NOVARTIS

Clinical Development

ICL670/ Deferasirox /Exjade®

Study number: CICL670E2419 / NCT01709838

An open label, multi-center, efficacy and safety study of deferasirox in iron overloaded patients with non-transfusion dependent thalassemia (THETIS)

Statistical Analysis Plan (SAP) – Final Analysis

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17-Oct-2018	*Prior to DB lock*	*Creation of final version*	*N/A - First version*	*NA*
dd-Mmm-2019		*Creation of amendment 1*	*Added clarification for primary endpoint*	*Section 2.5.1*
			Added sodium, C-reactive protein, uric acid, lactase dehydrogenase (LDH), urea (BUN) laboratory parameters which were missed in the previous version	*Section 2.7.3*

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List of abbreviations

AE	Adverse event
[redacted]	[redacted]
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	Area Under the Curve
[redacted]	[redacted]
BUN	Blood Urea Nitrogen
Cmax	Maximum (peak) observed plasma concentration after single dose administration
CSR	Clinical Study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
dw	Dry weight
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EOS	End of study
FAS	Full Analysis Set
FE	Iron
FSH	Follicle stimulating hormone
GGT	Gamma glutamyl transferase
HbE	Hemoglobin E
HbH	Hemoglobin H
[redacted]	[redacted]
LDH	lactase dehydrogenase
LH	Luteinizing hormone
LIC	Liver iron content
LPLV	Last patient last visit
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	Magnetic resonance imaging
[redacted]	[redacted]
NTDT	Non-transfusion-dependent thalassemia
o.d.	Once Daily
OS	Overall Survival
PedsQL™	Pediatric Quality of Life InventoryTM
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event

SAP	Statistical Analysis Plan
SD	Standard deviation
SF	Serum ferritin
SF-36	Medical Outcomes study short form-36
SF-6D	Short-Form Six-Dimension
SOC	System Organ Class
THALASSA	Novartis Study CICL670E2209
TFLs	Tables, Figures, Listings
[redacted]	[redacted]
Tmax	Time to reach maximum (peak) plasma concentration after single dose administration
TSH	Thyroid stimulating hormone
WHO	World Health Organization

1 Introduction

CICL670E2419 is a phase IV open label, multi-center, efficacy and safety study of deferasirox in iron overloaded patients with non-transfusion dependent thalassemia. This open-label, single-arm, multi-center 5-year study was designed to evaluate the efficacy and safety of deferasirox in iron overloaded NTDT patients, at least ten-years-old. A 1-year analysis was performed to assess the primary objective and selected secondary objectives. This study enrolled 134 patients including 68 Chinese and 66 non-Chinese, with 112 patients still on treatment at the time of the 1-year primary analysis.

The primary objective of this one-year analysis was met, confirming activity of deferasirox in the NTDT population, as observed in Study ICL670A2209. The absolute change in LIC from Baseline to Week 52 was statistically significantly different (Paired T-test, $p<0.0001$, two-sided). The absolute mean change in LIC (mg Fe/g dw) from Baseline to Week 52 was -6.68 (SD 7.018) with a 95% CI (-7.91, -5.45).

Pharmacokinetic analysis was performed on the data from 22 patients at Week 4. Mean (SD) AUCtau at 10 mg/kg/day was 773 (350) hr×µmol/L and was similar for the Chinese and non-Chinese groups (770 (405) and 776 (250) hr×µmol/L, respectively). Mean (SD) Cmax was 61 (27) µmol/L and was comparable between these two groups (Chinese 62 (33) µmol/L and non-Chinese 57 (14) µmol/L).

This analysis plan is written to analyze all data up to last patient last visit (LPLV) and to support final CSR.

1.1 Study design

This open label, single-arm, multi-center study to evaluate the efficacy and safety of deferasirox in NTDT patients with iron overload will include the following phases:

Screening (4 weeks) to determine patient eligibility

Open label treatment with deferasirox:

- Starting dose 10 mg/kg/day for 4 weeks;
- At Week 4, dose adjustments according to baseline LIC:
  - 20 mg/kg/day for patients with baseline LIC > 15 mg Fe/g dw
  - 15 mg/kg/day for patients with baseline LIC > 7 but ≤ 15 mg Fe/g dw
  - Dose will remain at 10 mg/kg/day for patients with baseline LIC ≥ 5 but ≤ 7 mg Fe/g dw
- Approximately every 6 months, starting at Week 24, dose adjustments according to LIC:
  - Increase dose by 5-10 mg/kg/day, if LIC > 15 mg Fe/g dw, maximum of 30 mg/kg/day
  - May increase dose by 5 mg/kg/day if LIC >7 but ≤ 15 mg Fe/g dw, maximum of 20 mg/kg/day
  - Same dose if LIC is ≥3 but ≤ 7 mg Fe/g dw, maximum of 10 mg/kg/day

The maximum dose of deferasirox throughout the study will be 30 mg/kg/day.
If LIC measurement is <3 mg Fe/g dw or SF is <300 ng/mL, treatment will be interrupted. Patients who have interrupted study treatment during the first year of the study due to LIC <3 mg Fe/g dw or SF <300 ng/mL will continue the monthly visit schedule. Patients who have treatment interruption due to LIC <3 mg Fe/g dw or SF<300 ng/mL after 52 weeks, will complete scheduled visit one month post-interruption and then be followed every three months.

Study treatment will restart at the previous effective dose when LIC ≥5 mg Fe/g dw and SF ≥ 300 ng/mL (maximum of 10 mg/kg/day). Once on treatment, patients will be followed monthly.

Approximately 117 patients were planned to be enrolled. Treatment duration will be 5 years. Pharmacokinetic analysis was conducted in a subset of 20 patients from selected participating centers.

During the screening phase, patient eligibility was determined, followed by an open-label phase with deferasirox up to five years. Completion of this study occurs after the Last Patient Last Visit of the study, and upon the availability and accuracy verification of the last data point required for final statistical analysis.

No randomization was done in this study. No formal interim analysis based on primary endpoint was planned for this study.

