NOVARTIS

Oncology Global Drug Development

Non-Interventional Study Protocol (PASS)

CICL670E2422

Title	An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload
Protocol version identifier	v04 (clean)
Date of last version of protocol	01-December-2015
EU PAS register number	EUPAS5914
Active substance	4-[3,5-Bis-(2-hydroxyphenyl)-[1,2,4]-triazol-1-yl]benzoic acid, deferasirox
Medicinal product	Deferasirox
Product reference	EU/1/06/356/001-019 (ref CTA)
Procedure number	EMA/H/C/000670

Marketing authorization holder(s)	Novartis Europharm Ltd.
Joint PASS	No
Research questions and objectives	The purpose of this observational study is to provide further assessment of the safety of deferasirox in NTDT pediatric patients with documented iron overload as defined in a local product label. • Primary objective: To characterize the long term safety profile of deferasirox in pediatric patients with NTDT with exposure up to 5 years • Secondary objectives: • Evaluate the incidence of serum creatinine and SGPT (ALT) increases in actual practice setting • Evaluate renal and hepatic safety parameters over time • Evaluate growth by gender • Evaluate sexual development by gender • Evaluate long term efficacy of deferasirox as measured by serum ferritin and LIC • Evaluate all other safety parameters
Country (-ies) of study	Thailand, United Arab Emirates, Saudi Arabia, Lebanon, France, United States of America, Egypt, Oman, Turkey
Authors	[redacted]; [redacted], MD. [redacted]; [redacted], PhD. [redacted]; [redacted], MD. [redacted]; [redacted], PhD. [redacted]; [redacted], RN, BSN, MBA. [redacted]; [redacted], PhD.

Marketing authorization holder(s)

Marketing authorization holder(s)	NOVARTIS Europharm, Ltd. Vista Buidling, Elm Park, Merrion Road Dublin 4 D04 A9N6 Ireland
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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase (Serum glutamic-pyruvic transaminase)
AST	Aspartate aminotransferase (Serum glutamic-oxalocetic transaminase)
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CMR	Cardiac magnetic resonance
CPO	Country Pharma Organization
CRF	Case Report/Record Form
CRO	Contract Research Organization
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
DT	Dispersible Tablet
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	electronic Case Report/Record Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOS	End of Study
EPO	Erythropoietin
EU	European Union
FDA	Food and Drug Administration
FM	Field Monitor
FCT	Film-coated tablets
GH	Growth hormone
GI	Gastrointestinal
GPP	Good Pharmacoepidemiology Practices
HbE	Hemoglobin E
HbH	Hemoglobin H
HPG	Hypothalamus-pituitary-gonadal
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
IWR	Interactive Web Response System
LIC	Liver iron concentration
MAH	Marketing Authorisation Holder
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not applicable
NIS	Non-interventional Study
NTDT	Non-transfusion dependent thalassemia
PASS	Post-Authorization Safety Study
PI	Principal Physician
PRAC	Pharmacovigilance Risk Assessment Committee

RBC	Red blood cell
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF	Serum ferritin
SGOT	Serum glutamic-oxalocetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
Sr Cr	Serum creatinine
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
ULN	Upper limit of normal
UPCR	Urinary protein creatinine ratio
US	United States
WHO	World Health Organization

1 Responsible parties

Table 1-1 Main responsible parties

Role	Person
Main protocol authors(s)	[redacted], MD Novartis Pharmaceuticals Corp. [redacted], RN, BSN, MBA Novartis Pharmaceuticals Corp. [redacted], PhD Novartis Pharmaceuticals Corp. [redacted], MD Novartis Pharma AG. [redacted], PhD Novartis Pharma AG. [redacted], PhD Novartis Pharmaceuticals Corp.
Principal physician (PI)	NA
MAH contact person	[redacted] Novartis Pharma AG

