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STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Serial Number:	21-882 / 000
Drug Name:	ICL670/Exjade (deferasirox) (125, 250, 500 mg) Tablets for Oral Suspension
Indication(s):	Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients as young as two years of age
Applicant:	Norvartis Pharmaceuticals Corporation
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TABLE OF CONTENTS

1. EXECUTIVE SUMMARY 3

1.1 CONCLUSIONS AND RECOMMENDATIONS 3
1.2 BACKGROUND 3
1.3 STATISTICAL ISSUES AND FINDINGS 3

2. INTRODUCTION 3

2.1 OVERVIEW 3
2.2 DATA SOURCES 4

3. STATISTICAL EVALUATION 4

3.1 EVALUATION OF EFFICACY 4
3.1.1 Study Design 4
3.1.1.1 Phase 3 Study CICL670A0107 4
3.1.1.2 Phase 2 Study CICL670A0108 5
3.1.2 Primary Efficacy Analysis 6
3.1.2.1 Phase 3 Study CICL670A0107 6
3.1.2.2 Phase 2 Study CICL670A0108 6
3.1.3 Important Secondary Efficacy and Subgroup Analyses 7
3.1.3.1 Phase 3 Study CICL670A0107 7
3.1.3.2 Phase 2 Study CICL670A0108 7
3.1.4 Phase 3 Study CICL670A0107 Results 8
3.1.4.1 Overall Study Descriptive Information 8
3.1.4.2 Primary Efficacy Results 8
3.1.4.3 Secondary Efficacy Results 9
3.1.5 Phase 2 Study CICL670A0108 Results 10
3.1.5.1 Overall Study Descriptive Information 10
3.1.5.2 Primary Efficacy Results 11
3.1.5.3 Secondary Efficacy Results 11
3.2 EVALUATION OF SAFETY 11

4. FINDINGS IN SUBGROUP POPULATIONS 12

4.1 GENDER, RACE, AND AGE 12
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS 12

5. CONCLUSIONS 12

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

1.2 Background

The Sponsor has submitted one randomized, open-label, active comparator controlled, parallel group, multicenter, multinational study and one open-label, multicenter, multinational study to evaluate the efficacy and safety of Exjade (deferasirox) in the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis). The design of the controlled study was developed with the Agency through a Special Protocol Assessment under IND 58,554 (Serial nos. 036, 037, and 039), as was the uncontrolled study. According to the Sponsor (Section 1, page 8 of protocol or page 7723 of submission):

> Because humans are unable to actively eliminate iron from the body, toxic and eventually lethal levels of iron will accumulate as a result of repeated transfusions, e.g. in β-thalassemia major … Excess iron is deposited in the form of hemosiderins (insoluble "iron cores" of ferritin) mainly in the liver, spleen, endocrine organs and in the myocardium. The exact mechanism of iron damage to these tissues is unknown, but it is established that organ failure correlates with iron burden in these tissues. Except for infectious diseases, cardiac complications are the major cause of death in patients with β-thalassemia major.
>
> Iron chelators slowly mobilize these iron deposits, probably by a process of continuously binding the microscopic amounts of soluble iron present in the "transit pool", which are in equilibrium with the insoluble hemosiderins. Solubilized, chelated iron is excreted in the urine and/or via the bile into feces, the route of elimination in part depending upon the chemical structure of the chelating agent.

The current reference chelating agent in patients with transfusional hemosiderosis is deferoxamine mesylate (DFO) and it is the active comparator used in this study. Its route of administration, subcutaneous infusions lasting at least 8 hours at doses between 20 and 60 mg/kg/day given for 5 days/week, accounts for patients opting not to have treatment and for poor compliance among patients who are treated with it.

The Sponsor's proposed indication for Exjade (deferasirox), an iron chelator, is:

> *Exjade is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients as young as two years of age.*

1.3 Statistical Issues and Findings

Statistical issues are failure in the protocol-specified primary efficacy analysis and the assessment of strength of evidence in secondary endpoints and subgroup analyses. Subgroup analyses are presented and discussed in Section 3.