1.2 Study objectives and endpoints

The study objectives and endpoints are presented in the following table.

Table 1-1 Objectives and endpoints

Objective	Endpoint
Primary	
Assess the efficacy of deferasirox in liver iron removal after 52 weeks of treatment	Change in LIC from baseline after 52 weeks of treatment
Secondary	
Assess response rates in subset of patients with baseline LIC>15 mg Fe/g dw	Proportion of patients with baseline LIC>15 achieving LIC<5 mg Fe/g dw and time to achieving LIC <5 mg Fe/g dw
Assess long-term efficacy of treatment to a target LIC of 3 mg Fe/g dw	Time from target LIC of 3 mg Fe/g dw to the first LIC ≥5 mg Fe/g dw in the follow up period
Evaluate the impact of deferasirox on adult QoL	Change in health-related outcomes using Medical Outcomes Study Form 36 (SF-36v2)
Evaluate the impact of deferasirox on pediatric QoL	Change in health-related outcomes using the Pediatric Quality of Life questionnaire (PedsQL™)

Evaluate the efficacy of deferasirox in liver iron removal	Change in LIC from baseline
Assess the correlation of change in SF and LIC	SF vs LIC at baseline and EOS
Confirm the efficacy of deferasirox in liver iron removal in NTDT syndrome	Change in LIC from baseline after 52 weeks of treatment by underlying NTDT syndrome
Assess the efficacy of deferasirox in decreasing SF after 52 weeks of treatment	Change in SF from baseline after 52 weeks of treatment
Evaluate the safety of deferasirox doses up to 30 mg/kg/day dose	Safety parameters, labs, adverse events (AEs)
Assess the efficacy of Deferasirox in endocrine function	Change from baseline during treatment period in total and free testosterone (males), LH and FSH (females), TSH, total and free T4, total and free T3, fasting plasma glucose, insulin, insulin resistance, and cortisol.
Conduct PK analysis in a subgroup of patients	PK parameters (AUC, Cmax, Tmax and trough levels) during the study period
Safety	
All safety objectives will be performed.	All safety events and assessments will be included
[redacted]	

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis according to the data analysis section 10 of the study protocol and its amendments.

All analyses will be performed by using SAS Version 9.2 or higher.

As described in Section 10 of the protocol, in addition to the overall population analysis, statistical analysis will be performed according to ethnicity groups: Chinese/non-Chinese patients.

All summaries described below will be performed by ethnicity group and all patients, if not otherwise stated.

2.1.1 General definitions

Observation periods for safety analysis

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last nonzero dose of study medication.
3. post-treatment period: starting at day 30+1 after last dose of study medication.

Safety summaries (tables, figures) include only data that from the pre-treatment period (to display the baseline status e.g. for ECG) and the on-treatment period, i.e. no data from the post-treatment period must be included if not otherwise requested from Health Authorities. In particular, summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the so-called treatment-emergent AEs. Similarly, summary tables and figures only include lab values observed during the on-treatment period. However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

The above defined observation periods will be only applicable for safety analysis. In particular, all post-baseline values will be used in the analyses of LIC, serum ferritin [redacted] defined in the protocol section 7.2.1 for efficacy assessment.

Study day, last assessment day and baseline

Study day

Since this is an open label study, for all variables (safety or efficacy), study day will be defined as the number of days since the date of first dose of study medication. For a particular date on or after first dose, it is calculated as:

Study day = Assessment date – Date of first dose of study medication + 1.

Therefore, the date of the first dose of study medication will be Day 1 by definition.

The day before this day will be defined to be Day -1, i.e., there is no Day 0. Study days before first dose of study medication will be calculated as:

Study day = Assessment date – Date of first dose of study medication.

In the above study day calculation, the date of the first day of study drug will be replaced with the study drug assignment date if the patient doesn't take any study drug.

So if the patient doesn't take the study drug, Day 1 is the study drug assignment date.

Definition of baseline value

For all variables, the baseline value will be defined to be the last available value prior to or on Day 1.

For serum ferritin the baseline value will be calculated from the mean of values measured prior to or on Day 1.

Last assessment day

For the safety assessment, the censoring date will be the last treatment date+30 days. For example, time to first specific adverse event will be censored at the last treatment date+30 days for a patient without the specified adverse event on-treatment.

End of treatment year 1

All data collected at Week 52 visit will be noted as End of treatment year 1

Month definition

Unless otherwise noted (e.g. for the calculation for month of exposure, 1 month = 365.25/12 days), one month will be defined as 30 days, with the exception of month 1 which consisted the first 45 days. When multiple values will be present for a month, the average value will be used unless otherwise noted. The grouping of each month will be according to the following rules:

- If the day is in (1, 30+15] assign to month 1.
- If the day is in (30*×x-15, 30*×x+15] assign to month x<12.
- If the day is in (345, 378] assign to month 12.

This would allow for a +/- 15 days window for each month.

Quarter definition

Unless otherwise noted, the quarter is defined as shown in the table below:

Visit Description	First day in window	Scheduled day in window	Last day in window	Quarter
Baseline	-35		1	
Week 2	2	14	21	1
Week 4	22	28	42	1
Week 8	43	56	70	1
Week 12	71	84	98	1
Week 16	99	112	126	2
Week 20	127	140	154	2
Week 24	155	168	182	2
Week 28	183	196	210	3
Week 32	211	224	238	3
Week 36	239	252	266	3
Week 40	267	280	294	4

Visit Description	First day in window	Scheduled day in window	Last day in window	Quarter
Week 44	295	308	322	4
Week 48	323	336	350	4
Week 52	351	364	378	4
Week 56	379	392	406	5
Week 60	407	420	434	5
Week 64	435	448	462	5
Week 68	463	476	490	6
Week 72	491	504	518	6
Week 76	519	532	546	6
Week 80	547	560	574	7
Week 84	575	588	602	7
Week 88	603	616	630	7
Week 92	631	644	658	8
Week 96	659	672	686	8
Week 100	687	700	714	8
Week 104	715	728	742	8
Week 108	743	756	770	9
Week 112	771	784	798	9
Week 116	799	812	826	9
Week 120	827	840	854	10
Week 124	855	868	882	10
Week 128	883	896	910	10
Week 132	911	924	938	11
Week 136	939	952	966	11
Week 140	967	980	994	11
Week 144	995	1008	1022	12
Week 148	1023	1036	1050	12
Week 152	1051	1064	1078	12
Week 156	1079	1092	1106	12

