 that is engaged in chelating iron. It can be used to provide an estimate of the dose of ICL670 theoretically required to excrete a given amount of iron. These methodologies were used in the long-term clinical trials.

Table 4-2 Calculation of iron balance parameters

Parameter	Formula
Iron intake (mg)	[PRBC (mL) x 1.08] **or** [whole blood (mL) x hematocrit x 1.08] or an estimated 200 mg for 1 adult unit of transfusion if the exact mL of PRBC is unknown
Total body iron (TBI) in mg	LIC (mg Fe/g dw) x 10.6 x body weight (kg)*
Total body iron excretion (TBIE) in mg/kg/day	[(Iron intake+($TBI_{baseline}$-$TBI_{end\text{-}of\text{-}study}$))/study duration in days]/body weight (kg)
Iron exretion/iron intake	[TBIE]/[Iron intake/body weight (kg)/study period (days)]
Iron chelation efficiency (%)	[(TBIE x 373 x 2)/(ICL670 dose (mg/kg/day) x 56)] x 100**

*from Angelucci et al, 2000
**374 and 56 are the molecular weights of ICL670 and iron, the factor 2 is the number of ICL670 molecules bound per iron atom

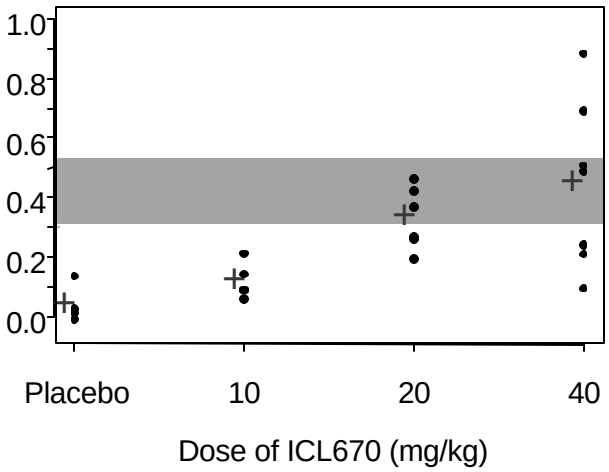
4.4.1 Short-term pharmacodynamic effect (Study 0104)

Study 0104 was a randomized, double-blind, placebo-controlled trial in which the ratio of iron excretion was directly measured in 23 β-thalassemia patients who received once daily placebo (n=5) or ICL670 at doses of 10 mg/kg (n=5), 20 mg/kg (n=6), or 40 mg/kg (n=7) for 12 days. Patients received a low iron diet and urine and stools were collected throughout the study period.

Dose-dependent iron excretion (almost entirely in the feces) was achieved at all three doses of active drug (Figure 4-1). As expected, iron excretion was negligible in the placebo group. Over the study period of 12 days, an ICL670 dose of 20 mg/kg once daily induced an average iron excretion rate of 0.329 mg Fe/kg/day (± 0.104 SD), which is a rate known to be necessary in order to maintain iron excretion approximately equivalent to iron intake in a typical regularly transfused adult patient receiving the equivalent of about 2 to 4 units of PRBC (Nisbet-Brown et al, 2003). A dose of 40 mg/kg/day induced a higher rate of iron excretion of 0.445 ± 0.282 mg Fe/kg/day.

The efficiency of chelation was similar in the three dose cohorts, ranging from 15% to 22%. As a reference, the efficiency of deferiprone has been reported to be about 4% and the efficiency of slowly infused subcutaneous (s.c.) DFO is about 10% (Al-Refaie et al, 1995; Porter, 2001a).

Figure 4-1 Study 0104: Average daily net iron excretion: individual patient data and mean value by ICL670 dose



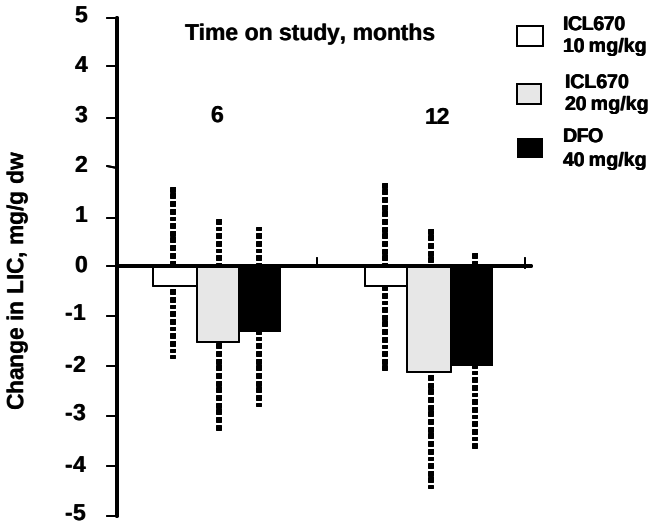
Each patient's average daily net iron excretion is represented by a dot; mean values of average daily net excretion for each dose group are represented by crosses; the horizontal grey area represents the range of iron received by thalassemia patients as a result of red blood cell transfusions (approximately 0.3 to 0.5 mg Fe/day).

4.4.2 Long-term pharmacodynamic effect (Study 0105)

Study 0105 was a randomized, controlled trial in which 71 adult β-thalassemia patients with iron overload (LIC 5 to 15 mg Fe/g dw) were randomized to receive once daily oral ICL670 at doses of 10 or 20 mg/kg/day or s.c. infusions of DFO 40 mg/kg/day for five days each week (n= 24, 24 and 23, respectively). The core period of the study was 3 months but provision was made for an additional comparative extension phase lasting for a total of at least 48 weeks. LIC was assessed non-invasively using SQUID at a single center, as this technology allowed repeated LIC measurements every three months.

The mean baseline LIC value for all patients was 8.4 mg Fe/g dw, and this value was similar across all three groups. As shown in Figure 4-2, at the end of 48 weeks, treatment with ICL670 at 10 mg/kg/day resulted in an overall stable LIC, whereas treatment with 20 mg/kg/day led to a fall in LIC that was similar to that observed when patients were treated with DFO at 40 mg/kg/day (-2.1 mg Fe/g dw and -2.0 mg Fe/g dw, respectively).

Figure 4-2 Study 0105: Change in LIC by SQUID



Actual initial doses administered, mean ± SD

Study 0105 indicated that in iron overloaded adult patients with ß-thalassemia receiving blood transfusions (average iron intake 0.37 mg/kg/day), a 20 mg/kg ICL670 dose could lead to a significant reduction in LIC that was comparable to that observed with 40 mg/kg of DFO. In contrast to the finding in Study 0104 in which it appeared to be less effective, in Study 0105 a 10 mg/kg dose of ICL670 appeared sufficient for maintaining net neutral iron balance on average. However there was considerable inter-patient variability, with a proportion of patients who received the 10 mg/kg dose showing increased LIC over the course of the study.

4.4.3 PK and PD study in children (Study 0106)

In this open-label, non-comparative study, 40 pediatric patients with transfusion-dependent ß-thalassemia major received daily oral 10 mg/kg doses of ICL670 over a period of 48 weeks. Patients previously treated with DFO for = 4 weeks on enrollment were analyzed for two age groups, children 2 to 11 years and adolescents 12 to 16 years. Average actual daily doses of ICL670 administered during study were 11.2 ± 2.0 mg/kg and 11.3 ± 2.5 mg, respectively. These doses led to moderate increases in LIC with values of LIC gradually increasing from 6.2 ± 2.5 mg Fe/g dw at baseline to 7.9 ± 2.5 mg Fe/g dw after 48 weeks in children ages 6 to 11, and increasing from 5.7 ± 2.2 mg Fe/g dw at baseline to 6.4 ± 2.1 mg Fe/g dw after 48 weeks in adolescents ages 12 to 16. Evaluations of serum concentrations of trace elements confirmed that copper, magnesium, and zinc were not being depleted.

Pharmacokinetic analysis of full plasma concentration profiles and trough concentrations obtained at various time points over the course of the study showed a slightly higher (by 9%) systemic exposure of ICL670 in the adolescents compared to the children. This difference is smaller than that identified by the population PK analysis conducted across multiple studies, and may be a reflection of the small size of the age groups investigated in Study 0106.

5 Dose selection rationale for Phase II and Phase III trials

Doses of ICL670

Dose selection for the large efficacy Studies 0107 and 0108 was based primarily upon the results of the comparative portion of Study 0105 since these data represented a longer-term evaluation of drug-effect (in comparison with the short term Study 0104) and had the potential to reflect drug efficacy using an estimate of iron removal from the liver (change in LIC).

In order to address the unmet medical need for a convenient oral agent for the treatment of adult and pediatric patients across the spectrum of iron overload (e.g., patients with LIC values < 5 and >15 mg Fe/g dw), refinement of the dose selection used in Study 0105 was considered necessary. An algorithm was developed in conjunction with clinical experts and investigators for the different doses of ICL670 according to baseline LIC categories. The desire to avoid potential safety issues due to excessive iron chelation in patients with lower iron burdens led to the selection of the conservative 5 and 10 mg/kg ICL670 doses in patients with lower LIC values (< 7 mg Fe/g dw) in whom maintenance of LIC was desirable. The 20 mg/kg dose was considered appropriate for patients requiring reduction of a moderate iron burden (7 to 14 mg Fe/g dw), and a higher dose of 30 mg/kg was felt to be appropriate for patients with iron burdens above the threshold for cardiac complications and early death requiring a more significant reduction in iron burden (>14 mg Fe/g dw).

Doses of deferoxamine (DFO) in comparative trials

Effective doses of deferoxamine have been well established in the literature (Olivieri, 1999; Porter, 2001a). Therapy is generally initiated with DFO once the serum ferritin value has reached 1000 µg/L or when the LIC value increases to above 3.2 mg Fe/g dw (Gabutti and Piga, 1996; Olivieri and Brittenham, 1997; Porter 2001a). DFO doses of 20 to 60 mg/kg are considered appropriate for the treatment of patients with iron overload, and are generally administered in proportion to the extent of iron overload. This led to the development, in collaboration with clinical experts of the four DFO categories (20 to 30, 25 to 35, 35 to 50, and = 50 mg/kg) for comparison to the four ICL670 doses used. Because of the complexities involved with parenteral administration, a range, rather than a fixed dose of DFO was used for each dose level. Patients previously treated with DFO who had LIC values in a range considered acceptable (between 2 to 7 mg Fe/g dw) could remain on their prior dosing regimen of DFO during the clinical studies even if these doses were higher than prescribed by the algorithm in the protocol. This exception was made due to concerns that patients already on an effective and safe DFO regimen would experience increase in LIC if their doses were reduced.

6 Clinical assessment of iron overload in the ICL670 program

6.1 Liver biopsy

There is no agreed international standard for the measurement of LIC in biopsy specimens (Porter, 2001a). Therefore, a single laboratory was selected for LIC determination in ICL670 clinical studies [Clinique des Maladies du Foie (Clinic for Liver Diseases), Centre Hospitalier Universitaire, Rennes, France]. Based on data from this laboratory indicating reproducible determination of LIC from samples with a minimum dry weight of 0.5 mg, lower sample weights were excluded (Deugnier et al, 1992; Olynyk et al, 1994).

6.2 SQUID

In the clinical registration studies with ICL670, SQUID was used in the first long term dose-finding trial (Study 0105), as it allowed repeated non-invasive measures of LIC over a one year interval. Subsequently, SQUID was used as the primary method for LIC determination in some studies (Studies 0106 and 0109), or as an alternative LIC determination method for certain pediatric patients and for individuals with contraindications to liver biopsy (Studies 0107 and 0108).

The three SQUID centers participating in the ICL670 program (Turin, Italy; Hamburg, Germany; Oakland, USA) worked according to a common protocol, and the consistency of measurements obtained at the three participating centers was assessed in a specific SQUID Calibration Study. In addition, a sub-study in 48 patients enrolled in Study 0107 examined the relationship between LIC values determined by biopsy and SQUID. There was a good correlation between values of LIC obtained with biopsy or SQUID with a regression coefficient of 0.95 (95% CI 0.79 to 1.10). However, the LIC data obtained using SQUID were generally lower than those obtained from liver biopsy by approximately one half (average ratio of SQUID/biopsy LIC of 0.46, 95% CI 0.32 to 0.67).