The following is the result of the analysis of the primary efficacy endpoint in patients with β-thalassemia major:

- Study CICL670A0107 does not demonstrate the non-inferiority of ICL670 to DFO in terms of treatment success in lowering liver iron content (lower bound of 95% confidence interval for difference in change from baseline for treatment success is not greater than –0.15 is the primary endpoint analysis).

2. INTRODUCTION

2.1 Overview

The Sponsor has submitted the following two studies:

- A controlled Phase 3 efficacy clinical study in male and female subjects at least 2 years of age with β-thalassemia and transfusional hemosiderosis and a liver iron content of at least 2mg/g dw and previously treated with deferoxamine (DFO) or never treated with any iron chelator
- An uncontrolled Phase 2 efficacy clinical study in male and female subjects at least 2 years of age with rare chronic anemias other than β-thalassemia and β-thalassemia and transfusional hemosiderosis and a liver iron content of at least 2mg/g dw and unable to be treated with DFO.

The controlled study is designed to assess the efficacy, in terms of non-inferiority, of ICL670 in the treatment of chronic iron overload (transfusional hemosiderosis) compared to the reference chelating agent, DFO, in patients with transfusional hemosiderosis. The target patient population of the Phase 3 study consists of 500 β-thalassemia outpatients with transfusional hemosiderosis and previously treated with DFO, randomized 1:1 to one of two groups of 250 patients each.

The uncontrolled study is designed to assess the efficacy of ICL670, in terms of success rate, in the treatment of chronic iron overload in patients with transfusional hemosiderosis. The target patient population of the Phase 2 study consists of 175 patients, of which 100 are outpatients with rare chronic anemias other than β-thalassemia (stratum 1) and 75 outpatients with β-thalassemia (stratum 2) with transfusional hemosiderosis unable to be treated with DFO. Table 2.1 presents a brief summary of the two studies addressed in this review.

Table 2.1
Brief Summary of Clinical Studies for Exjade

Study Number (No. and Location of Centers) and Dates of Study Conduct	Subject Population	Treatment	Number Randomized (Treated)	Design[1]
CICL670A0107 (Phase 3) (46 Europe, 3 N. Africa, 5 S. America, 2 Canada, 7 U.S.) 2-13-03 to 11-2-04	Male and female patients with β-thalassemia and transfusional hemosiderosis and a liver iron content of ≥2 mg Fe/g dry weight, at least 2 yrs. of age	Exjade (ICL670) Deferoxamine (DFO) **Total**	297 (296) 294 (290) **591 (586)**	OL, R, AC, PG, MC
CICL670A0108 (Phase 2) (29 Europe, 3 Canada, 6 U.S.) 1-27-03 to 11-5-04	Male and female patients with β-thalassemia, congenital or acquired chronic anemia, and transfusional hemosiderosis and a liver iron content of ≥2 mg Fe/g dry weight, at least 2 yrs. of age	Exjade (ICL670) **Total**	184 (184) **184 (184)**	OL, MC

Source: Statistical Reviewer's listing.
[1] OL = Open Label, R = Randomized, AC = Active Comparator, PG = Parallel Group, MC = Multicenter

The Sponsor's proposed indication for Exjade (deferasirox), an iron chelator, is:

Exjade is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients as young as two years of age.

My review presents the Sponsor's protocol-specified primary efficacy analyses for success of lowering LIC in detail and briefly presents clinically relevant secondary efficacy analyses.

2.2 Data Sources

The study reports and additional information for these studies were submitted electronically. The submitted SAS data sets for all studies were complete and well documented. These items were located in the Electronic Document Room at \\Cdsesub1\N21882\N_000\2005-04-29.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

3.1.1.1 Phase 3 Study CICL670A0107

In this study, screened eligible subjects went through a 5-day wash-out period before randomization to treatment. After randomization, the subject had visits every 4 weeks until end of study (1 year) or discontinuation. Subjects were randomized in a 1:1 ratio to receive ICL670 or Deferoxamine mesylate (Desferal- DFO), the active comparator and reference therapy.