Visit Description	First day in window	Scheduled day in window	Last day in window	Quarter
Week 160	1107	1120	1134	13
Week 164	1135	1148	1162	13
Week 168	1163	1176	1190	13
Week 172	1191	1204	1218	14
Week 176	1219	1232	1246	14
Week 180	1247	1260	1274	14
Week 184	1275	1288	1302	15
Week 188	1303	1316	1330	15
Week 192	1331	1344	1358	15
Week 196	1359	1372	1386	16
Week 200	1387	1400	1414	16
Week 204	1415	1428	1442	16
Week 208	1443	1456	1470	16
Week 212	1471	1484	1498	17
Week 216	1499	1512	1526	17
Week 220	1527	1540	1554	17
Week 224	1555	1568	1582	18
Week 228	1583	1596	1610	18
Week 232	1611	1624	1638	18
Week 236	1639	1652	1666	19
Week 240	1667	1680	1694	19
Week 244	1695	1708	1722	19
Week 248	1723	1736	1750	20
Week 252	1751	1764	1778	20
Week 256	1779	1792	1806	20
Week 260	1807	1820	1834	20

2.2 Analysis sets

The **Full Analysis Set (FAS)** consists of all patients who will be assigned at least one dose of study drug. The FAS will be used for all efficacy analyses.

The **Safety Set** consists of all patients who will receive at least one dose of study drug.

The **pharmacokinetic analysis set (PAS)** consists of all patients from FAS set who have evaluable pharmacokinetic (PK) data.

The **Ethnicity group**: The Patients will be grouped based on the ethnicity as Chinese patients, non-Chinese patients and all patients.

2.2.1 Subgroup of interest

The following subgroups will be considered for further analyses:

- Age categories (<18 years and ≥ 18 years)
- Baseline LIC categories (≤7, >7 - 15 and >15 mg Fe/g dw)
- NTDT diagnosis subtypes (Beta-thalassemia intermedia, HbE Beta-thalassemia, Alpha-thalassemia intermedia (HbH disease) and Other)
- Average actual daily dose (>0 - <7.5, 7.5 - 12.5, >12.5 - 17.5 and >17.5 mg/kg/day)

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and baseline characteristics will be summarized by ethnicity group and overall for the FAS.

Demographics include age, age group (<18 years, 18-<50 years, 50-<65 years, ≥65 years), gender, race. Other baseline characteristics include weight, weight group (<35 kg, 35-<55 kg, 55- <75 kg, ≥75 kg), main underlying disease, history of blood transfusion (Yes/No), history of splenectomy (Yes/No), history of chelation therapy (Yes/No), type of last chelation therapy prior to the study, hepatitis B and C status, medical history by MedDRA primary SOC and preferred term, clinically significant abnormality in baseline ECG (Yes/No), abnormality in baseline audiometric test (Yes/No) and (clinically significant/non-significant), abnormality in baseline ocular exam (Yes/No) and (clinically significant/non-significant), baseline LIC, baseline LIC group (<5, 5-≤7, >7-15, >15 mg Fe/g dw), baseline serum ferritin, baseline serum ferritin group (<300, ≥300-500, >500-1000, >1000-2500, >2500-5000, >5000 ng/mL), baseline creatinine, baseline creatinine group (≤upper limit of normal range (ULN), >ULN), baseline creatinine clearance, baseline creatinine clearance group (<60, 60-<90, 90-<160, ≥160 mL/min), baseline ALT, baseline ALT group (≤ULN, >ULN-5 ×ULN, >5 ×ULN), baseline AST, baseline AST group (≤ULN, >ULN-5×ULN, >5 ×ULN), urine protein/creatinine ratio(≤0.2 mg/mg,>0.2-1 mg/mg, >1 mg/mg).

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The duration of exposure is defined as the number of months between the start and end of study medication. One month of exposure corresponded to 365.25/12 days. So the duration of exposure in month will be calculated as (study medication end date-study medication start date+1)/30.4375.

The following variables will be summarized for the Safety Set : duration of exposure, in months and in categories (<3 months, 3-<6 months, 6-<9 months, and so on); average planned (mg/kg/day) and average actual daily dose (>0 -<7.5, 7.5 - 12.5, >12.5 - 17.5 and >17.5 mg/kg/day); cumulative planned (mg/kg) and actually administered dose (mg/kg); percentage of planned dose taken (as calculated from DAR); number, mean length, and total length of treatment interruptions per patient; duration of treatment excluding interruptions relative to the overall follow-up time; frequency of dose change in planned dose by reason as recorded in the eCRF.

The total patient-years while on treatment, calculated as the sum of (overall drug exposure) / 365.25 will be provided by ethnicity group and for all patients.

The average daily dose (planned or actual, in mg/kg) will be calculated as the mean dose over all days between first and last dose, including interim days with zero dose (interruptions). The cumulative dose (planned or actual, in mg/kg) will be calculated as the sum over the daily doses of all days between first and last dose. The current weight of subject will be used when calculating the actual daily dose.

The percentage of planned dose taken will be derived as 100 × cumulative actual dose (mg/kg)/ cumulative planned dose (mg/kg).

The overall follow-up time will be the number of days between start of study medication and the day before the final visit, both inclusive.

An interruption will be a period of days with a zero actual dose. Only interruptions between start and end of study medication will be taken into account. A patient could have multiple interruptions during the study.

Dose increase and dose reduction will be summarized at week 4, week 24 and approximately every 6 months thereafter. Patient has dose increase at visit if the dose assignment at the visit will be higher than the last available one before the visit. Patient has dose decrease or reduction at visit if the dose assignment at the visit will be nonzero and lower than the last available one before the visit.