6.2.1 Serum ferritin

In the clinical studies with ICL670, blood samples for serum ferritin measurements were taken every two to four weeks in all patients, resulting in a database that included several thousand determinations. All these measurements were performed using standardized assays in central laboratories.

7 Overview of the clinical development program

ICL670 has been developed for the intended indication of the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderois) in adult and pediatric patients as young as two years of age. Since frequently transfused patients with ß-thalassemia major have been best characterized in terms of the complications of iron overload, agreement was reached with FDA that it was reasonable to assess the efficacy and safety of ICL670 primarily in this reference population while further supplementing the safety from other types of anemia populations.

FDA completed Special Protocol Assessments (SPA) for the three main protocols in the clinical trial program in January 2003: Study 0107 (ß-thalassemia), Study 0108 (ß-thalassemia and other rare anemias) and Study 0109 (sickle cell disease)(Table 7-1). The agency commented on the design of these studies (sample sizes, patient populations, endpoints, efficacy, and safety assessments) and the intended labeling. Close consideration was given to these SPA comments in the design, conduct, and analyses of these studies.

The clinical trial program conducted in support of the indication represents the largest prospectively conducted series of studies examining an iron chelator. Initial tolerability, safety, pharmacokinetic and pharmacodynamic short-term trials were conducted in adult patients with ß-thalassemia. Healthy volunteers were used for several studies investigating biopharmaceutic and PK properties of ICL670, after emerging data in patients indicated that periodic single dose administration to healthy subjects would likely be safe and tolerated. Since pediatric patients with ß-thalassemia and other rare anemias receive transfusions at a young age and also suffer from iron overload, Novartis prospectively planned to include pediatric patients in the pivotal clinical trials.

Table 7-1 Summary of efficacy and safety trials

Study No.	Design	No. of patients	Drug dose and treatment duration	Objectives
Phase II trials				
0108	Non-comparative trial of ICL670 in patients with ß-thalassemia unable to receive or to tolerate DFO or with other anemias	184 (adults & children)	ICL670 5, 10, 20 or 30 mg/kg 1 year duration	Efficacy Safety
0109	Open-label, randomized phase II trial of ICL670 vs DFO in patients with sickle cell disease and transfusional iron overload	195 (adults & children)	ICL670: 5, 10, 20,or 30 mg/kg DFO: 20-60 mg/kg 1 year duration	Safety Efficacy
Phase III trials				
0107	Open-label, randomized phase III trial of ICL670 vs DFO in patients with ß-thalassemia	586 (adults & children)	ICL670 5, 10, 20 or 30 mg/kg DFO 20-60 mg/kg 1 year duration	Efficacy Safety Population PK

8 Patients and methods

8.1 Patients

Patients enrolled in clinical trials had chronic iron overload due to blood transfusions administered for ß-thalassemia, SCD or other types of anemia (Table 8-1).

Table 8-1 Patient selection in pivotal clinical trials

Trial	Patient population	Previous chelation	Age	Baseline LIC (mg Fe/g dw)
0107	ß-thalassemia	Previously treated with and able to tolerate DFO, or never treated with DFO	Adults Children = 2 years	= 2.0 (biopsy or SQUID*)
0108	ß-thalassemia Other anemias requiring blood transfusion[a]	Non-compliant to, unable to receive or to tolerate DFO	Adults Children = 2 years	= 2.0 (biopsy or SQUID*)
0109	Sickle cell disease[b]	Previously treated with and able to tolerate DFO, or never treated with DFO	Adults Children = 2 years	= 2.0 (SQUID)

[a] Including but not limited to MDS, Diamond-Blackfan anemia, Fanconi's anemia

[b] SCD requiring either regular transfusions or with a prior history of intermittent transfusions with = 20 units of packed RBC

*SQUID performed in children and patients with contraindications to liver biopsy

Patients who had never been treated with DFO were eligible for Studies 0107 and 0109. Baseline iron overload was documented in Study 0107 by an elevated baseline LIC as measured by liver biopsy or SQUID or in Study 0109 by an elevated baseline serum ferritin (defined as = 1000 µg/L).

Exclusion criteria common to all protocols included notably: patients with liver transaminases >250 U/L (about 5 times the upper limit of normal), patients with serum creatinine above upper limit of normal and significant proteinuria defined as a urinary protein to creatinine ratio of greater than 0.5, patients with history of cataract or other iron-chelation related ocular toxicity, patients with serological evidence of active chronic hepatitis B or evidence of clinically active hepatitis, patients with A-V block or clinically relevant QTc interval prolongation, pregnant or breast-feeding females.

As liver biopsy is the most robust method to date for determining LIC, this was the primary method used for LIC determination in Studies 0107 and 0108. However, SQUID was used in these studies for patients with contraindications to biopsy and for some pediatric patients.

8.2 Design of pivotal clinical trials

8.2.1 Study 0107

This was a randomized, comparative, open-label phase III trial comparing the efficacy and safety of ICL670 and DFO in patients with ß-thalassemia receiving at least 8 blood transfusions per year. The primary objective of this open-label trial was to demonstrate that ICL670 was non-inferior to DFO in maintaining or reducing LIC. Patients were randomized in a 1:1 ratio and were assigned to starting doses of study treatments depending on their baseline LIC according to Table 8-2.

Table 8-2 Selection of starting doses of ICL670 and DFO based on LIC

Baseline LIC	ICL670 dose (mg/kg/day)	DFO dose** (mg/kg, 5 days/week)
2 – 3 mg Fe/g dw *	5	20-30
> 3 – 7 mg Fe/g dw *	10	25-35
> 7 – 14 mg Fe/g dw	20	35-50
> 14 mg Fe/g dw	30	= 50

* Patients in these lower LIC groups who were randomized to treatment with DFO were allowed to continue on their current DFO dosage, even if this was higher than recommended in this table.

**applicable to Studies 0107 and 0109

LIC, the primary outcome variable for the demonstration of non-inferiority to DFO, was assessed at baseline and after 12 months of therapy by liver biopsy or, in some patients, non-invasively by SQUID. LIC was determined by SQUID in 16% of patients and by biopsy in the remainder. In addition, results of the trial were also analyzed according to LIC determination method: biopsy or SQUID. Serum ferritin was measured monthly throughout the trial, and was compared with the LIC measurements obtained.

8.2.2 Study 0108

This was a multi-center, open-label, non-comparative, Phase II trial to assess the efficacy and safety of ICL670 in pediatric and adult patients with congenital and acquired anemia complicated by chronic iron overload who were considered unsuitable for treatment with DFO due to contraindications, non-compliance, or underlying disease. Unsuitable for treatment with DFO was defined as documented unacceptable toxicity, non-compliance (< 50% of prescribed chelation therapy taken), or when administration of DFO was contraindicated due to complications of the underlying diseases (e.g., thrombocytopenia). A non-comparative design was necessitated by these inclusion criteria. Patients were allocated to the ICL670 starting doses shown in Table 8-2. LIC was assessed by liver biopsy or, in some pediatric patients and in adults with contraindications to liver biopsy, non-invasively by SQUID after one year of treatment. Serum ferritin values were collected monthly throughout the trial.

8.2.3 Study 0109

This was a multi-center, open-label, randomized, phase II trial in pediatric and adult patients with SCD. The primary objective of the study was characterization of the safety of ICL670 versus DFO in the SCD patient population. Patients were randomized 2:1 to receive either ICL670 or DFO for one year. Efficacy assessments were secondary objectives. In the absence

of prior data in SCD, a conservative starting dose of ICL670 10 mg/kg daily was used when the protocol was released on 02-Dec-02. After an evaluation of the safety data of the first 21 patients enrolled in the study by the Study Monitoring Committee, an amendment to the protocol on 24-Nov-03 introduced the same LIC-based dosing algorithm shown in Table 8-2. Subsequently, once results from Studies 0107 and 0108 became available and it was evident that doses of 5 and 10 mg/kg were too low another amendment was issued on 21-Dec-04 after all patients were enrolled adjusting doses in most patients to 20-30 mg/kg.

8.3 Statistical considerations for the pivotal trials

8.3.1 Primary efficacy endpoint

Evaluation for the primary efficacy assessment in Study 0107 and Study 0108 was measurement of LIC by liver biopsy. Measurement of LIC by SQUID was permitted for pediatric patients with access to SQUID and for adults with contraindications to liver biopsy (e.g., thrombocytopenia). LIC was assessed at baseline and reassessed after 12 months of therapy in each patient using the same methodology as used at baseline.

The primary endpoint of these trials was a dichotomous variable defining "success" and "failure" according to baseline LIC levels and was developed in conjunction with clinical experts and investigators based upon their clinical experience. Individual success criteria for efficacy evaluation in Study 0107 and Study 0108 are listed in Table 8-3.

Table 8-3 Success criteria based on LIC

LIC at baseline	Success, if LIC after 1 year	Failure, if LIC after 1 year
2 to < 7 mg Fe/g dw	1 to < 7 mg Fe/g dw	< 1 mg Fe/g dw or =7 mg Fe/g dw
= 7 to < 10 mg Fe/g dw	1 to < 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

As LIC values greater than 7 mg Fe/g dw have been reported in the literature to be associated with an increased risk of complications, reduction to below this level was desirable as an endpoint. However, because it was considered unrealistic to expect such a reduction to occur in heavily iron overloaded individuals (LIC > 10 mg Fe/g dw), a decrease of at least 3 mg Fe/g dw was selected as a reasonable target to be accomplished in one year, since in most patients such an annual reduction would lead to safe iron levels within a few years. The endpoint construct was agreed upon with health authorities in the United States and Europe.

Statistical Methods

Study 0107 was a randomized comparator-controlled trial designed to demonstrate the efficacy and safety of ICL670 in patients with ß-thalassemia. As agreed with FDA, ICL670 was to be declared non-inferior to DFO if the lower limit of the 95% confidence interval (two-sided using the normal approximation) for the difference in the percentage of treatment successes of ICL670 and DFO was above -15%. The success rate for DFO was assumed to be 60 to 75% based on data in the literature. The sample size was calculated to demonstrate non-inferiority at a two-sided alpha level of 5% if the success rates of ICL670 and DFO were both 50% (i.e., at maximal variance). Thus, 468 patients (234 per arm) would have been required to

achieve a power of 90%. The protocol intended to recruit 500 patients (250 per arm). The percentage of success for each treatment was calculated in the per protocol (PP-1) population representing all patients who completed both LIC assessments or who discontinued due to safety concerns (considered as failures).

Study 0108 was a non-comparator trial designed to provide supportive efficacy data and safety data in patients with ß-thalassemia and other rare anemias unable to be treated with DFO. It utilized the same non-parametric success criterion as Study 0107 to investigate the hypothesis that ICL670 had efficacy in maintaining or reducing LIC. Since there was no comparator arm, success was to be declared if the lower limit of the 95% confidence interval exceeded 50% in the overall population of patients treated. The size of the trial was calculated to demonstrate this with a one-sided alpha level of 0.025, provided that the expected rate was 65%. Thus 113 evaluable patients were required to achieve a power of 90% (using the normal approximation of the binomial distribution). In this study 175 patients were planned to be recruited in order to have sufficient representation of specific patient subgroups (e.g., ß-thalassemia and other rare anemias).

Study 0109 was a randomized comparator-controlled trial in which patients were allocated 2:1 to ICL670 or DFO in order to provide safety data and preliminary efficacy data in patients with sickle cell disease. Ninety patients were planned to be treated to give a reasonable chance to detect an AE occurring in at least 4% of patients in the ICL670 arm. Assuming a 20% drop-out rate, it was planned to randomize 170 patients in order to have 90 and 45 patients in the ICL670 and DFO arms, respectively.