The initial dose selected at start of study treatment depended on the LIC determined at screening. ICL670 is administered as an oral dose between 5 and 30 mg/kg/day. DFO is administered as subcutaneous infusions lasting at least 8 hours at doses between 20 and 60 mg/kg/day given for 5 days/week. Patients with a baseline LIC between 2 and 7 mg Fe/g dw were allowed to continue their previous doses and schedules of DFO treatment, even if not meeting the requirements given in Table 3.1 below. Table 3.1 gives the dose administered depending on the value

of the screening LIC. The initial dose is fixed during the one-year study period, unless safety concerns, e.g. overchelation, during the study support a dose adjustment.

Table 3.1
Study CICL670A0107: Initial Dose of Study Treatment Based on Screening Liver Iron Content (LIC)

Screening LIC	Initial ICL670 Dose	Initial DFO Dose
2 to 3 mg Fe/g dw	5 mg/kg/day	20 - 30 mg/kg/day
> 3 to 7 mg Fe/g dw	10 mg/kg/day	25 - 35 mg/kg/day
> 7 to 14 mg Fe/g dw	20 mg/kg/day	35 - 50 mg/kg/day
> 14 mg Fe/g dw	30 mg/kg/day	≥ 50 mg/kg/day

Source: Statistical Reviewer listing.

All patients underwent a baseline liver biopsy that was repeated one year later. Liver biopsy was the reference technique for standardized determination of LIC in all patients (in pediatric patients, where liver biopsy was not practicable, the use of SQUID was discussed with the Sponsor on a case by case basis). Biopsy analysis was performed at one pathology laboratory. The Sponsor stated that (Section 3.2, page 15 of protocol or page 7730 of submission):

> SQUID is a new technology for the non-invasive determination of liver iron, based on the measurement of the magnetic susceptibility of the liver, and has been shown to be accurate and provide results that reproducibly correlate with those achieved by standard methods of iron determination in liver biopsy samples.

The Clinical Reviewer investigated this claim and determined that the Sponsor's conclusions were based on one article that utilized "First preliminary results in phantoms and in 4 patients" (Starr TN, et.al. A new generation SQUID biosusceptometer, Nenonen J, Ilmoniemi RJ, Katila T (eds): Biomag 2000: Proceedings 12th Int Conf Biomagnetism, Section 3.3).

The Sponsor stated in the study report (Section 9.1, page 78) that:

> LIC measured by SQUID consistently gave lower results than when measured by liver biopsy. Of the 90 SQUID evaluations at baseline in the PP-1 population, 64 (71.1%) gave LIC values <7 mg Fe/g dw in comparison to only 108/463 (23.3%) liver biopsies. On average, LIC values measured by SQUID were about 50% of those measured by biopsy.
>
> As a consequence, patients with baseline SQUID assessments were more likely to have a LIC <7 mg Fe/g dw and should therefore have received lower doses of study drug when compared to patients undergoing liver biopsy. However, this situation preferentially affected patients randomized to ICL670 because the protocol allowed patients randomized to DFO to continue on their previous dose if baseline LIC was <7 mg Fe/g dw whereas patients randomized to ICL670 were dosed strictly according to the protocol. This inherent dosing bias flawed the comparison of ICL670 and DFO patients in the PP-1 population with LIC <7 mg Fe/g dw. This bias did not occur in the two higher dose cohorts since patients with LIC ≥7 mg Fe/g dw had to take both DFO and ICL670 according to baseline LIC.

Given that SQUID underestimates LIC and is not a validated method to determine liver iron content (per the Clinical Reviewer), its utility as a method to provide (useful, valid, quality) data for efficacy analysis has not been determined. As described in Section 3.1.3, the above issues with SQUID prompted the Clinical Reviewer to request additional subgroup analyses to describe efficacy.

3.1.1.2 Phase 2 Study CICL670A0108

The design of study CICL670A0108 is similar to that of study CICL670A0107, as described above, except in the following two aspects:

- It is a Phase 2, uncontrolled study, without DFO as a comparator
- SQUID LIC assessment was performed in patients with a medical contraindication to liver biopsy (such as coagulation problems in patients with myelodysplastic syndrome), as determined on a case by case basis with the Sponsor.

The same problems with SQUID, as described above, are also relevant in this study.