Selected efficacy and safety parameters will be summarized by age.

Selected safety data will be summarized by baseline LIC categories

NTDT syndromes or main underlying diseases are Beta-thalassemia intermedia, HbE Betathalassemia, Alpha-thalassemia intermedia (HbH disease) or other. LIC will be summarized by NTDT syndrome.

Selected safety parameters will be summarized by average actual daily dose.

Protocol deviations and patient disposition will be summarized by ethnicity group and listed.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications and significant non-drug therapies will be summarized through frequency tables according to their WHO ATC class and WHO generic term. Prior medications will be defined to be drugs taken prior to the first dose of study medication. Concomitant medications will be medications taken between the first and last day with study medication, excluding medications started on the last day of study medication. Medications which started prior to the first dose of study medication and continued thereafter will be counted in both summaries.

The number of transfusions and the total RBC transfused during the study (mL/kg) will be summarized by ethnicity groups and overall. The amount of RBC transfused denoted the amount of RBC contained in the blood, i.e. (amount of blood transfused [mL])×hematocrit / 100). For each transfusion, the amount of blood given, expressed in mL, will be divided by the last available weight to calculate the amount transfused in mL/kg. For each patient, the total RBC transfused over the whole study will be calculated, summing up the amount received at each transfusion. Only transfusion dates on or after start of ICL670 will be considered for this analysis.

Missing day information for start date of prior chelation therapy or start date of history of blood transfusions will be imputed by the 1st of the Month. If the month is missing it will be imputed by January.

Time since start of first chelation therapy/blood transfusion = (Screening Visit date – start of first chelation/transfusion date + 1)/365.25.

Relevant medical history and current medical conditions will be coded and frequencies summarized for patients in the safety analysis set.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The trial is designed to assess the efficacy of deferasirox in patients with non-transfusion dependent thalassemia based on absolute change in LIC from baseline after one year of treatment. The analysis for primary objective was performed at one-year (data cut-off date : 03-Jan-2015). The study met its primary objective. The primary endpoint, absolute change in LIC (mg Fe/g dw) at Week 52 from baseline, was statistically significantly different from 0 (Paired T-test $p<0.0001$, two-sided). The absolute change in LIC at Week 52 from baseline had mean (SD) -6.68 (7.018) (mg Fe/g dw) and a 95% confidence interval (-7.91, -5.45) (mg Fe/g dw).

As done in previous studies within patients with transfusional iron overload, a normal distribution will be assumed for LIC absolute change.

LIC will be measured at screening (Visit 1), Week 24 (Visit 15) and Week 52 (Visit 25) in treatment year 1. The primary efficacy variable will be the absolute change from baseline in LIC at Week 52, i.e. the difference of LIC at Week 52 minus LIC at baseline.

The absolute change in LIC from baseline after one year of treatment will be analyzed using the FAS set.

The following estimates will be provided:

- point estimate of the absolute change at Week 52,
- the ordinary 2-sided 95% confidence interval,
- p-value (descriptive only).

Also, LIC values at Week 52 will be computed with their corresponding 95% CI.

Handling of missing values/censoring/discontinuations

In case of missing LIC at Week 52, the last available post-baseline LIC value before Week 52 will be used in the calculation of the primary endpoint. Patients without post-baseline LIC at or before Week 52 or baseline LIC will be excluded from the analyses.

Supportive analyses

In order to further assess the absolute change and the relative change in LIC from baseline at Week 52, the estimates and the 95% confidence intervals will be provided for the following proportions (In case of missing LIC at Week 52, the last available post-baseline LIC value before Week 52 will be used):

- The proportion of patients with an LIC decrease by at least 3 mg Fe/g dw from baseline (LIC decrease >= 3 mg Fe/g dw) at Week 52; i.e., proportion of LIC decrease >=3 mg Fe/g dw = subjects with ((baseline LIC – LIC at Week 52)>=3) divided by total number of subjects
- The proportion of patients with an LIC decrease by at least 30% from baseline (LIC decrease >=30%) at week 52. i.e., proportion of LIC decrease >=30% = subjects with ((100*(Baseline LIC – LIC at Week 52)/Baseline LIC) >=30%) divided by total number of subjects.

2.6 Analysis of secondary efficacy objective(s)

All p-values provided for the secondary efficacy endpoints will be considered as exploratory only.

2.6.1 Secondary endpoints

2.6.1.1 Response analysis in patients with baseline LIC>15 mg Fe/g dw

Subjects who achieved the target baseline LIC >15 mg Fe/g will be included in this analysis. The proportion of patients with baseline LIC>15 mg Fe/g dw achieving a post-baseline LIC <5 mg Fe/g dw during the study will be presented with a 95% confidence interval. The normal approximation will be used for the distribution, i.e. the confidence interval will be calculated as follows (Agresti and Coull 1998):

$100*(p + z_{0.975}^2/2n +/- z_{0.975}*\text{sqrt}((p(1-p) + z_{0.975}^2/4n)/n) / (1 + z_{0.975}^2/n)$

Where p denotes the proportion, n the corresponding number of values, $z_{0.975}$ the 97.5% quantile of the standard normal distribution, and sqrt the square root function (see also Brown, Cai, DasGupta, 2001).

Time to the first LIC <5 mg Fe/g dw among patients with baseline LIC >15 mg Fe/g dw will be analyzed based on the Kaplan-Meier method. Kaplan-Meier curves for time to first LIC<5 mg Fe/ g dw and the medians along with 95% confidence intervals will be presented.

If a subject does not achieve a first post-baseline LIC <5 mg Fe/g dw, the day of the last LIC assessment during the study will be used in the Kaplan-Meier analyses for censoring.

If the last assessment date will be incomplete, the earliest possible date will be imputed (first of month if day will be missing, first of year if both day and month will be missing). This imputation rule will be only used for the derivation of the last assessment day.