8.3.2 Secondary efficacy endpoints

In Studies 0107 and 0108 secondary efficacy endpoints included change in LIC in patients with baseline LIC = 7 mg Fe/g dw. The protocol included the plan for hypothesis testing of the difference with ICL670 and between ICL670 and DFO. For the treatment difference a covariance model with baseline LIC as covariate and treatment as the main effect was to be fitted. The effect of ICL670 on LIC in patients with baseline LIC = 7 mg Fe/g dw was to be tested using Student's t-test. In order to claim that ICL670 was able to reduce LIC in patients with LIC = 7 mg Fe/g dw, the null hypothesis H0 change = 0 was to be tested at a = 0.025 (one-sided).

Addition secondary efficacy variables included change in LIC, change over time in serum ferritin levels, and the iron balance as indicated by the ratio of iron excretion to iron intake. These parameters were evaluated in an exporatory manner without the plan to test for treatment differences or effects.

In Studies 0107 and 0108, for the secondary endpoint of change in LIC in patients with LIC = 7 mg Fe/g dw, a sample size of 25 patients was considered sufficient to provide a power of at least 90% in demonstrating reduction of LIC over one year.

9 Patients and treatments in pivotal trials

9.1 Patients enrolled

9.1.1 Study 0107

Between March and November 2003, 586 patients (296 on ICL670; 290 on DFO) were randomized and treated in 12 countries. The majority (68%) was enrolled in four Mediterranean countries (Greece, Italy, Turkey and Tunisia), and in Belgium, France, Germany, United Kingdom, Brazil, Argentina, USA and Canada. Fifty-one percent of the patients were less than 16 years of age. Just over 85% of patients were Caucasian, and gender distribution was approximately equal. Only 15 (2.6%) patients had not received prior chelation therapy; of these, seven were randomized to ICL670 and eight to DFO. The number of blood transfusion episodes was similar across all treatment groups resulting in relatively similar iron intake from blood transfusion. The two arms were well balanced for baseline demographic characteristics, disease characterisitics, and transfusion history (Table 9-1).

Table 9-1 Study 0107: demographics and baseline characteristics

Study 0107		ICL670 N = 296	DFO N = 290	All Patients N = 596
Gender	Male	140 (47.3%)	142 (49.0%)	282 (48.1%)
	Female	156 (52.7%)	148 (51.0%)	304 (51.9%)
Race	Caucasian	263 (88.9%)	251 (86.6%)	514 (87.7%)
	Black	2 (0.7%)	1 (0.3%)	3 (0.5%)
	Oriental	9 (3.0%)	10 (3.4%)	19 (3.2%)
	Other	22 (7.4%)	28 (9.7%)	50 (8.5%)
Age (years)	Mean ± SD	17 ± 9.47	17.3 ± 9.96	17.2 ± 9.71
	Median	15	15.5	15
	Range	2 - 49	2 - 53	2 - 53
Age groups	< 6	30 (10.1%)	28 (9.7%)	58 (9.9%)
	6 - < 12	67 (22.6%)	68 (23.4%)	135 (23.0%)
	12 - < 16	57 (19.3%)	49 (16.9%)	106 (18.1%)
	16 - < 50	142 (48%)	144 (49.7)	286 (48.8%)
	50 - < 65	0 (0%)	1 (0.3%)	1 (0.2%)
LIC (mg Fe/g dw)	Mean ± SD	14.1 ± 10.0	13.2 ± 9.4	13.7 ± 9.7
	Median	11.3	11.0	11.1
	Range	2.1 - 48.1	2.1 - 55.1	2.1 - 55.1
Serum ferritin	Mean ± SD	2765 ± 1897	2597 ± 1835	2682 ± 1867
	Median	2212	2091	2143
	Range	321 - 12646	453 - 15283	321- 15283

The primary efficacy population (per protocol-1, PP-1) consisted of patients with LIC evaluations at baseline and after 52 weeks or who discontinued due to safety reasons (AE, abnormal laboratory value or test procedure result, iron overload-related death) and were counted as treatment failures in the primary analysis (Table 9-2). Certain secondary analyses (change in LIC, iron balance) requiring data obtained at baseline and end of study were performed on the per-protocol-2 (PP-2) population which consisted only of the patients with

both a baseline and an end-of-study LIC measurement. Other secondary analyses (change in serum ferritin) were performed in the safety population.

Table 9-2 Populations analyzed in study 0107

Analysis Population	Definition	ICL670 n (%)	DFO n (%)	All patients n (%)
Intent-to-treat population (ITT)	All patients randomized	297 (100.0)	294 (100.0)	591 (100.0)
Safety population (Safety)	All patients randomized receiving at least one dose of study medication	296 (99.7)	290 (98.6)	586 (99.2)
Per protocol-1 population (PP-1)	All patients completing both LIC assessments or discontinuing due to safety (considered treatment failures)	276 (92.9)	277 (94.2)	553 (93.6)
Per protocol-2 population (PP-2)	All patients that completed both LIC assessments	268 (90.2)	273 (92.9)	541 (91.5)

9.1.2 Study 0108

Between March and November 2003, 184 patients were enrolled: 85 with ß-thalassemia; 99 with other anemias (47: MDS; 30: DBA; 22: other). Thirty-five patients were less than 16 years of age. Thirty-seven patients had not received prior chelation therapy. LIC was determined by SQUID in 64 patients (34.7%).The primary efficacy analysis was performed on the intent-to-treat (ITT) population (Table 9-3). Secondary analyses were performed on populations as for Study 0107 above.

Table 9-3 Populations analyzed in study 0108

Analysis Population	Definition	b-thal n (%)	Rare anemia n (%)	All patients n (%)
Intent-to-treat population (ITT)	All patients	85 (100.0)	99 (100.0)	184 (100.0)
Safety population (Safety)	All patients receiving at least one dose of study medication	85 (100.0)	99 (100.0)	184 (100.0)
Per protocol-1 population (PP-1)	All patients completing both LIC assessments or discontinuing due to safety (considered treatment failures)	80 (94.1)	85 (85.9)	165 (89.7)
Per protocol-2 population (PP-2)	All patients that completed both LIC assessments	76 (89.4)	71 (71.7)	147 (79.9)

9.1.3 Study 0109

Between May 2003 and August 2004, 195 patients were randomized and treated (132 on ICL670, 65 on DFO). The majority of the patients were enrolled in the United States (85%) and the remainder of the patients were enrolled from Canada, France, Great Britain, and Italy. About half of the patients (50.3%) were under age 16 and 89% were Black. Prior chelation therapy was reported for 83 (62.9%) of patients randomized to receive ICL670 and 37 (58.7%) of patients randomized to received DFO. The primary objective (safety and tolerability) was assessed in all patients receiving at least one dose of study medication.

9.2 Study treatments

9.2.1 Study 0107

After randomization, patients were assigned by investigators to receive ICL670 or DFO at doses according to their baseline LIC value (Table 8-2). The median duration of treatment was approximately 53 weeks in both arms of the study. The mean doses of ICL670 actually administered were near those indicated by the dosing algorithm (Table 9-4). Mean DFO doses administered were higher than those specified by the algorithm for patients with baseline LIC values < 7 mg Fe/g dw because of the provision in the protocol that patients could be maintained on their pre-study DFO doses. In fact, more than 50% of the patients assigned to the two lower DFO dosing groups received higher starting doses than those specified.

Table 9-4 Study 0107: Average daily dose by LIC category

	Baseline LIC in mg Fe/g dw (regardless of method)			
	<=3	**>3-7**	**>7-14**	**>14**
ICL670 (N = 296)	**N=15**	**N=78**	**N=84**	**N=119**
Protocol 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 DFO: ICL670 dose	**5.47:1**	**3.60:1**	**2.18:1**	**1.89:1**

Of note regarding the doses of ICL670 administered in Study 0107, preclinical data and pharmacodynamic data from Study 0105 suggested that an approximately 2:1 ratio of DFO to ICL670 would produce comparable efficacy. In retrospect, the ratio of average DFO to ICL670 doses for the two lower LIC categories was disproportionately high (about 4:1) compared to the two upper LIC categories (about 2:1)(Table 9-4).

9.2.2 Study 0108

In a similar manner to Study 0107, patients were assigned to receive a given dose of ICL670 after enrollment according to baseline LIC (Table 9-5). There was no comparator in this study. The median duration of treatment was 52.6 weeks.

Table 9-5 Study 0108: Average daily dose by LIC category

	Baseline LIC in mg Fe/g dw (regardless of method)			
	<=3	**>3-7**	**>7-14**	**>14**
ICL670 (N = 296)	**N=7**	**N=18**	**N=52**	**N=107**
Protocol assigned initial dose	**5 mg/kg**	**10 mg/kg**	**20 mg/kg**	**30 mg/kg**
Average daily dose (mg/kg/day)				
Mean ± SD	5.7 ± 1.0	9.7 ± 1.1	18.4 ± 2.5	27.9 ± 3.4
Median	5.0	10.0	20.0	29.8
Minimum -Maximum	4.9 – 7.5	5.5 – 20.0	11.6 – 20.0	15.6 – 30.0

In the low LIC categories, dose assignment was complicated by the utilization of SQUID in 35% of patients for the determination of LIC. Compared to liver biopsy determined values, LIC was underestimated by approximately 50% when using this methodology. This even resulted in the assignment of a number of patients in the LIC = 7 - 14 mg Fe/g dw group to lower doses than they would have received had they been assessed by biopsy.

9.2.3 Study 0109

In the original protocol for Study 0109 patients were randomized to receive ICL670 10 mg/kg or DFO at doses of 20 to 60 mg/kg. As noted above, prior to the enrollment of the large majority of patients, the trial was amended to use the same dosing algorithm as Studies 0107 and 0108. As this study was ongoing at the time of analysis of the two other trials, the issue of bias introduced by the dosing algorithm or by SQUID was addressed approximately mid-way through with the introduction of an amendment eliminating 5 and 10 mg/kg doses of ICL670 for most patients, and replacing these with a dose of 20 mg/kg for the remainder of the trial.

Because of the elimination of the 5 and 10 mg/kg doses midway through the trial and because more patients received DFO according to the specified doses in the algorithm, the ratio of DFO to ICL670 doses in this trial was approximately 2:1 (Table 9-6). In the overall population of patients the mean ICL670 dose was 17.3 ± 6.0 mg/kg (n = 132) and the mean DFO dose was 36.0 ± 11.4 mg/kg (n = 63). The median duration of treatment was 51 weeks.

Table 9-6 Study 0109: Average daily dose by LIC category

	Baseline LIC in mg Fe/g dw (regardless of method)			
	<=3	**>3-7**	**>7-14**	**>14**
ICL670 (N = 132)	**N=4**	**N=64**	**N=46**	**N=18**
Protocol assigned initial dose	**5 mg/kg**	**10 mg/kg**	**20 mg/kg**	**30 mg/kg**
Average daily dose (mg/kg/day)				
Mean ± SD	9.5 ± 3.2	13.0 ± 1.2	19.7 ± 2.06	28.0 ± 2.8
Median	10.4	13.1	20.0	29.8
Minimum -Maximum	5.0 – 12.3	8.4 – 23.9	10.0 – 24.5	22.8 – 30.0
DFO (N = 63)	**N=6**	**N=21**	**N=20**	**N=16**
Protocol assigned initial dose	**20-30 mg/kg**	**25-35 mg/kg**	**35-50 mg/kg**	**>=50 mg/kg**
Average daily dose (mg/kg/day)				
Mean ± SD	22.9 ± 3.9	28.7 ± 3.2	36.6 ± 9.5	50.0 ± 7.3
Median	21.0	29.0	36.2	50.0
Minimum -Maximum	22.9 – 29.5	21.6 – 34.4	7.0 – 52.6	32.4 – 62.0
Average DFO dose: ICL670 dose	**2.4:1**	**2.2 : 1**	**1.9 :1**	**1.8 : 1**

10 Overview of efficacy

Primary and secondary efficacy results are presented in this section. Although it is relevant to note at the outset that the primary endpoints were not met for the overall patient population in both Studies 0107 and 0108, the primary efficacy variable was positive in the population of evaluable patients with LIC values = 7 mg Fe/g dw.