3.1.2 Primary Efficacy Analysis

3.1.2.1 Phase 3 Study CICL670A0107

The primary objective of study CICL670A0107 is to demonstrate the non-inferiority of ICL670 to DFO in terms of effects on LIC assessed by liver biopsy after one-year treatment in β-thalassemia patients with transfusional hemosiderosis. In some cases in the pediatric population, where liver biopsy was not practicable SQUID alone was used to assess LIC. For patients where SQUID and liver biopsy was available, the biopsy data was used for the primary efficacy analysis.

The protocol-specified primary analysis was based on success rate, defined as a binary outcome indicating a successful or failed treatment effect on LIC, and analyzed in terms of non-inferiority. As presented in Table 3.2, depending on the LIC at baseline, different criteria had to be met to achieve a treatment success or failure. Non-inferiority was to be demonstrated if the lower bound of the two-sided 95% confidence interval (CI) of the difference in success rate (ICL670 - DFO) was greater than -0.15. The CI is estimated based on asymptotic normal approximation for the difference of two binomial probabilities.

Table 3.2
Study CICL1670A0107: Success Criteria for Primary Efficacy Evaluation

LIC at Baseline	Success, if LIC is	Failure, if LIC is
2 to < 7 mg Fe/g dw	1 to <7 mg Fe/g dw	<1 mg Fe/g dw ≥7 mg Fe/g dw
≥7 to <10 mg Fe/g dw	1 to <7 mg Fe/g dw	<1 mg Fe/g dw ≥7 mg Fe/g dw
≥10 mg Fe/g dw	Decrease in LIC ≥3 mg Fe/g dw	Decrease in LIC <3 mg Fe/g dw

Source: Statistical Reiviewer's listing.

The primary efficacy analysis population was the protocol-specified per protocol (PP-1). The PP-1 population included patients that received study drug and who had an LIC determination at baseline and at end of study, using the same technique as at baseline. Also included were patients who had to permanently discontinue study medication due to any of the following safety reasons: adverse event, abnormal laboratory value, abnormal test procedure results, or iron overload related death. Subjects with no LIC result available at one year using the same technique as at baseline were counted as treatment failures in the PP-1 population. Patients who discontinued study drug for the safety reasons indicated in the PP-1 definition were considered treatment failures, since the treatment was obviously not tolerated and the patient could not benefit from the drug. Patients prematurely discontinued due to any other reason were excluded from this population.

3.1.2.2 Phase 2 Study CICL670A0108

The primary objective of Phase 2 study CICL670A0108 is to demonstrate a pre-specified success rate for ICL670 in terms of effects on LIC assess by liver biopsy after one-year treatment in outpatients with rare chronic anemias other than β-thalassemia and outpatients with β-thalassemia with transfusional hemosiderosis unable to be treated with DFO. In some patients with a medical contraindication to liver biopsy, SQUID alone was used to assess LIC.

The protocol-specified primary analysis was based on success rate, defined as a binary outcome indicating a successful or failed treatment effect on LIC, and analyzed in terms of comparison to a pre-specified threshold. As presented in Table 3.2, depending on the LIC at baseline, different criteria had to be met to achieve a treatment success or failure. In order to claim that the success rate of ICL670 is greater than 50%, a test statistic based on the standardized normal approximation of the binomial distribution was used at one-sided alpha level of 0.025.

The primary efficacy analysis population was the ITT population, which included all patients that successfully passed screening and were chosen to start study treatment. In addition, an analysis using the PP-1 population was planned to be reported. Subjects with no LIC result available at one year using the same technique as at baseline, were counted as treatment failures in the ITT and PP-1 populations.

For hypothesis testing in the ITT and PP-1 populations, data from both strata, β-thalassemia and rare anemias, were pooled. No separate hypothesis testing was planned to be performed per stratum, but estimates of the success rate and corresponding confidence intervals were calculated for both strata.

3.1.3 Important Secondary Efficacy and Subgroup Analyses

3.1.3.1 Phase 3 Study CICL670A0107

The Clinical Reviewer requested that an important protocol-specified secondary endpoint analysis, the comparison of the change in LIC value from baseline between patients treated with ICL670 and DFO for patients that had a LIC of ≥7 mg Fe/ g dw at baseline, be reviewed. The protocol-specified analysis was the fitting of an analysis of covariance model (ANCOVA) with baseline LIC value as the covariate and treatment group as the main effect. A between treatment comparison was performed using the least square means obtained from the model, with the least square estimated difference, two-sided 95% confidence interval, and p-value presented.