2.6.1.2 Long-term efficacy of treatment to target LIC of 3 mg Fe/g dw followed by one or more treatment holidays until the LIC is greater or equal to 5 mg Fe/g dw

Subjects who achieved the target LIC <3 mg Fe/g will be included in this analysis. Time from the target LIC <3 mg Fe/g dw to the first LIC ≥5 mg Fe/g dw in the follow-up period will be analyzed by using the Kaplan-Meier method. Kaplan-Meier curves for time to first LIC ≥5 mg Fe/g dw and the medians along with 95% confidence intervals will be presented.

If the subject does not have a first LIC ≥5 mg Fe/g dw in the follow-up period, the day of the last LIC assessment during the study will be used in the Kaplan-Meier analyses for censoring.

If the last assessment date will be incomplete, the earliest possible date will be imputed (first of month if day will be missing, first of year if both day and month will be missing). This imputation rule will be only used for the derivation of the last assessment day.

2.6.1.3 Absolute change in LIC measured by MRI from baseline over time

Absolute changes from baseline LIC at all scheduled LIC evaluation weeks will be analyzed. Patients without any LIC post-baseline value at or prior to the scheduled LIC evaluation week had missing values and will be not included in the analyses for the scheduled weeks. Descriptive statistics and box plots will be provided for:

- LIC at baseline, at all scheduled LIC evaluation weeks (24, 52, 76, 104, 128, 156, 180, 208, 232, 260) and for last available LIC measurement
- Absolute change from baseline LIC at all scheduled LIC evaluation weeks (24, 52, 76, 104, 128, 156, 180, 208, 232, 260) and for last available LIC measurement.

2.6.1.4 Absolute change in LIC measured by MRI from baseline over time by underlying disease

Absolute changes from baseline LIC at all scheduled LIC evaluation weeks will be analyzed by underlying disease. Patients without any LIC post-baseline value at or prior to the scheduled LIC evaluation week had missing values and will be not included in the analyses for the scheduled weeks.

Descriptive statistics will be provided for:

- LIC at baseline, at all scheduled LIC evaluation weeks (24, 52) and for last available LIC measurement in treatment year 1;
- Absolute change from baseline LIC at all scheduled LIC evaluation weeks (24, 52) and for last available LIC measurement in treatment year 1.

2.6.1.5 Absolute change in SF from baseline over time

Baseline serum ferritin as average of all available ferritin values from screening to last sample prior to or on the day of first intake of study medication;

Descriptive statistics and box plots will be provided for:

- SF at baseline, quarterly SF up to week 260;
- Absolute changes of quarterly SF at quarter 1, 2, …,20 from baseline.

Quarter is defined as average of available ferritin values from visit corresponding to end of quarter, visit prior, and visit after (e.g. end of first quarter includes average ferritin values from Visits 11, 12, and 13).

Absolute change from baseline at week 52 will be tested using a 2-sided one sample t-test. The p-value will be considered as exploratory with no multiplicity considerations.

2.6.1.6 Correlation between serum ferritin and LIC at baseline and EOS

Scatter plots with pearson correlation coefficient and simple linear model will be provided without imputing any missing data:

- LIC versus serrum ferritin at baseline, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260
- LIC versus serrum ferritin at baseline, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260 on log scale
- Absolute changes in LIC versus absolute changes in serrum ferritin at baseline, Week 24, Week 52, Week 104, Week 156, Week 208, Week 260

2.6.1.7 Medical Outcomes Study Short Form-36 (SF-36)

The Medical Outcomes Study Short Form 36 (SF-36v2) is a self-administered questionnaire for adults (greater than 18 years of age) and contains 36 items which measure eight dimensions: Physical functioning (10 items), Role limitation due to physical health problems (4 items), Bodily pain (2 items), General health perceptions (5 items), Vitality (4 items), Social functioning (2 items), Role limitations due to emotional problems (3 items) and General mental health (5 items). There is an additional single item giving information on health change over the past year. Item scores for each dimension are coded, summed and transformed to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). The higher values indicate a better evaluation of health. Two summary scores of physical and mental health can also be calculated and scoring is normbased, with normative values at 50 and no floor or ceilings. In addition, the SF-6D, a utility measure of health states, can be derived

from the SF-36 and the scoring for the SF-6D utility values will also be assessed using the scoring methods from the developers.

Descriptive statistics will be provided for all dimensions, PCS/MCS summary scores and SF-6D scores (including absolute change from baseline) by visit (baseline, week 52, 104, and 156).

Absolute change from baseline at week 52, 104, and 156 will be tested as exploratory using a 2-sided one sample t-test. P-values will be considered as exploratory with no multiplicity considerations.

2.6.1.8 Pediatric Quality of Life Questionnaire

The PedsQL™ is a modular approach to measuring health-related quality of life (HRQOL) in children and adolescents. This will be administered to children between the ages of 13 to 18 years. The approach includes both a child self-report and parent proxy-report. The 23-item PedsQL™ Generic Core Scales encompass the essential core domains for pediatric HRQOL measurement: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items). The Generic Core Scales are designed to enable comparisons across patient and healthy populations.

Scores are transformed on a scale from 0 to 100. Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0.

- Score by Domains: If more than 50% of the items in the scale are missing, the scale scores should not be computed,

  Mean Score of domain = Sum of the items in the domain over the number of items answered in that domain.

- Psychosocial Health Summary Score = sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales
- Physical Health Summary Score = Physical Functioning Scale Score
- Total Score = Sum of all the items over the number of items answered on all the scales.

If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

Descriptive statistics will be provided for all domains scores (including absolute change from baseline) by visit (baseline, week 52, 104, and 156).

Absolute change from baseline at week 52, 104, and 156 will be tested as exploratory using a 2-sided one sample t-test.

P-values will be considered as exploratory with no multiplicity considerations.