The primary reason for not meeting the endpoints was underdosing of ICL670 in patients with baseline LIC < 7 mg Fe/g dw who received ICL670 doses of 5 or 10 mg/kg, which led to a lack of efficacy. This underdosing occurred because:

1. A more conservative dosing algorithm was used for ICL670 than for DFO
2. Patients with LIC values < 7 mg Fe/g dw were allowed to be maintained on pre-study DFO doses
3. SQUID assessments often resulted in assignment to lower dosing cohorts than biopsy, and this impacted patients on ICL670 more than DFO because of the two points above.

The positive results of the primary efficacy variable in the population of patients with LIC values = 7 mg Fe/g dw along with several positive preplanned secondary analyses indicate that doses of 20 and 30 mg/kg of ICL670 are effective in reducing total body iron burden. Even though patients administered doses of 5 and 10 mg/kg did not achieve reductions in LIC, iron excretion was still apparent in these patients and, indeed, a dose response effect from doses of 5 to 30 mg/kg was demonstrated. It should be noted that, in the absence of adequate chelation, the LIC is predicted to rise due to the continuing administration of transfusions. Thus, the data from these studies demonstrate that although the primary endpoint was not met due to the reasons cited above, efficacy was demonstrated with doses of 20 and 30 mg/kg in the population of patients with LIC values = 7 mg Fe/g dw. In addition, given the demonstration of a dose-response effect and a relatively constant efficiency of chelation

across a variety of conditions, the data can be extrapolated to support the use of the 20 mg/kg dose in patients with LIC < 7 mg Fe/g dw at baseline.

10.1 Primary efficacy results in pivotal trials

10.1.1 Study 0107

The primary analysis of the success rates in the overall PP-1 population across all dose groups did not meet the boundary established for claiming non-inferiority (lower bound of 95% CI of -15%) based on the comparison of success rates in the PP-1 population across all dose groups (Table 10-1). This was caused by the maintenance of high pre-study DFO doses and the disproportionately low dosing of patients with ICL670 at 5 and 10 mg/kg/day relative to the DFO doses.

Table 10-1 Study 0107: Success rates (PP-1 population)

	ICL670	DFO
Biopsy & SQUID	**n=276**	**n=277**
Average daily dose (mg/kg/day)	20.0 ± 8.3	43.5 ± 9.5
Success rate (n (%))	146 (52.9)	184 (66.4)
95% CI	47.0, 58.8	60.9, 72.0
Difference [95% CI]	-13.5 [-21.6, -5.4]	

The success rate was investigated in patients (n=463) who had their LIC assessed by liver biopsy only. The rates were similar to those in the overall population (ICL670 51.1%, DFO 62.8%). In addition, success rates in children (2 to 11 years) and adolescents (12 to <16 years) were similar to those observed in adults (Table 10-2), although in the subgroup of patients age 2 to 6 years the success rate for ICL670 was somewhat lower than for DFO. This may be due to the lower drug exposure in this age group as determined by population PK analysis (see Section 4.3).

Table 10-2 Study 0107: Success rates by pediatric age group

Age (years)	**2 to 6**		**6 to 12**		**12 to <16**	
	ICL670	**DFO**	**ICL670**	**DFO**	**ICL670**	**DFO**
Biopsy & SQUID	**n=28**	**n=28**	**n=63**	**n=67**	**n=57**	**n=49**
Success rate (n (%))	12 (42.9)	20 (71.4)	41 (65.1)	45 (67.2)	36 (63.2)	36 (73.5)
95% CI	24.5, 61.2	54.7, 88.2	53.3, 76.9	55.9, 78.4	50.6, 75.7	61.1, 85.8
Difference [95% CI]	-28.6 [-53.4, -3.8]		-2.1 [-18.4, 14.2]		-10.3 [-27.9, 7.3]	

Includes all pediatric patients completing both efficacy assessments or discontinuing due to safety (considered treatment failures)

After enrollment was complete, and before the database had been locked, the inherent bias in the dosing algorithm utilized for the pivotal trials was realized. This was based on: 1) emerging data from the pediatric safety Study 0106 indicating that the 10 mg/kg was unable to maintain LIC; 2) emerging data that the correspondence of LIC by biopsy and SQUID was approximately 2:1; and 3) the number of requests by investigators for dose increases due to lack of response as assessed by serum ferritin in patients receiving ICL670 doses of 5 and 10 mg/kg. In order to further evaluate the impact of this finding, an investigation of the non-

inferiority of ICL670 to DFO in patients with baseline LIC values = 7 mg Fe/g dw was added to the analysis plan.

Non-inferiority was demonstrated in the group of patients with baseline LIC levels = 7 mg Fe/g dw who were allocated to the higher dose groups (ICL670 doses of 20 or 30 mg/kg and DFO dose of = 35 mg/kg) (Table 10-3). These patients represented the majority of patients enrolled in the PP-1 population (69%). In these patients, overall success rates for ICL670 and DFO as analyzed by biopsy and SQUID were comparable (58.6% vs. 58.9%), and the lower limit of the 95% confidence interval (-10.2%) was above the non-inferiority threshold of -15% specified. Additionally, the success rates for patients assessed by biopsy only were also comparable (59.7% versus 58.7%) and the lower limit of the 95% confidence interval (-9.2%) was also above the predefined non-inferiority threshold of -15%. As these results are robust, the statistical significance will remain if multiplicity adjustment is considered.

Table 10-3 Study 0107: Success rates (PP-1 population) by baseline LIC

Biopsy and SQUID	ICL670	DFO
LIC < 7 mg Fe/g dw	**n=85**	**n=87**
Average daily dose (mg/kg/day)	9.5 ± 1.9	35.7 ± 8.1
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**
Average daily dose (mg/kg/day)	24.7 ± 5.2	47.1 ± 7.8
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]**	

10.1.2 Study 0108

In the primary efficacy analysis considering all patients including those without a final LIC determination who were considered as treatment failures (ITT population), the success rate was 50.5% (p=0.441; 95% CI 43.3-57.8; n=184) and therefore not significantly higher than the 50% specified to meet the primary endpoint. In the PP-1 population, which excluded patients who discontinued due to reasons other than safety, the success rate was 56.4% (p=0.051; 95% CI 48.8-63.9; n=165). Failure to achieve the primary efficacy endpoint in Study 0108 resulted primarily from inadequate dosing of patients due to the fact that 35% of patients had LIC values determined by SQUID and were thereby frequently assigned to receive a lower dose of ICL670 than they would have if assessed with liver biopsy. However, the relatively high drop-out rate in the entire population, due mainly to disease progression and deaths in the MDS group, and treated as the equivalent of treatment failure in the analysis, contributed also to this result.

The success rate was below 50% for patients with baseline LIC <7 mg Fe/g dw (i.e. those patients allocated to low ICL670 doses of 5 or 10 mg/kg), but statistically significantly above 50% (58.5%; p=0.022; 95% CI 50.3 - 66.6; n=142) for patients in the PP-1 population with a baseline LIC = 7 mg Fe/g dw (i.e. those patients allocated to ICL670 doses of 20 to 30 mg/kg).

Success rate was also calculated for patients with the following sub-types of congenital and acquired types of anemia: MDS, DBA, and other anemias. The overall success rates in the PP-1 population were 56.4% (95% CI 40.8 - 72.0, n=39), 51.9% (95% CI 33.0 - 70.7, n=27), and 63.2% (95% CI 41.5 - 84.8, n=19), respectively. Although the patient numbers in each of these subgroups is small, the success rate appears similar for all three disease sub-types.

10.2 Secondary efficacy results in pivotal trials

10.2.1 Study 0107: secondary efficacy

Consistent positive results were noted in several preplanned secondary efficacy analyses including: 1) a dose-dependent reduction in LIC, 2) a dose-dependent reduction in serum ferritin levels over time, and 3) a dose-dependent change in iron balance (defined as the ratio of iron excretion to iron intake). Analyses of other secondary endpoints were performed on the PP-2 population (patients completing the study with baseline and end of study primary efficacy assessments), except for serum ferritin for which all available values in the safety population were analyzed.

Reduction in LIC

As stated in the protocol as a pre-planned analysis, the aim of one of the secondary efficacy analyses was to test the hypothesis that for ICL670 the reduction in LIC after one year in patients with baseline LIC = 7 mg Fe/g dw was statistically significantly greater than 0 (Student's t-test, one-sided, alpha=0.025). In addition, for comparison of LIC reduction between patients treated with ICL670 and DFO, a covariance model with baseline as covariate and treatment as main effect was fitted. These analyses were planned to include only patients with LIC assessments at baseline and end of study (PP-2 population) with baseline LIC being = 7 mg Fe/g dw.

In the 185 patients on ICL670 who had LIC = 7 mg Fe/g dw at baseline and an evaluation at end of study, a statistically significant reduction in LIC was observed after one year (-5.3 ± 8.0 mg Fe/g dw, $p<0.001$, t-test)(Table 10-4). Although the average reduction was greater in the ICL670 arm than in the DFO arm, it was not statistically significantly different from DFO ($p=0.367$). This lack of difference to DFO was confirmed in the subgroup of patients assessed by biopsy ($p=0.325$).

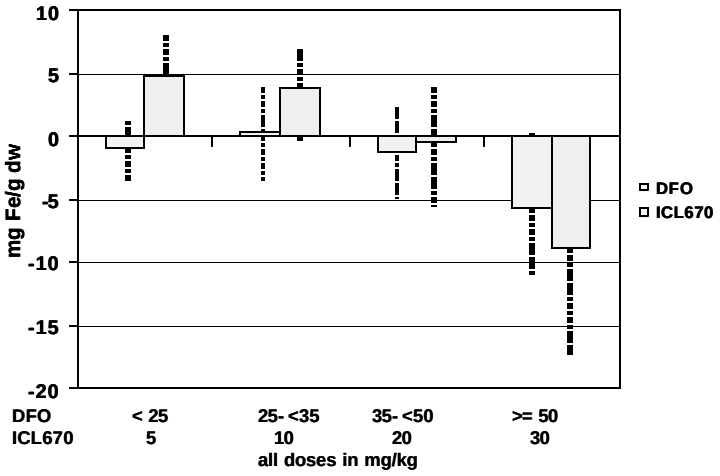
Table 10-4 Study 0107: Change in LIC by method of determination and baseline LIC value (PP-2 population)

	ICL670 All patients, n=268	DFO All patients, n=273
Biopsy & SQUID	**n=268**	**n=273**
Mean ± SD	-2.4 ± 8.2	-2.9 ± 5.4
LIC < 7 mg Fe/g dw	**n=83**	**n=87**
Mean ± SD	4.0 ± 3.8	0.13 ± 2.2
LIC = 7 mg Fe/g dw	**n=185**	**n=186**
Mean ± SD	-5.3 ± 8.0	-4.3 ± 5.8
p-value	**p<0.001***	
Biopsy only	**n=224**	**n=230**
Mean ± SD	-3.0 ± 8.8	-3.2 (5.7)
LIC < 7 mg Fe/g dw	**n=52**	**n=55**
Mean ± SD	5.6 ± 3.8	0.5 ± 2.5
LIC = 7 mg Fe/g dw	**n=172**	**n=175**
Mean ± SD	-5.6 ± 8.2	-4.4 ± 6.0
p-value	**p<0.001***	

*one-sample Students' t-test (1-sided, alpha=2.5%)

Initial ICL670 doses of 20 and 30 mg/kg administered to patients with a baseline LIC = 7 mg Fe/g dw induced stable or reduced mean LIC levels after one year, whereas doses of 5 and 10 mg/kg appeared too low to induce reduction or stabilization of LIC values obtained by biopsy or SQUID (Figure 10-1). A similar trend was observed using data obtained by biopsy and SQUID alone.