In addition to the important secondary efficacy endpoint analysis, the Clinical Reviewer also requested that the following *post hoc* subgroup analyses of the primary and important secondary efficacy endpoint listed in Table 3.3 be presented to investigate efficacy in these subgroups. These 14 analyses, presented by the Sponsor, consist of 2 protocol-specified and 12 *post hoc* analyses. The following are some clinical reasons for these subgroup analyses:

- SQUID is not a validated technique for measuring LIC and underestimates the LIC by at least 50%.
- The lower initial doses of ICL670 for those with baseline LIC <7 mg Fe/g dw may not be efficacious.
- The effect of inaccurate SQUID LIC values resulted in patients being underdosed with ICL670.

Table 3.3
Study CICL670A0107: Listing of Important Protocol-Specified Secondary Endpoint Analysis and *Post Hoc* Subgroup Analyses of the Primary Efficacy Endpoint and Important Secondary Endpoint

Endpoint Type	Endpoint Description	Subgroup Analysis	Number of Analyses	Protocol-Specified or *Post Hoc* Analysis
Primary	Treatment success rate	Biopsy	1	*Post hoc*
		SQUID	1	*Post hoc*
		Baseline LIC group*	2	*Post hoc*
		Biopsy X Baseline LIC group*	2	*Post hoc*
		SQUID X Baseline LIC group*	2	*Post hoc*
Secondary	LIC value change from baseline	Baseline LIC <7 mg Fe/g dw	1	*Post hoc*
		Baseline LIC ≥7 mg Fe/g dw	1	Protocol-specified
		Biopsy X Baseline LIC group*	2	*Post hoc*
		SQUID X Baseline LIC group*	2	*Post hoc*

Source: Statistical Reviewer listing.
* The two baseline LIC groups are as follow: <7 mg Fe/g dw and ≥7 mg Fe/g dw.

All secondary efficacy analyses utilized another protocol-specified per population, the PP-2 population, which included patients who had an end of study LIC value, using the same technique as at baseline. Also, the above listed secondary and *post hoc* analyses were not taken into account for powering the study, so the results are exploratory.

3.1.3.2 Phase 2 Study CICL670A0108

The Clinical Reviewer requested that the following three *post hoc* analyses presented in Table 3.4 be reviewed. Descriptive statistics of success rate and its 95% confidence interval are presented.

Table 3.4
Study CICL670A0108: Listing of *Post Hoc* Subgroup Analyses of the Primary Efficacy Endpoint

Endpoint Description	Subgroup Analysis	Protocol-Specified or *Post Hoc* Analysis
Treatment success rate	Biopsy patients in PP-1 population	*Post hoc*
	Biopsy patients with baseline LIC ≥7 mg Fe/g dw in ITT population	*Post hoc*
	β-thalassemia biopsy patients with baseline LIC ≥7 mg Fe/g dw in PP-1 population	*Post hoc*

Source: Statistical Reviewer listing.

This review presents the protocol-specified and *post hoc* primary efficacy analyses and briefly presents the important secondary efficacy analyses, both protocol-specified and *post hoc* for both studies.

3.1.4 Phase 3 Study CICL670A0107 Results

3.1.4.1 Overall Study Descriptive Information

The following section presents demographic and baseline characteristics, subject disposition, and distribution of liver iron content measurement techniques.

Demographic and baseline characteristics are comparable among the treatment groups in the treated population. The subjects' mean age is 17 years for ICL670 and 17.3 years for DFO. The majority of subjects are Caucasian (88.9% for ICL670 and 86.6% for DFO) and female (52.7% for ICL670 and 51% for DFO).