2.6.1.9 Endocrine function

The endocrine function will be assessed using the following parameters: Total and Free testosterone (males), LH and FSH (females), TSH, total and free T4, total and free T3, fasting plasma glucose, insulin, insulin resistance, and cortisol. Insulin resistance will be derived by HOMA method:

Insulin resistance= fasting Glucose (mmol/L) x fasting Insulin (mU/L) / 22.5

Descriptive statistics will be provided for the values of all parameters and also for their corresponding absolute change from baseline by scheduled visits (Week 12, 24, 36, 52, 64, 76, 88, 104, 116, 128, 140, 156, 168, 180, 192, 208, 220, 232, 244 and 260)

2.7 Safety analyses

All safety analyses will be based on the Safety Set. Post-baseline safety data included values up to 30 days after last non-zero dose.

2.7.1 Adverse events (AEs)

AEs and the principal cause of death will be coded using MedDRA 20.1.

All summaries of AEs only included treatment emergent AEs, i.e., AEs which started or worsened on or after the day with first study medication intake and not more than 30 days after last study medication.

The incidence of AEs (number and percentage of patients with AEs) will be summarized by MedDRA primary SOC and preferred term, and separately by preferred term only. These two summaries will be generated for all AEs, serious AEs (SAEs), AEs with suspected relationship to study medication, SAEs with suspected relationship to study medication, AEs leading to discontinuation of study medication, and AEs leading to dose adjustment or interruption. AEs will be also summarized by MedDRA primary SOC, preferred term, and maximum severity. Non-serious AEs (i.e. excluding SAEs) will be also summarized by primary SOC and preferred term.

2.7.1.1 Adverse events of special interest / grouping of AEs

Specific groupings of adverse events of special interest will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of adverse events for which there is a specific clinical interest in connection with Deferasirox treatment. Note that certain adverse events may be reported within multiple groupings/AESIs.

AESIs are defined by MedDRA terms. Definition for retrieval (maintenance of terms considered AESI) is in a separate document in the Novartis Documentum management system at the path “CREDI Projects/I/ICL670A/Integrated Medical Safety”. The latest document has to be used (The name of the retrieval document should be “ICL670 AESI_MedDRA xx.x_DDMmmYY”, where xx.x is the MedDRA version number. At the time of approval of this report analysis plan, the latest retrieval document is “ICL670 AESI_MedDRA 20.1_08Nov17”). The MedDRA codes will be used to generate the outputs.

For adverse event started before and ended after one-year cutoff date, the end date of the adverse event would be set as “missing”, but reported as “Ongoing” in listings.

2.7.2 Deaths

All Deaths and on-treatment deaths will be summarized by MedDRA primary system organ class (SOC) and preferred term of the principal cause of death.

2.7.3 Laboratory data

For safety monitoring, the following laboratory parameters will be assessed during the study:

- hematology: hemoglobin, hematocrit, white blood cell (WBC) count with differential, platelet count, red blood cell (RBC) count, mean corpuscular volume (MCV), absolute Neutrophil Count (ANC) and reticulocyte count
- biochemistry: albumin, alkaline phosphatase, total/fractionated bilirubin, calcium, chloride, creatinine, gamma-glutamyl transpeptidase (GGT), fasting glucose, inorganic phosphorus, potassium, total protein, sodium, C-reactive protein, uric acid, lactase dehydrogenase (LDH), urea (BUN), serum glutamic pyruvic transaminase (SGPT)/alanine aminotransferase (ALT), serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST), , creatinine clearance, serum creatinine;
- urinalysis (dipstick): urinary protein/creatinine ratio, pH, specific gravity, urine blood, urine glucose, urine protein, urine bilirubin, urine ketones, and urine leukocyte esterase.

All hematology and biochemistry laboratory values will be converted into standard international (SI) units and categorized according to laboratory normal ranges (low/normal/high). All values reported on the same day will be first averaged and then used as the result for that day.

In addition to the laboratory data measured by the central laboratory, creatinine clearance will be calculated based on two different formulae (Cockroft-Gault equation, Schwartz formula for pediatric population). All results for creatinine clearance presented will be based on the Cockroft-Gault/Schwartz formula.

For selected laboratory tests, additional flags for notable ranges as defined in Table 2-1 will be generated. Laboratory values assessed more than 30 days after discontinuation of study medication will be excluded from the analysis.

Table 2-1 Definition of notable ranges for laboratory tests

Laboratory test	Criteria for notable ranges
Platelet count	< 100 x 109/L (extended range <50×109/L)
Absolute neutrophils	< 1.5 x 109/L (extended range <0.5×109/L)
Serum creatinine	> 33% increase from baseline and > ULN at two consecutive measurements at least 7 days apart
Creatinine clearance	<60 mL/min at two consecutive measurements at least 7 days apart (extended range <40 mL/min at two consecutive measurements at least 7 days apart)
Urinary protein/urinary creatinine ratio	> 1.0 (mg/mg) at two consecutive measurements at least 7 days apart
SGOT/ALT and SGPT/AST	>5 x ULN and 2 x baseline (extended range >10×ULN and >2×baseline value)

The number and percentage of patients with post-baseline laboratory results (scheduled and unscheduled) meeting the criteria for notable values (see Table 2-1) will be displayed in a

frequency table, by quarter A patient with a notably abnormal value of serum creatinine, or creatinine clearance will be counted in the period during which the second of the two consecutive abnormally high (or low) measurements occurred.

All notable laboratory abnormalities will be listed.

- Shift tables will be generated for each hematology and biochemistry test, cross-tabulating normal/notable/extended ranges baseline laboratory values against worst postbaseline values.
- Listing of all laboratory data with values flagged to show the corresponding normal/notable/extended ranges

Furthermore, observed values and changes from baseline (absolute and relative to baseline) will be summarized for each laboratory test with descriptive statistics quarterly (baseline, Quarter 1, Quarter 2 etc.). If a time period included more than 1 test result from central lab for serum creatinine, the average will be analyzed. For others, if a time period included more than 1 test result from central or local lab, the average will be analyzed.

Boxplots over time will be generated for selected laboratory test (see Table 2-1). Data will be summarized by period and presented at the midpoint of the respective period. If a time period included more than 1 test result, the average will be analyzed.