Figure 10-1 Study 0107: Change in LIC by dose (PP-2 population)



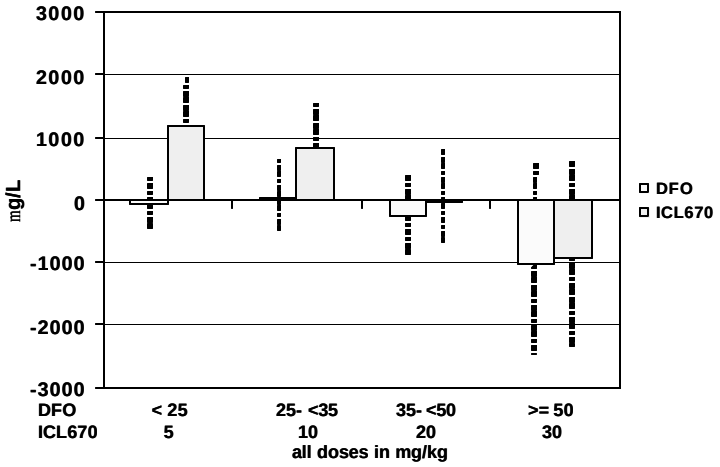
Mean ± SD

In summary, doses of 5 and 10 mg/kg of ICL670 were too low to maintain or reduce LIC in this population of transfused patients. The 5 mg/kg dose was associated with a 5 mg Fe/g dw increase in LIC in this population. Doses of 20 mg/kg and 30 mg/kg were able to maintain or reduce LIC, respectively.

Change in serum ferritin

Dose-dependent effects on serum ferritin levels over time that paralleled the changes in LIC were observed in both ICL670 and DFO treated patients (Figure 10-2). Serial serum ferritin measurements were analyzed and correlated with changes in LIC. The correlation coefficient between the change in serum ferritin and the change in LIC over one year was 0.63 ($p<0.001$) in patients treated with ICL670 and evaluated by liver biopsy in Study 0107 and Study 0108. This supports the utility of regularly monthly measurements of serum ferritin in the monitoring of chelation therapy.

Figure 10-2 Study 0107: Change in ferritin by dose (safety population)



Mean ± SD

Changes in serum ferritin, calculated iron balance, and LIC levels measured by liver biopsy or SQUID over a one year interval were consistent (Table 10-5).

For both ICL670 and DFO these three parameters corresponded well with one another. In addition, a clear and consistent dose response relationship is apparent for ICL670. For patients with baseline LIC values = 7 mg Fe/g dw (corresponding to ICL670 5 or 10 mg/kg) all three parameters indicated an increase in iron burden; for those with a baseline LIC between 7 and = 14 mg Fe/g dw (corresponding to ICL670 20 mg/kg) they indicated that iron burden was essentially unchanged; and for those with an baseline LIC > 14 mg Fe/g dw (corresponding to 30 mg/kg) they indicated that iron burden was reduced.

Although ICL670 doses below 20 mg/kg are not associated with maintenance or reduction of LIC or serum ferritin in these frequently transfused patients they still produce iron excretion in a dose dependent manner (10 mg/kg > 5 mg/kg) (Table 10-5).

Table 10-5 Study 0107: Changes in LIC, serum ferritin, and iron balance (PP-2 and safety populations)

LIC in mg Fe/g dw	Median dose mg/kg/day ICL670	DFO	n	Mean ± SD ICL670	n	Mean ± SD DFO
Change in LIC (mg Fe/g dw)						
LIC = 3	5	30	15	+4.8 ± 3.77	13	+0.5 ± 1.11
LIC >3-7	10	35	68	+3.8 ± 3.85	75	+0.0 ± 2.36
LIC >7-14	20	41	77	-0.4 ± 4.70	87	-1.9 ± 2.93
LIC >14	30	51	108	-8.9 ± 8.07	98	-6.4 ± 6.93
Change in serum ferritin (µg/L)						
LIC = 3	5	30	15	+1189 ± 700	13	+211 ± 459
LIC >3-7	10	35	73	+833 ± 817	77	+32 ± 585
LIC >7-14	20	41	80	-36 ± 721	89	-364 ± 614
LIC >14	30	51	115	-926 ± 1416	101	-1003 ± 1428
Iron balance						
LIC = 3	5	30	15	0.58 ± 0.328	13	0.95 ± 0.101
LIC >3-7	10	35	68	0.67 ± 0.365	75	0.98 ± 0.217
LIC >7-14	20	41	77	1.02 ± 0.398	87	1.13 ± 0.241
LIC >14	30	51	108	1.67 ± 0.716	98	1.44 ± 0.596

PP-2 population represents all patients with baseline and end of study LIC values

Safety population represents all patients receiving at least one dose of study medication

The PP-2 population was used for analysis of LIC and iron balance and the safety population was used for analysis of ferritin

10.2.2 Study 0108: secondary efficacy

According to the protocol, the aim of the secondary efficacy analysis was to test the hypothesis that ICL670 is able to reduce iron burden in patients with baseline LIC = 7 mg Fe/g dw. In the 126 patients on ICL670 who had LIC = 7 mg Fe/g dw at baseline and an evaluation at end of study (PP-2 popuulation), a statistically significant reduction in LIC was observed after one year (-5.5 ± 7.4 mg Fe/g dw, p<0.001, t-test) (Table 10-6). This statistically significant reduction was present when the data were analyzed by biopsy and SQUID and by biopsy only.

Table 10-6 Study 0108: Change in LIC (PP-2 population)

	Beta-thalassemia	Rare anemias	All patients
Biopsy & SQUID	**n=76**	**n=71**	**n=147**
Mean ± SD	-4.7 ± 8.6	-3.7 ± 6.5	-4.2 ± 7.7
LIC < 7 mg Fe/g dw	**n=9**	**n=12**	**n=21**
Mean ± SD	6.0 ± 4.0	1.6 ± 3.1	3.5 ± 4.1
LIC = 7 mg Fe/g dw	**n=67**	**n=59**	**n=126**
Mean ±	-6.1 ± 8.0	-4.8 ± 6.5	-5.5 (7.4)
p-value (1-sided, alpha=2.5%)			**p<0.001**
Biopsy only	**n=61**	**n=40**	**n=101**
Mean ± SD	-5.8 ± 9.1	-5.5 (7.5)	-5.7 ± 8.5
LIC < 7 mg Fe/g dw	**n=5**	**n=0**	**n=5**
Mean ± SD	8.8 ± 2.7	-	8.8 ± 2.7
LIC = 7 mg Fe/g dw	**n=56**	**n=40**	**n=96**
Mean ± SD	-7.1 ± 8.3	-5.5 ± 7.5	-6.5 ± 8.0
p-value (1-sided, alpha=2.5%)			**p<0.001**

Mean LIC was maintained or reduced only in the group of patients with an LIC = 7 mg Fe/g dw receiving a dose of 20 or 30 mg/kg (Table 10-5, Table 10-6).

The 10 mg/kg dose led to approximate maintenance of LIC in patients with rare anemias in Study 0108 whereas a substantial increase in LIC was noted for thalassemic patients. This may be due to the fact that patients in the rare anemia category received fewer blood transfusions during the study. Those patients who were assigned to receive ICL670 at 5 mg/kg had clear increases in LIC and serum ferritin values in all disease groups. This increase at a dose too low to prevent accumulation of transfusional iron serves as an internal control helping to document the dose-dependent efficacy of ICL670 in this non-comparative study.

In parallel with LIC changes, similar dose-dependent effects on iron balance (ratio of iron excretion to intake) and on serum ferritin were observed. The correspondence between the changes in serum ferritin and LIC again indicates that trends in ferritin are useful for the monitoring of response to chelation therapy (Table 10-7).

Table 10-7 Study 0108: Changes in LIC, serum ferritin, and iron balance (PP-2 and safety populations)

			ß-thalassemia		Rare anemias	
LIC in mg Fe/g dw	Median dose mg/kg/day ß-thal.	Rare	n	Mean ± SD ICL670	n	Mean ± SD DFO
Change in LIC (mg Fe/g dw)						
LIC = 3	5	6.4	1	+11.4 ± (n.a.)	4	+3.7 ± 1.98
LIC >3-7	10	10	8	+5.3 ± 3.68	8	+0.5 ± 3.01
LIC >7-14	20	19.3	17	-1.3 ± 3.58	22	-4.0 ± 4.21
LIC >14	29.7	29.8	50	-7.7 ± 8.48	37	-5.3 ± 7.61
Change in serum ferritin (µg/L)						
LIC = 3	5	6.4	2	+896 ± 1662	4	+2584 ± 2021
LIC >3-7	10	10	10	+1116 ± 642	9	+1116 ± 642
LIC >7-14	20	19.7	21	+498 ± 834	24	-545 ± 1140
LIC >14	29.9	29.8	52	-1023 ± 1648	43	-662 ± 1803
Iron balance						
LIC = 3	5	6.3	1	0.36 ± (n.a.)	4	0.62 ± 0.270
LIC >3-7	10	10	8	0.60 ± 0.270	8	1.41 ± 1.434
LIC >7-14	20	20	17	1.09 ± 0.313	21	1.43 ± 0.648
LIC >14	29.9	29.8	50	1.75 ± 0.983	36	1.53 ± 1.071

PP-2 population represents all patients with baseline and end of study LIC values

Safety population represents all patients receiving at least one dose of study medication

The PP-2 population was used for analysis of LIC and iron balance and the safety population was used for analysis of ferritin

10.2.3 Study 0109 in sickle cell disease

In Study 0109 secondary efficacy parameters included LIC assessment by SQUID, change in serum ferritin, and iron balance. Because the doses of ICL670 administered during the trial were adjusted by amendment, for determining drug exposure the mean doses of ICL670 and DFO are relevant. The mean doses of ICL670 and DFO given were 17.3±6.0 and 36.0 ± 11.4 mg/kg, and transfusional iron intake was 0.21 ± 0.13 and 0.23 ± 0.12 mg/kg/day, respectively. As shown in Table 10-8, the results of Study 0109 are consistent with those of Studies 0107 and 0108. The 2:1 ratio of DFO to ICL670 mean doses administered (Table 9-5) produced comparable reductions in LIC and comparable change in iron balance.

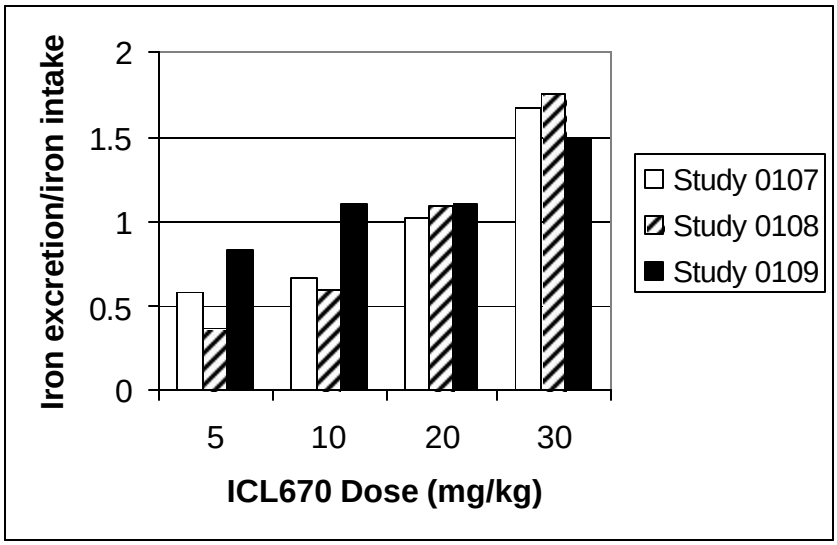
Table 10-8 Study 0109: Changes in LIC, serum ferritin and iron balance

Mean dose mg/kg/day		Parameter	n	Mean ± SD ICL670	n	Mean ± SD DFO
ICL670	DFO					
17.3	36.0	LIC change (mg Fe/g dw)	113	-1.3 ± 3.1	54	-0.7 ± 2.6
		Ferritin change (µg/L)	83	-183 ± 1651	33	-558 ± 951
		Iron balance	105	1.14 ± 0.60	52	1.20 ± 0.78

10.3 Analysis of ratio of iron balance across studies

As illustrated in Figure 10-3 integrating the data from the 3 pivotal trials, the effect of ICL670 treatment on iron balance was clearly related to dose across the three studies. A measurable iron excretion was observed at all doses, even in patients with a low baseline LIC and iron intake that exceed excretion who were receiving a dose of ICL670 of 5 to 10 mg/kg. Iron balance was neutral or negative at doses of 20 to 30 mg/kg in patients with ß-thalassemia and sickle cell disease. However, the ratio was also neutral or negative with a lower dose of 10 mg/kg/day in Study 0109 and in Study 0108 in the subset of patients with other transfusion-dependent anemias such as MDS who had a lower iron intake from blood transfusions.