Table 3.5 presents the number of randomized subjects and their disposition. Subjects were randomized in a 1:1 fashion to each treatment group as specified in the protocol. After randomization, but before starting study treatment, five patients (one ICL670, four DFO) withdrew consent. So, 296 patients on ICL670 and 290 patients on DFO began therapy. Study discontinuation is 5.7% in the ICL670 group and 4.1% in the DFO group. The primary reasons for study discontinuation in the ICL670 group are adverse events and withdrawal of consent, and in DFO group are withdrawal of consent and death. Overall, the subjects were balanced in the PP-1 and PP-2 analysis population groups.

Table 3.5
Summary of Subject Disposition and Analysis Populations for Controlled Study CICL670A0107

	ICL670	DFO
Randomized (ITT)	297	294
Treated	296 (99.7)	290 (98.6)
Completed Treatment*	279 (94.3)	278 (95.9)
Discontinued Treatment* n (%)	17 (5.7)	12 (4.1)
Discontinued Due to Adverse Events** n (%)	*7 (41.2)*	*1 (8.3)*
Death	*1 (5.9)*	*3 (25.0)*
Protocol Violation	*2 (11.8)*	*2 (16.7)*
Withdrawal of Consent	*7 (41.2)*	*6 (50.0)*
Per Protocol Population 1 (PP-1)* n (%)	276 (93.2)	277 (95.5)
Per Protocol Population 2 (PP-2)* n (%)	268 (90.5)	273 (94.1)

Source: Table 7-1, page 62, Study ICL670A0107 report.
* With respect to number of treated subjects.
** With respect to number of all discontinuations.

In the per protocol population 1 (PP-1), the majority of LIC measurements were made using biopsy (229/276 = 83.0% for ICL670 and 234/277 = 84.5% for DFO) compared to SQUID.

3.1.4.2 Primary Efficacy Results

The Sponsor's results for the protocol-specified primary efficacy analysis of non-inferiority and *post hoc* subgroup analyses requested by the Clinical Reviewer are presented in Table 3.6. The protocol-specified primary efficacy analysis is presented in the shaded area. Non-inferiority of ICL670 to DFO has not been demonstrated because the lower bound of the 2-sided 95% confidence interval for the difference in treatment success rate (ICL670 - DFO) is greater than –0.15.

Results for the subgroup analyses are as follow:

- For all patients, the lower bound of the 95% C.I. for the difference in treatment success rate was not greater than –0.15 for either the biopsy or SQUID subgroup.
- For those patients with a baseline LIC < 7mg Fe/g dw, the lower bound of the 95% C.I. for the difference in treatment success rate was not greater than –0.15 for either the biospy & SQUID, biopsy or SQUID subgroup.
- For those patients with a baseline LIC ≥ 7mg Fe/g dw, the lower bound of the 95% C.I. for the difference in treatment success rate was greater than –0.15 for the biospy & SQUID and biopsy subgroups but not for the SQUID subgroup.

Table 3.6
Study CICL0A0107: Success Rates Based on Change in Liver Iron Content (PP-1 population) for ICL670 and DFO

	Overall		LIC < 7 mg Fe/g dw		LIC ≥ 7 mg Fe/g dw	
LIC Measurement Technique	**ICL670**	**DFO**	**ICL670**	**DFO**	**ICL670**	**DFO**
Biopsy & SQUID†						
N	276	277	85	87	191	190
Success Rate (n)	52.9 (146)	66.4 (184)	40.0 (34)	82.8 (72)	58.6 (112)	58.9 (112)
Difference and 95% C.I.*	-13.5 [-21.6, -5.4]		-42.8 [-55.9, -29.7]		-0.3 [-10.2, 9.6]**	
Biopsy						
N	229	234	53	55	176	179
Success Rate (n)	51.1 (117)	62.8 (147)	22.6 (12)	76.4 (42)	59.7 (105)	58.7 (105)
Difference and 95% C.I.*	-11.7 [-20.7, -2.8]		-53.7 [-69.6, -37.8]		-1.0 [-9.2, 11.2]**	
SQUID						
N	47	43	32	32	15	11
Success Rate (n)	61.7 (29)	86.0 (37)	68.8 (22)	93.8 (30)	46.7 (7)	63.6 (7)

Source: Table 9-1, page 77, ICL0A0107 Study Report.
† Primary efficacy analysis.
* The two-sided, 95% confidence interval is based on an asymptotic normal approximation for the difference of two binomial probabilities.
** The lower bound of the 95% confidence interval is greater than the –0.15 non-inferiority bound.