2.7.4 Other safety data

Data from vital signs, body weight, ECG, ocular, and auditory examination will be listed and summarized with descriptive statistics as appropriate. Any significant findings after start of study will be documented as AEs and reported as such.

2.7.4.1 ECG, audiometric test and ocular examination

ECG, audiometric test, ocular examination and echocardiography will be performed at baseline, Week 52 and Week 260. Abnormalities will be reported together with an overall interpretation of the findings. Any abnormalities at baseline will be summarized. At Week 260, the investigator flagged all abnormalities which will be new or worsened since baseline. All new or worsened abnormalities are recorded on the AE CRF page. All findings of patients with new or worsened clinically significant abnormalities will be listed.

2.7.4.2 Vital signs

Measurements of vital signs and body weight done more than 30 days after discontinuation of study medication will be excluded from the analysis.

The change from baseline in diastolic blood pressure, systolic blood pressure, pulse rate, and weight will be summarized by scheduled visit with n, mean, SD, minimum, median, and maximum values. Furthermore, the number (%) of patients with notably abnormal vital signs or weight will be presented by visit and for time point 'at any time after baseline'.

The criteria for notably abnormal vital signs and weight are displayed in Table 2-2.

Table 2-2 Definition of notable ranges for vital signs and weight

Parameter	Criteria for notable ranges
Systolic blood pressure	≥180 mmHg / ≤90 mmHg with increase / decrease from baseline of ≥20 mmHg
Diastolic blood pressure	≥105 mmHg / ≤50 mmHg with increase / decrease from baseline of ≥15 mmHg
Pulse rate	≥120 bpm / ≤50 bpm with increase / decrease from baseline of ≥15 bpm
Weight	≥7% increase or decrease from baseline weight

The vital sign data of patients with notably abnormal vital signs will be listed. Similarly body weight data of patients with notably abnormal body weight will be listed.

2.7.4.3 Tolerability

The following GI events (grouped) will be analyzed:

- Abdominal pain/ GI pain (preferred terms of Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, or Gastrointestinal pain)
- Dyspepsia (preferred terms of Dyspepsia)
- Diarrhoea (preferred terms of Diarrhoea, Diarrhoea neonatal, or Frequent bowel movements)
- Constipation (preferred terms of Constipation, Faeces hard, or Infrequent bowel movements)
- Vomiting (preferred terms of Discoloured vomit, Nausea, Retching, or Vomiting)
- Abdominal distension (preferred terms of Abdominal distension)
- Oesophagitis (preferred terms of Oesophageal discomfort, Oesophageal irritation, Oesophageal mucosa erythema, Oesophageal pain, or Oesophagitis)

These events will be investigated with regards to frequency, time to onset, duration and outcome (event end yes/no). For each patient and type of event the following will be determined:

- Number of events
- Time to first event
- Duration of first event

All variables of type 'number of events' will be summarized in frequency tables showing the number and percentage of patients with 0, 1, 2, ≥ 3 events, and with descriptive statistics (n, mean, SD, minimum, median, maximum, sum). The median time to first event and the median duration of first event will be estimated using Kaplan-Meier methods. The analysis of the duration of first event only included patients with event. In the analysis of time to first event,

patients without event will be considered censored at their last assessment date. In the analysis of duration of first event, patients without end of event will be considered censored at their last assessment date. Incidences of grouped gastro-intestinal adverse events will be presented.

2.8 Pharmacokinetic endpoints

PAS will be used in all pharmacokinetic data analysis and PK summary statistics. Only patients with valid PK samples will be included in PAS.

The following criteria will be used to flag not valid PK samples:

For pre-dose samples (at Week 4, Week 12 and Week 24):

- PK sample time should be +/- 20% around 24 hrs (or 24 hr +/- 4.8 hr) after the previous dose.
- PK sample time should be prior to dosing time on the PK sampling date.
- PK sample should be taken at steady state.
- No vomiting should occur within 4 hours post-dose on the day prior to PK pre-dose sampling.
- No vomiting should occur within 4 hours prior to PK pre-dose sampling

For post-dose samples (at Week 4):

- Taken at steady state

A second flag will identify those PK samples which are or which are not at steady-state. For a patient to be at steady state, the study medication should be administered for 4 consecutive days before the PK sampling date without any interruption or change in actual daily dose administered.

Excluded PK samples will be flagged and listed in the PK data listing. Valid PK samples will be considered for the summary statistics. Biofluid concentrations will be expressed in µmol/L. All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

Descriptive statistics of all pharmacokinetic data (pre-dose concentration) and PK parameters (AUCtau in µmol/L*hr, Cmax in µmol/L and Tmax in hr) will be provided by incident dose (i.e. dose administered over the 4 days prior to PK sampling) included arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum. Zero concentrations will be not included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

Scatter plots between PK pre-dose concentrations at Week 4, 12 and 24 and selected PD endpoints (SF at Week 4, 12 and 24, LIC at Week 24 – absolute values and relative change from baseline) will be presented.

[redacted]

2.10 Interim analysis

No formal interim analysis based on primary endpoint was planned.

3 Sample size calculation

Sample size is based on results from ICL670A2209 (THALASSA) study, which was a prospective, double-blind, placebo controlled trial of deferasirox in starting doses of 5 and 10 mg/kg/day in patients with NTDT.

166 patients with randomized to starting doses of 5 mg (n=55) or matching placebo (n=28) and 10 mg (n=55) or matching placebo (n=28).

See in Table 3-1 below results for absolute change in LIC for this study:

Table 3-1 Absolute change in LIC (mg Fe/g dw), Full Analysis Set

Time point Value	ICL670 5.mg/kg (N=55)	ICL670 10.mg/kg (N=55)	Placebo (N=56)
Baseline Value			
N	55	55	55
Mean	13.11	14.56	15.94
SD	7.290	7.921	10.845
Baseline Value			
N	51	54	54
Mean	11.56	10.58	16.38
SD	7.928	7.667	10.606
Baseline Value			
N	51	54	54
Mean	-1.85	-3.78	0.26
SD	3.078	4.150	3.501

Note: Absolute change from baseline: value at timepoint – baseline value. Summary only includes patients with a value both at baseline and at considered timepoint. Source: [Table 14.2-1.9 from the ICL670A2209 trial] (29-Sep-2011 CSR).