Figure 10-3 Dose versus iron balance in studies 0107, 0108, 0109



A ratio of 1 indicate a neutral iron balance (iron excretion=iron intake), a ratio<1 a positive iron balance (iron excretion<iron intake) and a ratio >1 a negative iron balance (iron excretion>iron intake)]

10.4 Chelation efficiency

Chelation efficiency with ICL670 was relatively constant across all of the doses administered to patients, and was independent of baseline LIC (Table 10-9). In other words, these data indicate that for any given dose of ICL670 administered the fraction of iron bound is similar.

Table 10-9 Calculated efficiency of chelation in studies 0107 and 0108 combined

ICL670 dose	Chelation efficiency	
mg/kg	Mean, % ± SD	Median
5	31.6 ± 26.3	25.5
10	27.5 ± 18.4	27.6
20	27.0 ± 10.3	26.3
30	27.3 ± 12.4	27.2

10.5 Efficacy in patients with low baseline iron burden

Individuals with LIC values = 7 mg Fe/g dw at baseline who are receiving ongoing transfusions will relatively rapidly develop LIC values > 7 mg Fe/g dw in the absence of effective chelation therapy.

This is clearly demonstrated in Studies 0107 and 0108 in the group of patients treated with ICL670 5 mg/kg. In these patients there was a mean increase in LIC of 5 mg Fe/g dw over the course of 1 year to values of LIC > 7 mg Fe/g dw, which may serve as a first approximation of no chelation therapy, even though there was indeed some iron excretion with this dose as noted below. Such individuals who were receiving ongoing transfusions clearly require effective chelation therapy in the near-term if they are not to be placed at risk for the complications associated with iron overload.

Patients with LIC values = 7 mg Fe/g dw were treated with sub-optimal doses of ICL670 in clinical trials and non-inferiority to DFO was only shown in patients with high baseline LIC values treated with the higher doses. However, several lines of evidence support the conclusion that these individuals with low LIC values, such as those described above, will benefit from ICL670 treatment:

- The chelation efficiency of ICL670 is similar across a range of doses (Table 10-9). Irrespective of baseline LIC, the efficiency of ICL670 in chelating iron has been shown to be similar at different doses in studies conducted by direct measurement (15 to 22%, Study 0104) and in studies conducted by calculated measurement (~27% in Studies 0107 and 0108). These values are also consistent with the preclinical data in iron-overloaded marmosets.
- A dose-response effect in terms of iron excretion was apparent in the clinical studies. In the absence of blood loss or the administration of an effective iron chelating agent, there is minimal iron excretion from the body. Daily iron excretion in response to placebo in Study 0104 for a 50 kg individual was found to be about 2 mg (0.04 mg/kg). In Study 0107, even though 5 and 10 mg/kg doses of ICL670 did not reduce LIC or ferritin, they did lead to some iron excretion, resulting in loss of an average of 11.5 and 13 mg of iron per day for a 50 kg individual. For comparison, the iron loss with administration of 20 and 30 mg/kg doses for a 50 kg individual was an average of 20 or 30 mg per day, respectively.
- Because an iron chelator acts as an escape vehicle for iron from the body, it must be administered over time in proportion to the desired amount of iron removal. Based on this mechanism of action and the data provided above, it is reasonable to predict that a 20 mg/kg dose of ICL670 administered to patients with baseline LIC values = 7 mg Fe/g dw (those treated with 5 and 10 mg/kg) would have led to additional iron excretion in proportion to the dose of ICL670 administered.

11 Overview of safety

11.1 Safety evaluation

Evaluation of safety parameters included monitoring for the known complications of other chelation therapies (agranulocytosis, adverse effects on growth and development, auditory changes), and for potential adverse effects identified from preclinical studies with ICL670 (ocular toxicity, renal toxicity). Routine evaluations in all clinical studies included complete blood counts, renal and liver function tests, as well as ophthalmologic and auditory evaluations. Pediatric patients were also evaluated for changes in growth, development, and the development of sexual maturity.

The general safety of ICL670 across all pivotal trials in the program was monitored regularly by an independent Program Safety Board (PSB) and included a hematologist with expertise in iron overload, a clinical pharmacologist, two hepatologists with specific expertise in the clinical aspects of hepatic iron overload, and a statistician. In addition, a renal safety sub-committee consisting of 5 nephrologists reviewed renal parameters and adverse events.

11.2 Safety population and patient exposure

11.2.1 Major safety population

ß-thalassemia was used as the model disease for the demonstration of safety and efficacy and therefore the key safety population for the analysis of safety. This population comprised the pooled 421 ß-thalassemia patients from Studies 0106, 0107 and 0108 who were treated with ICL670 for one year. Safety data from patients in other trials were not pooled and were analyzed separately because of intrinsic differences in complications of the underlying disease states. In addition, ß-thalassemia patients who received ICL670 for up to three years in Study 0105E2 were analyzed separately for long-term safety.

To demonstrate the safety of ICL670 in other populations, patients with MDS, DBA and less common congenital and acquired anemias were enrolled in Study 0108, and an additional trial was conducted in patients with sickle cell disease (Study 0109). Altogether, a total of 1005 patients with transfusional iron overload in various diseases (ß-thalassemia, SCD, rare anemias) were recruited in Studies 0106, 0107, 0108 and 0109. Of these patients, 652 received ICL670 and 353 received DFO. Almost half (46.7%) were patients < 16 years of age. In patients receiving ICL670, 52 (8.0%) were < 6 years, 121 (18.6%) were between 6 and 12 years and 119 (18.3%) were between 12 and 16 years of age. An additional 22 (3.4%) patients were aged 50-< 65 and 30 (4.6%) were aged = 65 years (Table 11-1).

Table 11-1 Demographics features of patient populations receiving ICL670

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

Pooled thalassemia: Studies 0106, 0107, 0108; MDS, DBA, Other Anemia: Study 0108, SCD: Study 0109

The mean duration of patient exposure to ICL670 in ß-thalassemia, rare anemias and SCD was 51.6, 44.3 and 48.3 weeks, respectively. The mean daily doses administered to patients with ß-thalassemia, rare anemias and SCD were 19.8, 21.5 and 17.3 mg/kg (Table 11-2), and the mean daily doses of DFO (given 5 days/week) were 43.8 and 36.0 mg/kg in patients with ß-thalassemia and SCD, respectively.

Table 11-2 Exposure to ICL670 according to patient population

Duration of exposure	Pooled ß-thalassemia N=421	MDS N=47	DBA N=30	Other anemias N=22	Sickle cell disease N=132
	n (%)	n (%)	n (%)	n (%)	n (%)
<12 weeks	4 (1.0)	7 (14.9)	-	-	3 (2.3)
12 - <24 weeks	11 (2.6)	7 (14.9)	1 (3.3)	1 (4.5)	6 (4.5)
24 - <36 weeks	7 (1.7)	3 (6.4)	-	4 (18.2)	2 (1.5)
36 - <48 weeks	5 (1.2)	3 (6.4)	1 (3.3)	3 (13.6)	7 (5.3)
>=48 weeks	394 (93.6)	27 (57.4)	28 (93.3)	14 (63.6)	114 (86.4)
Mean ± SD	51.6 ± 8.55	38.6 ± 19.97	51.6 ± 5.88	46.8 ± 12.47	48.3 ± 10.76
Minimum - Maximum	1.3 - 67.9	0.7 - 58.6	23.7 - 58.1	15.7 - 66.9	0.1 - 60.1
P10 - P90	49.3 - 57.0	4.1 - 55.4	51.1 - 55.4	28.1 - 56.4	50.1 – 52.4
Median	53.0	51.6	52.4	52.1	51.1
Average daily dose (mg/kg)					
Mean ± SD	19.8 ±8.32	20.0 ± 8.31	23.6 ± 7.36	21.9 ± 6.51	17.3 ± 6.01
Minimum - Maximum	4.3 - 30.0	4.9 - 30	6.3 - 30	10 - 30	5.0 - 30.0
Median	20.0	20.0	25.9	21.2	16.7

11.3 Adverse clinical events

11.3.1 Most frequently occurring adverse events

The most frequently occurring adverse events differed somewhat depending on the underlying type of anemia (Table 11-3). The most common adverse events reported were diarrhea, vomiting, nausea, headache, abdominal pain, pyrexia, and cough. For Study 0107 patients receiving ICL670 had a higher incidence of abdominal pain, diarrhea, nausea, and skin rash than their counterparts receiving DFO. Aside from these differences, DFO and ICL670 had a relatively similar safety profile. The interpretation of these data must take into account that the patients enrolled in study 0107 were selected for their good tolerance of and their ability to comply with DFO treatment.

Table 11-3 No. of patients with most frequent AEs (> 10% or more in any group)

	ICL670			DFO	
	Pooled ß-Thal.	**Sickle Cell**	**Rare Anemias**	**ß-Thal.**	**Sickle Cell**
No. of patients studied	421	132	99	290	63
No. (%) of patients with AE(s)	378 (89.8)	127 (96.2)	97 (98.0)	246 (84.8)	62 (98.4)
AE preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Abdominal pain*	100 (23.8)	37 (28.0)	28 (28.3)	41 (14.1)	9 (14.3)
Pyrexia	98 (23.3)	28 (21.2)	22 (22.2)	69 (23.8)	11 (17.5)
Headache	83 (19.7)	38 (28.8)	24 (24.2)	59 (20.3)	21 (33.3)
Cough	80 (19.0)	18 (13.6)	20 (20.2)	55 (19.0)	13 (20.6)
Diarrhea*	70 (16.6)	26 (19.7)	42 (42.4)	22 (7.6)	3 (4.8)
Nasopharyngitis	59 (14.0)	18 (13.6)	19 (19.2)	42 (14.5)	13 (20.6)
Vomiting	58 (13.8)	28 (21.2)	29 (29.3)	28 (9.7)	10 (15.9)
Rash*	52 (12.4)	18 (13.6)	12 (12.1)	10 (3.2)	3 (4.8)
Nausea	50 (11.9)	30 (22.7)	27 (27.3)	14 (4.8)	7 (11.1)
Creatinine increased**	49 (11.6)	9 (6.8)	15 (15.2)	0 (0.0)	0 (0.0)
Pharyngolaryngeal pain	49 (11.6)	19 (14.4)	7 (7.1)	43 (14.8)	6 (9.5)
Pharyngitis	47 (11.2)	3 (2.3)	2 (2.0)	30 (10.3)	0 (0.0)
Influenza	44 (10.5)	3(2.3)	6 (6.1)	29 (10.0)	3 (4.8)
Rhinitis	42 (10.0)	3 (2.3)	7 (7.1)	22 (7.6)	2 (3.2)
Upper respiratory tract infection	41 (9.7)	24 (18.2)	13 (13.1)	23 (7.9)	12 (19.0)
Bronchitis	36 (8.6)	6 (4.5)	8 (8.1)	32 (11.0)	0 (0.0)
Arthralgia	34 (8.1)	20 (15.2)	6 (6.1)	14 (4.8)	9 (14.3)
Back pain	34 (8.1)	24 (18.2)	12 (12.1)	32 (11.0)	10 (15.9)
Constipation	27 (6.4)	13 (9.8)	9 (9.1)	7 (2.4)	9 (14.3)
Fatigue	26 (6.2)	8 (6.1)	10 (10.1)	14 (4.8)	1 (1.6)
Asthenia	19 (4.5)	7 (5.3)	10 (10.1)	11 (3.8)	2 (3.2)
Chest pain	18 (4.3)	12 (9.1)	5 (5.1)	6 (2.1)	8 (12.7)
Transfusion reaction	12 (2.9)	4 (3.0)	8 (8.1)	14 (4.8)	8 (12.7)
Pain in extremity	11 (2.6)	19 (14.4)	4 (4.0)	8 (2.8)	8 (12.7)
Viral infection	5 (1.2)	6 (4.5)	0 (0.0)	8 (2.8)	7 (11.1)
Sickle cell disease with crisis	n/a	44 (33.3)	n/a	n/a	20 (31.7)