3.1.4.3 Secondary Efficacy Results

The protocol-specified secondary analysis is presented in the shaded area of Table 3.7 below. The other secondary analyses are *post hoc*, presented by the Sponsor, and what the Clinical Reviewer requested be presented.

The result of the protocol-specified secondary analysis is as follows:

- In patients with a baseline LIC ≥7 mg Fe/g dw, there was no difference in the change from baseline in LIC between the ICL670 and DFO treatment groups (95% C.I is from –1.79 to 0.66).

Results of the *post hoc* secondary analyses are as follow:

- In patients with a baseline LIC <7 mg Fe/g dw, all subgroups (biopsy & SQUID, biopsy alone, SQUID alone) there was an increase in the change from baseline in LIC between the ICL670 and DFO treatment groups. That is, there was a greater increase in LIC from baseline for ICL670 than for DFO (the lower bounds of all 95% C.I.s. are >0.0).
- In patients with a baseline LIC ≥7 mg Fe/g dw, for the biopsy alone and SQUID alone subgroups, there was no difference in the change from baseline in LIC between the ICL670 and DFO treatment groups (both 95% C.I.s include zero).

Table 3.7
Study CICL0A0107: Change from Baseline in Liver Iron Content between Treatments by Baseline Liver Iron Content Category (PP-2 population)

	LIC < 7 mg Fe/g dw			LIC ≥ 7 mg Fe/g dw		
LIC Measurement Technique	**ICL670**	**DFO**	**Difference**	**ICL670**	**DFO**	**Difference**
Biopsy & SQUID						
n	83	87		185	186	
Mean (s.e.)*	3.99 (0.34)	0.15 (0.33)	3.84 (0.48)	-5.08 (0.44)	-4.52 (0.44)	-0.56 (0.62)
95% C.I.*	[3.32, 4.66]	[-0.50, 0.80]	[2.90, 4.77]	[-5.94, -4.22]	[-5.38, -3.66]	[-1.79, 0.66]
Biopsy						
n	52	55		172	175	
Mean (s.e.)*	5.54 (0.44)	0.54 (0.43)	5.00 (0.62)	-5.31 (0.47)	-4.66 (0.46)	-0.65 (0.66)
95% C.I.*	[4.68, 6.40]	[-0.30, 1.38]	[3.77, 6.22]	[-6.23, -4.39]	[-5.56, -3.76]	[-1.95, 0.65]
SQUID						
n	31	32		13	11	
Mean (s.e.)*	1.40 (0.31)	-0.52 (0.31)	1.92 (0.44)	-1.62 (0.89)	-2.81 (0.98)	1.19 (1.34)
95% C.I.*	[0.79, 2.01]	[-1.13, 0.09]	[1.04, 2.80]	[-3.36, 0.12]	[-4.73, -0.89]	[-1.60, 3.98]

Source: Post-text Table 9.2-16, pages 3570 and 3571, ICL0A0107 Study Report and Statistical Reviewer analyses.
* Mean, standard error, and 95% confidence interval based on an ANCOVA model with baseline LIC as covariate.

3.1.5 Phase 2 Study CICL670A0108 Results

3.1.5.1 Overall Study Descriptive Information

The following section presents demographic and baseline characteristics, subject disposition, and distribution of liver iron content measurement techniques.

The subjects' mean age is 35 years, the majority of subjects are Caucasian (78.8%), and equal representation of male and female subjects (50%).

Table 3.8 presents the number of enrolled subjects and their disposition. All 184 enrolled patients began ICL670 therapy. Study discontinuation is 17.4%, with the primary reasons for study discontinuation being adverse events and withdrawal of consent.