The population of patients planned to be enrolled in this study covered a broader type of patients (e.g. including patients treated with hydroxyurea, erythropoietin and butyrate) and from multiple countries. This will be likely to lead to more heterogeneity and thus to an increased variability compared to the one observed in the ICL670A2209 study.

Assuming a true SD as high as 6 mg Fe/g dw and a drop-out rate of 20%, a sample size of 117 patients will be required to obtain 90% power to detect a LIC absolute change of at least 2 mg

Fe/g dw at Week 52 from the baseline value and using a paired t-test at 0.05 two-sided significance level.

Table below provides number of patients required according to different scenarios that ensure 80% power in case of lower true SD than expected (the others hypotheses remaining same):

SD (mg Fe/g dw)	4.5	5	5.5
Power (%)	80	80	80
N patients	51	63	75

Sample size had been computed using PASS 2008.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

Partially or completely missing AE onset dates and concomitant medication dates will be imputed according to the standard Novartis imputation rules as the following:

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. Missing date for AE will be handled according to STL standard.

A partial date is simply an incomplete date e.g.,

ddOCT2001 the days will be missing from this DDMMMYYYY date

Partial adverse event start dates, if left partial, would ultimately mean the following

- It would not be possible to place the adverse event in time.
- Therefore the treatment/dosage at the time of the event would be unknown.
- Therefore the event could not be reported/summarized appropriately – if at all.

Therefore it will be important to perform date imputation to ensure that as many data events will be represented as correctly as possible. Of course partial and/or missing dates should also be caught as edit checks and passed back to the investigator for resolution.

There **will be no** attempt to impute the following

- **Missing** AE start dates
- AE start dates **missing the year**
- Partial/missing AE **end dates**

Table 5-1 explains the abbreviations used.

Table 5-1 AE/Treatment Date Abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

Table 5-2 describes the possible combinations and their associated imputations. In the light grey boxes the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-2 Imputation Algorithm

	AEM MISSING	**AEM < TRTM**	**AEM = TRTM**	**AEM > TRTM**
AEY MISSING	**NC** Uncertain	**NC** Uncertain	**NC** Uncertain	**NC** Uncertain
AEY < TRTY	**(B)** Before TRTSTD	**(C)** Before TRTSTD	**(C)** Before TRTSTD	**(C)** Before TRTSTD
AEY = TRTY	**(B)** Uncertain	**(C)** Before TRTSTD	**(B)** Uncertain	**(A)** After TRTSTD
AEY > TRTY	**(E)** After TRTSTD	**(A)** After TRTSTD	**(A)** After TRTSTD	**(A)** After TRTSTD

The legend to the above table is shown in Table 5-3

Table 5-3 Relationship and Imputation legend

Realtionship	
Before TRTSTD	Indicates AE start date **prior** to Treatment Start Date
After TRTSTD	Indicates AE start date **after** Treatment Start Date
Uncertain	**Insufficient to determine** the relationship of AE start date to Treatment Start Date
Imputation Calculation	
NC / Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1

(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

5.2 Laboratory parameters derivations

Percentages in shift tables cross-tabulating baseline versus post-baseline values will be based on all patients with a non-missing post-baseline value in the respective treatment group and analysis set.

Hepatitis B, C and other

The following preferred terms, in the medical history dataset, will be used to identify patients with hepatitis B, hepatitis C or other forms of hepatitis.

- Hepatitis B preferred terms: hepatitis B, hepatitis B positive, hepatitis B surface antigen positive, hepatitis B virus test positive, hepatitis B e antigen positive, hepatitis B antigen positive
- Hepatitis C preferred terms: hepatitis C, hepatitis C positive, hepatitis C RNA positive, hepatitis C virus test positive
- Hepatitis other preferred terms: autoimmune hepatitis, hepatitis non-A non-B, chronic hepatitis, hepatitis acute, hepatitis chronic active, hepatitis post transfusion, hepatitis viral, hepatitis chronic nos, hepatitis D, hepatitis D antibody positive, hepatitis D antigen positive, hepatitis D virus test positive, hepatitis cholestatic, hepatitis chronic persistent, granulomatous liver disease, hepatitis

The preferred term list will be discussed with clinicians prior to finalizing outputs.

Creatinine clearance re-calculation

Cockroft Gault formula (≥ 18 years of age)

Male patients: CrCl (mL/min) = (140 - age) × weight/(815 × 0.001 × SCr)

Female patients: CrCl (mL/min) = (140 - age) × weight × 0.85/(815 × 0.001 × SCr).

Schwartz formula (< 18 years of age)

CrCl (mL/min) = (k × height) / (SCr × 0.01131) with

- k = 0.55 for children from 1 to 12 years
- k = 0.55 for girls ≥ ≥ 13 years
- k = 0.70 for boys ≥ ≥ 13 years

Calculation of the amount of RBC transfused

In calculating the amount of RBC transfused, the hematocrit value will be as reported in the eCRF for each transfusion. If the transfusion record's hematocrit value is missing, it will be imputed by the hematocrit value provided by the respective center. If no value is provided by center, 65% will be imputed.

If the amount of blood transfused is expressed in Unit, it will be first converted to mL according to the average amount of blood per unit as provided by the respective center. In the case of the average amount per unit being unknown from a center and the amount is reported in Unit, it will be assumed that each unit contains 185 mL of RBC according to ICL670 project standard.

6 Reference

Agresti A., Coull BA (1998). Approximate is better than "Exact" for interval estimation of binomial proportions. The American Statistician. May 1998 Vol.52, No. 2, 119-126.
Brown LD, Cai TT, Dasgupta A (2001). Interval estimation for a binomial proportion. Statistical Science. 2001, Vol. 16, No. 2, 101-133.