AEs are included with an incidence of > 10% patients in any population, sorted by descending order of frequency in ß-thalassemia
* Grouped term ** includes 'Blood creatinine increased' / 'Blood creatinine abnormal'

In the pooled ß-thalassemia patient population, the most frequently reported AEs were abdominal pain, pyrexia and headache. As regards a relationship to dose, in the 30 mg/kg dose group, the most frequently reported AEs were abdominal pain, diarrhea and increased serum creatinine. Of AEs that might plausibly be related to ICL670, a dose response effect was apparent for nausea, rash, and increased serum creatinine. Most of these events were mild to moderate in severity and led to a low incidence of discontinuation of study drug.

The adverse event profile for ICL670 was relatively similar across the pediatric and adult populations treated. Patients less than 6 years of age with ß-thalassemia had an increased incidence of pyrexia, cough, diarrhea, rhinitis, and upper respiratory tract symptoms

compared to older patients (Table 11-4). The incidence of increased creatinine was lower across the entire pediatric population when compared to adults. No adverse effects of ICL670 on growth or development were detected in pediatric patients.

Table 11-4 Most frequently reported AEs (>10% of all patients) for ICL670 by age in the pooled beta-thalassemia population

	<6 years N=39 n (%)	6-<12 years N=85 n (%)	12-<16 years N=81 n (%)	>=16 years N=216 n (%)	Total N=421 n (%)
Abdominal pain*	8 (20.5)	13 (15.3)	19 (23.5)	60 (27.8)	100 (23.8)
Pyrexia	15 (38.5)	23 (27.1)	21 (25.9)	39 (18.1)	98 (23.3)
Headache	2 (5.1)	15 (17.6)	23 (28.4)	43 (19.9)	83 (19.7)
Cough	13 (33.3)	19 (22.4)	17 (21.0)	31 (14.4)	80 (19.0)
Diarrhea*	12 (30.8)	7 (8.2)	13 (16.0)	38 (17.6)	70 (16.6)
Nasopharyngitis	5 (12.8)	12 (14.1)	10 (12.3)	32 (14.8)	59 (14.0)
Vomiting	4 (10.3)	19 (22.4)	9 (11.1)	26 (12.0)	58 (13.8)
Rash*	2 (5.1)	11 (12.9)	10 (12.3)	29 (13.4)	52 (12.4)
Nausea	2 (5.1)	9 (10.6)	5 (6.2)	34 (15.7)	50 (11.9)
Creatinine increased**	1 (2.6)	2 (2.4)	6 (7.4)	40 (18.5)	49 (11.6)
Laryngeal pain	0 (0.0)	5 (5.9)	9 (11.1)	35 (16.2)	49 (11.6)
Pharyngitis	3 (7.7)	8 (9.4)	16 (19.8)	20 (9.3)	47 (11.2)
Influenza	5 (12.8)	5 (5.9)	9 (11.1)	25 (11.6)	44 (10.5)
Rhinitis	8 (20.5)	10 (11.8)	6 (7.4)	18 (8.3)	42 (10.0)

AEs are included with an incidence of >10% patients in the ß-thalassemia population, sorted by descending order of frequency in the 'All patients' column
* Grouped term ** includes 'Blood creatinine increased' / 'Blood creatinine abnormal'
*** Upper respiratory tract infection

11.3.2 Discussion of adverse events by organ system

Gastrointestinal disorders

Gastrointestinal (GI) disorders including abdominal pain, nausea, vomiting, diarrhea, and possibly constipation all appear to be related to the administration of ICL670. These events were generally mild to moderate in severity and were transient in duration lasting several days (Table 11-5). About 26% of patients experienced GI symptoms that were assessed as related to ICL670. A dose-response relationship was apparent for abdominal pain, nausea, diarrhea, constipation and vomiting. These symptoms have generally been manageable with supportive measures and have rarely required the permanent discontinuation of therapy. This is supported by the evidence that in 25% of patients (95% of cases) the GI disorders which were considered related to study drug were graded as mild or moderate and only in 1% of patients (5% of cases) these symptoms were graded as severe.

Table 11-5 Most common adverse events that were more frequently observed with ICL670 by severity

	ICL670			DFO	
	Pooled ß-Thal.	Sickle Cell	Rare Anemias	ß-Thal.	Sickle Cell
No. of patients studied	421	132	99	290	63
AE preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Mild					
Abdominal pain*	79 (18.8)	20 (15.2)	18 (18.2)	32 (11.0)	6 (9.5)
Diarrhea*	63 (15.0)	18 (13.6)	32 (32.3)	16 (5.5)	3 (4.8)
Vomiting	54 (12.8)	19 (14.5)	26 (26.3)	20 (6.9)	7 (11.1)
Nausea	43 (10.2)	22 (16.7)	24 (24.2)	13 (4.5)	5 (7.9)
Rash*	30 (7.1)	16 (12.1)	9 (9.1)	9 (3.1)	3 (4.8)
Creatinine increased**	34 (8.1)	5 (3.8)	9 (9.1)	0 (0.0)	0 (0.0)
Moderate					
Abdominal pain*	16 (3.8)	13 (9.8)	9 (9.1)	8 (2.8)	2 (3.2)
Diarrhea*	7 (1.7)	7 (5.3)	9 (9.1)	5 (1.7)	0 (0.0)
Vomiting	3 (0.7)	7 (5.3)	3 (3.0)	6 (2.1)	3 (4.8)
Nausea	5 (1.2)	7 (5.3)	3 (3.0)	1 (1.3)	2 (3.2)
Rash*	18 (4.3)	2 (1.5)	3 (3.0)	1 (0.3)	0 (0.0)
Creatinine increased**	15 (3.6)	4 (3.0)	6 (6.1)	0 (0.0)	0 (0.0)
Severe					
Abdominal pain*	5 (1.2)	4 (3.0)	1 (1.0)	1 (0.3)	1 (1.6)
Diarrhea*	0 (0.0)	1 (0.8)	1 (1.0)	1 (0.3)	0 (0.0)
Vomiting	1 (0.2)	2 (1.5)	0 (0.0)	2 (0.7)	0 (0.0)
Nausea	2 (0.5)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Rash*	4 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine increased**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

* Grouped term ** includes 'Blood creatinine increased' / 'Blood creatinine abnormal'

Skin and subcutaneous tissue disorders

Maculopapular skin rash was observed more commonly in patients receiving ICL670 than DFO in Study 0107 and appears to be both drug- and dose-related. Most episodes were of mild to moderate severity and resolved with continued therapy, even in the absence of dose adjustment (Table 11-5). In more severe episodes that have required temporary discontinuation of ICL670, reintroduction of ICL670 was often been possible at a reduced dose with subsequent re-escalation of the dose. This overall pattern is not typical of a drug-hypersensitivity rash. As the rash has appeared on body surfaces that are normally covered by clothing during the daytime, the cause also does not appear to be phototoxicity.

In patients receiving DFO, as would be expected, skin-related disorders were primarily related to infusion site reactions.

Renal disorders

Increases in serum creatinine of at least 33% when compared to baseline at = 2 consecutive visits occurred in 36% of all patients treated in with ICL670 (Table 11-6). In a small percentage of these patients, the creatinine increases also exceeded the upper limit of normal (ULN) but were never more than 2-fold and were generally only marginally above the ULN. No cases of progressive increases in serum creatinine and no cases of renal failure were observed.

Table 11-6 Number (%) of patients with increases in serum creatinine

	ICL670			DFO	
	Pooled ß-Thal.	**Sickle Cell**	**Rare Anemias**	**ß-Thal.**	**Sickle Cell**
No. of patients studied	421	132	99	290	63
Patients affected	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with creatinine increase >33% at = 2 consecutive post-baseline visits	137 (32.5)	48 (36.4)	23 (23.2)	40 (13.8)	14 (22.2)
No. patients with creatinine increase >33% **and >ULN** at = 2 consecutive post-baseline visits	10 (2.4)	3 (2.3)	16 (16.2)	1 (0.3)	2 (3.2)

Each patient with an increase in serum creatinine is included in only one of the above categories

The highest percentage of creatinine increases that exceeded the upper limit of normal occurred in the rare anemia population. A number of these individuals, particularly those with MDS, were older and had serum creatinine values that were at or near the ULN at baseline. In all patient populations, the creatinine changes were more commonly seen in patients treated with ICL670 at 20 and 30 mg/kg than at lower doses.

A dose reduction algorithm resulted in normalization or stabilization of the serum creatinine value in about 25% and 60% of patients, respectively. The remaining patients had values that fluctuated between baseline and the maximal increase observed, and no patient discontinued study because of progressive increases in serum creatinine. In patients on Study 0105E2 treated with ICL670 for periods of up to 35 months, progressive increases in serum creatinine have not been observed, suggesting no long-term effect on serum creatinine over time.

Transfusional iron intake appears to be inversely associated with the reporting of increased creatinine as an AE. In the pooled population of patients with ß-thalassemia the highest frequency of AE reports of a creatinine increase occurred in patients with the lowest average daily transfusional iron intake (< 0.3 mg/kg/day) who were treated with ICL670 at doses of 20 and 30 mg/kg. In contrast, only two of the 71 patients with the highest average daily iron intake (> 0.5 mg/kg/day) had an increase in serum creatinine reported as an AE, both at the 30 mg/kg dose. The majority of patients had an average daily iron intake of 0.3 - 0.5 mg/kg/day and this group had an intermediate frequency of AE reports of creatinine increases that was clearly dose-dependent. This finding suggests that the increase in serum creatinine is due to the administration of a dose of ICL670 that is high in relation to the amount of iron administered.

Ear and labyrinth disorders

Deafness, neurosensory deafness or hypoacusis were reported irrespective of drug relationship in 11 patients on ICL670 and ten patients on DFO in Study 0107. These symptoms were considered to be related to treatment in 1/296 patients (0.3%) on ICL670 and 5/290 patients (1.7%) on DFO. In Study 0108, six patients had some degree of hearing loss and a relationship to ICL670 was suspected in two of these patients. In Study 0109 the dose of DFO was reduced because of hearing loss in two patients on DFO and in none on ICL670. DFO appears to cause a neurosensory hearing deficit which typically affects high-frequency hearing. Unfortunately, specific details of the type of hearing loss are not available for many patients. Overall, the relationship between auditory abnormalities and treatment with ICL670 is unclear.

Ophthalmology findings

Lens abnormalities, sometimes described as early cataracts, have been reported in seven patients on ICL670 in Studies 0106, 0107, 0108, and 0109. Four of these episodes were reported as AEs but only one case out of two reported in Study 0107 was assessed as related to ICL670. For comparison, in Study 0107 lens abnormalities were observed in five patients receiving DFO, and a relationship to DFO was assessed in four cases.