Table 3.8
Summary of Subject Disposition and Analysis Populations for Uncontrolled Study CICL670A0108

	ICL670
Enrolled (ITT)	184
Treated	184 (100.0)
Completed Treatment*	152 (82.6)
Discontinued Treatment* n (%)	32 (17.4)
Discontinued Due to Adverse Events** n (%)	*13 (40.6)*
Death	*5 (15.6)*
Study Drug No Longer Required	*4 (12.5)*
Withdrawal of Consent	*10 (31.3)*
Per Protocol Population 1 (PP-1)* n (%)	165 (89.7)

Source: Table 7-1, page 62, Study ICL670A0107 report and Table 7-1, page 55, Study ICL670A0108 report.
* With respect to number of treated subjects.
** With respect to number of all discontinuations.

Of the 184 enrolled (ITT) patients in Study CICL670A0108, 85 had β-thalassemia and 99 had other rare anemias. Of the 165 patients in the PP-1 population, 80 had β-thalassemia and 85 had other rare anemias.

In the ITT population, the majority of LIC measurements were made using biopsy (120/184 = 65.2%) compared to SQUID.

3.1.5.2 Primary Efficacy Results

The Sponsor's results for the protocol-specified primary efficacy analysis of success rate and additional protocol-specified analyses of success rate are presented in Table 3.9. The protocol-specified primary efficacy analysis is presented in the shaded area. The study failed to show that the lower bound of the 95% confidence interval for the true success rate was greater than 50% .

Results for the additional protocol-specified analyses of success rate are as follow:

- For all patients in the PP-1 population, the study failed to show that the lower bound of the 95% confidence interval for the true success rate was greater than 50%.
- In β-thalassemia patients in the PP-1 population, the 95% confidence interval for success rate is [45.4, 67.1].
- In rare anemia patients in the PP-1 population, the 95% confidence interval for success rate is [45.9, 67.0].

Table 3.9
Study CICL0A0108: Success Rates Based on Liver Iron Content for ICL670

	ITT Population	PP-1 Population		
LIC Measurement Technique	**All Patients**	**All Patients**	**β-thalassemia**	**Rare Anemias**
Biopsy & SQUID†				
N	184	165	80	85
Success Rate (n)	50.5 (93)	56.4 (93)	56.3 (45)	56.5 (48)
95% C.I.*	[43.3, 57.8]	[48.8, 63.9]	[45.4, 67.1]	[45.9, 67.0]
p-value (1-sided, α=0.25)	0.441	0.051		

Source: Table 9-1, page 75, ICL0A0108 Study Report.
† Primary efficacy analysis.
* The two-sided, 95% confidence interval is based on an asymptotic normal approximation for the binomial distribution.

3.1.5.3 Secondary Efficacy Results

The three *post hoc* descriptive analyses, presented by the Sponsor and what the Clinical Reviewer requested be reviewed, are presented in Table 3.7. Results of the *post hoc* descriptive analyses are as follow:

- In biopsy patients in the PP-1 population, the 95% confidence interval is [51.8, 70.0].
- In biopsy patients with a baseline LIC ≥7 mg Fe/g dw in the ITT population, the 95% confidence interval is [50.2, 68.4].
- In β-thalassemia patients with a baseline LIC ≥7 mg Fe/g dw in the PP-1 population, the 95% confidence interval is [55.2, 79.3].

Table 3.10
Study CICL0A0108: Success Rates Based on Liver Iron Content in Patients with Biopsy for ICL670

LIC Measurement Technique	All Patients in PP-1 Population	All Patients with LIC ≥ 7 mg Fe/g dw in ITT Population	β-thalassemia Patients with LIC ≥ 7 mg Fe/g dw in PP-1 Population
Biopsy			
N	110	113	58
Success Rate (n)	60.9 (67)	59.3 (67)	67.2 (39)
95% C.I.	[51.8, 70.0]	[50.2, 68.4]	[55.2, 79.3]

Source: Table 9-1, page 75, ICL0A0108 Study Report.
* The two-sided, 95% confidence interval is based on an asymptotic normal approximation for the binomial distribution.

3.2 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. For information, reference the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

The Sponsor has presented efficacy analyses by gender and age. There are no clinically important differences among groups defined by values of these variables. Of greater interest are findings by the subgroups described in section 4.2 below.

4.2 Other Special/Subgroup Populations

The subgroup populations of interest are listed in Tables 3.3 and 3.4 and addressed in Sections 3.1.4.3 and 3.1.5.3.

5. CONCLUSIONS