Other laboratory parameters

Transaminase elevations were particularly difficult to assess in these patient populations due to a high background incidence of chronic viral hepatitis and of liver damage secondary to chronic iron overload. As a consequence, many patients had elevated levels of transaminases at study entry, sometimes to >5 x ULN. Although transaminase elevations to >5 x ULN were seen more frequently in patients treated with ICL670 than in patients on DFO (in 17 versus 5 patients in study 0107), the values showed marked fluctuations and were not clearly progressive. In some patients treated at 5 and 10 mg/kg, the transaminase increases were paralleled by increases in serum ferritin, suggesting that the increases may have been related to inadequate chelation. In one patient in Study 0107 and in one patient in Study 0109 there were marked (>10-fold above the ULN) increases in ALT during ICL670 treatment that resolved with discontinuation and recurred with rechallenge, suggesting drug-induced change. In both cases the ALT values returned to baseline after subsequent drug discontinuation.

There were no drug-related changes in hematology parameters in patients receiving ICL670, with the exception of one patient who developed mild neutropenia (lowest value of ANC 1.37×10^9/L) secondary to hepatitis that was probably related to ICL670. No cases of drug-related agranulocytosis were observed.

11.3.3 Deaths, SAEs, adverse events leading to treatment discontinuation

A similar percentage of patients receiving ICL670 and DFO experienced serious adverse events (SAEs) in comparative studies (0107 and 0109)(Table 11-7). The relatively high rate of SAEs in patients with SCD receiving ICL670 or DFO was primarily related to sickle cell crises in 22.0 and 23.8% of patients, respectively. Such events would be expected during a

long-term study in this patient population. If sickle cell crises are excluded, the rate of SAEs in patients with ß-thalassmia and SCD is quite similar.

SAEs with a suspected relationship to ICL670 were reported relatively infrequently (Table 11-7). Of the 652 patients receiving ICL670 in the main safety and efficacy studies (0106, 0107, 0108, 0109), 17 (2.6%) patients reported drug-related SAEs. These included four skin rashes, four GI AEs, and three increases in liver transaminases.

Table 11-7 Number (%) of patients who died, had SAEs or AEs leading to discontinuation or dose adjustment

No. (%) of patients with type of event	ICL670 Pooled ß-thal. N=421 n (%)	ICL670 Sickle cell N=132 n (%)	ICL670 Rare anemias N=99 n (%)	DFO ß-thalassemia N=290 n (%)	DFO Sickle cell N=63 n (%)
No. (%) with AEs	**378 (89.8)**	**127 (96.2)**	**97 (98.0)**	**246 (84.8)**	**62 (98.4)**
No. (%) with related AEs	169 (40.1)	51 (38.6)	64 (64.6)	55 (19.0)	16 (25.4)
No. (%) dose adjustments due to AEs	**145 (34.4)**	**49 (37.1)**	**53 (53.5)**	**54 (18.6)**	**21 (33.3)**
No. (%) adjustm. due to related AEs	89 (21.1)	15 (11.4)	34 (34.3)	14 (4.8)	4 (6.3)
No. (%) discontinuation due to AEs	**13 (3.1)**	**7 (5.3)**	**14 (14.1)**	**4 (1.4)**	**2 (3.2)**
No. (%) discont. due to related AEs	11 (2.6)	5 (3.8)	3 (3.0)	0 (0.0)	0 (0.0)
No. (%) with SAEs*	**42 (10.0)**	**61 (46.2)**	**27 (27.3)**	**25 (8.6)**	**27 (42.9)**
No. (%) with related SAEs*	13 (3.1)	5 (3.8)	2 (2.0)	1 (0.3)	0 (0.0)
No. (%) discontinuation due to SAEs*	**6 (1.4)**	**3 (2.3)**	**9 (9.1)**	**4 (1.4)**	**2 (3.2)**
No. (%) discont. due to related SAEs*	4 (1.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
No. (%) who died	**1 (0.2)**	0 (0.0)	**5 (5.1)**	**3 (0.1)**	0 (0.0)
No. (%) with related death	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*SAEs include fatal events

The number of discontinuations due to AEs and SAEs was relatively similar in patients with ß-thalassemia and SCD receiving ICL670 (Table 11-7). Though the discontinuation rate was somewhat lower in patients receiving DFO, this was probably because acceptable tolerability to DFO was an inclusion criterion for study enrollment. The most frequent reasons for discontinuation of ICL670 were skin rash, GI symptoms, and liver transaminase elevations. The number of discontinuations, as well as the incidence of SAEs was higher in the population of patients with rare anemias, and particularly in patients with MDS. These patients were on average older and had a variety of co-morbid conditions. Several of these individuals discontinued due to disease progression.

There were four deaths in Study 0107 (one patient on ICL670, three patients on DFO) and five in Study 0108. Only one death in studies with ICL670 was assessed by the investigator as study drug related: the sudden death of a three-year old splenectomized ß-thalassemia patient from Tunisia enrolled in Study 0107 who had received ICL670 30 mg/kg for several months. Since an autopsy was not performed, the actual cause of death is not known. An independent Program Safety Board (PSB) determined that rather than being related to ICL670, the cause of death was more likely overwhelming sepsis related to splenectomy at an early age. The deaths during Study 0108 were considered related to the underlying disease (sepsis, cardiac arrest, pulmonary embolism) and occurred in patients with MDS (four patients) and DBA (one

patient). The three deaths in patients receiving DFO during Study 0107 were all assessed as disease-related.

11.4 Safety in patients with low baseline iron burden

Per protocol, ICL670 doses of 20 and 30mg/kg were not administered as initial doses to patients with LIC < 7 mg Fe/g dw. However, administration of ICL670 was not associated with an excess of adverse events in 30 patients receiving doses of 20 and 30 mg/kg with baseline serum ferritin values < 1000 µg/L in the pooled ß-thalassemia population.

Additionally, in Studies 0107 and 0108, 73 patients were identified who were treated with ICL670 doses of 20 or 30 mg/kg and in whom LIC fell to < 7 mg Fe/g dw during the study. The LIC values of these patients declined from a mean of 14 mg Fe/g dw at baseline to a mean of 4 mg Fe/g dw at end of study. Assuming a linear decrease in LIC during the study, the average estimated time that these individuals spent with an LIC value below 7 mg Fe/g dw was 3 months. In these patients, very few AEs were reported during the time period when the LIC levels were < 7 mg Fe/g dw. The majority of AEs, including increases in creatinine, were reported during the initial months of therapy in the period when the LIC was = 7 mg Fe/g dw.

12 Recommended use

The clinical trial program was conducted using determination of LIC as an endpoint in order to demonstrate changes in a reliable and accepted measure of body iron burden. However, it was understood prior to initiation of the trials that it would be highly desirable to dose the drug on the basis of readily available clinical parameters, as it was clear that dosing based on LIC by biopsy or SQUID would not be practical. Serum ferritin is a commonly used, relatively non-invasive method used by physicians to assess patients for iron overload. Chelation therapy is initiated when the serum ferritin rises consistently above 1000 µg/L (Porter, 2001a). Long term maintenance of ferritin < 2500 µg/L is correlated with reduced death from cardiac causes (Olivieri and Brittenham, 1997). Therefore, serum ferritin was monitored in all clinical studies with the goal of demonstrating a correlation between trends in serum ferritin levels and the change in LIC over time.

In addition to the above, the 5 and 10 mg/kg doses of ICL670 were shown to be inadequate in patients with ongoing blood transfusions, and therefore these doses are not being recommended as starting doses, though they may be appropriate in individual patients for maintenance by dose titration.

Indication and dosage

ICL670 is proposed for use in the treatment of chronic iron overload from blood transfusions (transfusional hemosiderosis) in adult and pediatric patients at least 2 years of age. Consideration should be given to the initiation of therapy with ICL670 after the transfusion of approximately 20 units (equivalent to 100 mL/kg) of PRBC or when there is evidence from clinical monitoring that chronic iron overload is present (e.g., serum ferritin > 1000 µg/L).

The recommended initial daily dose of ICL670 is 20 mg/kg body weight.

An initial daily dose of 30 mg/kg may be considered for patients with severe iron overload (e.g., serum ferritin > 2500 µg/L).

Monitoring

It will be recommended that serum ferritin be assessed monthly and the dose of ICL670 should be increased or decreased, if appropriate, every three to six months in order to achieve the desired therapeutic effect of maintenance or reduction of body iron burden, as indicated by stable or falling levels of serum ferritin. As changes in iron excretion induced by ICL670 appear to be linear, dose adjustments in 5 to 10 mg/kg increments are recommended, with subsequent observation after a dose adjustment for three to six months in order to determine whether further dose adjustment is necessary. Such dose titration will allow optimization of the dose for each patient regardless of their underlying age, iron burden, or anemic condition. Monitoring of serum creatinine and liver transaminases will also be recommended.

13 Overall benefit/risk

Regardless of the underlying disease state, chronic iron overload due to blood transfusions leads to significant morbidity and early mortality unless adequate chelation therapy is administered. DFO is the reference chelation therapy that has a well established safety and efficacy profile in the treatment of chronic iron overload due to blood transfusions, and is known to reduce morbidity and mortality in patients with transfusional iron overload. However, because DFO must be administered by prolonged subcutaneous or intravenous infusion, patient acceptance of, and compliance with, therapy is often poor, resulting in poor patient outcomes despite the availability of an effective agent. The availability of a conveniently administered oral iron chelator with similar efficacy to DFO would greatly facilitate patient acceptance and adherence to treatment.

ICL670 is proposed for use in the treatment of chronic iron overload from blood transfusions (transfusional hemosiderosis) in adult and pediatric patients at least 2 years of age. The clinical program for ICL670 is the largest and most comprehensive ever prospectively conducted in this indication and the pivotal program has involved the administration of ICL670 to 700 patients as part of single-arm and randomized trials of one year's duration, including a large Phase III study comparing ICL670 to DFO. Similar efficacy to DFO was demonstrated in patients with baseline LIC values = 7 mg Fe/g dw treated with doses of 20 and 30 mg/kg, even though the primary statistical objectives were not met in the overall patient population. Multiple secondary objectives were positive and were supportive of efficacy in this population of patients. In addition, based upon the relatively constant efficiency of chelation observed across all doses of ICL670 administered as well as the dose-effect observed on iron balance, it can be extrapolated that ICL670 can effectively be used to treat patients across the full spectrum of severity of iron overload.

The most common adverse effects that were associated with drug administration were gastrointestinal events, rash, and mild non-progressive increases in serum creatinine. These adverse events infrequently led to drug discontinuation. The increases in serum creatinine never exceeded twice the upper limit of normal and stabilized or returned to normal with dose reduction and continued drug administration in the large majority of those affected. Elevated

liver transaminase values to greater than 10 times the upper limit of normal were occasionally observed (0.3%). The risk related to elevated serum creatinine and liver transaminase levels can be minimized by monthly monitoring. Drug-related agranulocytosis has not been observed in preclinical models or in patients treated with ICL670. In addition, ICL670 does not appear to have adverse effects on growth or development in pediatric patients.

Overall, ICL670 has a favorable benefit to risk profile when administered at starting doses of 20 and 30 mg/kg. At these doses, ICL670 has similar efficacy to DFO but is not associated with the complications and burden of subcutaneous or intravenous infusion. In fact, the greatest risk of DFO therapy may be non-compliance which leads to potential morbidity and mortality due to iron overload. Although gastrointestinal events are more common with ICL670 therapy compared to DFO, these were mostly mild to moderate in severity and resulted in few discontinuations of therapy. The monthly monitoring of serum ferritin and safety markers (serum creatinine, liver function tests) allows effective dose titration in which the benefit/risk ratio is optimized for the individual, regardless of their underlying age, iron burden or anemic condition. Therefore, the availability of ICL670 would fulfill an unmet medical need for an effective oral chelation therapy that can be instituted early in childhood and be continued through adolescence into adulthood, thus preventing the development of complications of iron overload.

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