2 Abstract

Title	An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload
Version and Date	v04 (10-June-2020)
Name and affiliation of main author	[redacted], Novartis Pharmaceuticals Corp.
Rationale and background	The purpose of this observational study is to provide further assessment of the safety of deferasirox in NTDT pediatric patients with documented iron overload as defined in the local product label. In addition, growth in this population and the sexual development of children between age ≥ 10 to <18 will be assessed.
Research question and objectives	This observational study will evaluate the long term safety of deferasirox therapy in pediatric patients ≥ 10 to <18 years with NTDT in actual practice setting. The primary objective of this study is to characterize the long term safety profile of deferasirox in pediatric patients with NTDT with exposure up to 5 years.
Study design	The registry is observational and does not impose a therapy protocol, diagnostic/therapeutic interventions or a strict visit schedule. Patients will be treated with deferasirox in accordance with the local (country-specific) deferasirox prescribing information. Pediatric patients aged ≥ 10 to <18 years at enrollment with non-transfusion dependent thalassemia and treated with deferasirox will be followed for up to 5 years from the start of deferasirox treatment. Retrospective data collection will be conducted for patients who have started deferasirox 12 months or less prior to enrollment. The baseline is defined as the timeframe before the patient starts treatment with deferasirox. In patients who have protocol specified assessments performed prior to the date of first deferasirox treatment, the baseline data will be collected if it is within the following timeframe prior to the date of starting deferasirox treatment (see also table 7-2): • 1.5 months for all laboratory assessments

	• 6 months for vital signs, weight, height, LIC, ECG, ECHO, CMR, ocular and audiometry assessments • 12 months for pubertal assessments (Tanner stage). Post baseline data will be collected from the start date of deferasirox treatment and then on for up to five years.
Setting and study population	Pediatric patients aged ≥ 10 to <18 years at enrollment with non-transfusion dependent thalassemia treated with deferasirox. The study will enroll patients planned to be treated with deferasirox and patients who started deferasirox treatment 12 months or less prior to enrollment. Number of patients planned is a minimum of 40. At least 20 patients will be enrolled for the two age categories (10 to ≤12 and >12 to <18)
Variables	● serum creatinine, creatinine clearance, serum ferritin, urea, SGOT (AST), SGPT (ALT), alkaline phosphatase, bilirubin and proteinuria, ● LIC, CMR, echocardiography, ECG, vital signs, ● cardiac events potentially related to cardiac iron overload, ● height, weight ● sexual development according to Tanner stage (ages ≥10 and <18 years) ● audiometry and ophthalmology examination findings, ● transfusion requirements, ● concomitant medication at time of renal or hepatic AE, ● adverse event (AE)
Data sources	Primary data source / health care provider
Study size	A minimum of 40 patients will be enrolled in this study. At least 20 patients will be enrolled for the two age categories (10 to ≤12 and >12 to <18)
Data analysis	This is an observational study and statistical analyses will only be descriptive for all endpoints. Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, 25th-percentile, median, 75th percentile and maximum. Categorical variables will be summarized by absolute and relative frequencies.
Milestones	EMA Protocol version 01 submitted to PRAC: 25 Jul 2013 PRAC 1st response regarding protocol finalization: 11 Oct 2013 Registration in the EU PAS register: 30 Nov 2013 PRAC 2nd response regarding protocol finalization: 15 Jan 2014 PRAC 3rd response regarding protocol finalization: 3 Apr 2014 Protocol version 02 submitted to PRAC: 02 May 2014 PRAC 4th response regarding protocol finalization : 10 Jul 2014 PRAC 5th response regarding protocol finalization: 04 Dec 2014 PRAC 6th response regarding protocol finalization/PRAC approval of protocol version 02: 09 Jan 2015 Protocol version 3.0 submitted to PRAC: 21 Aug 2015 PRAC response regarding protocol version 3.0: 11 Nov 2015 Protocol version 3.1 submitted to PRAC: 03 Dec 2015 Protocol version 3.1 approved by the PRAC: 17 Mar 2016 FDA Draft E2422 protocol submitted to FDA: 08 Aug 2013 FDA comments received in the General Advice letter dated: 09 Oct 2013 Final protocol submitted to FDA with response to above FDA comments: 22 Nov 2013 Protocol submitted to FDA: 30 Aug 2013 FDA accepted the protocol submitted: 13 Mar 2014 Protocol amendment based on PRAC comments submitted to FDA: 10 Nov 2014

	Start of data collection: 13 Aug 2014 End of data collection: 30 Jul 2025 Interim report 1: 31 Dec 2014 Interim report 2: 31 Dec 2015 Interim report 3: 31 Dec 2016 Interim report 4: 31 Dec 2017 Interim report 5: 31 Dec 2018 Interim report 6: 31 Dec 2019 Interim report 7: 31 Dec 2020 Interim report 8: 31 Dec 2021 Interim report 9: 31 Dec 2022 Interim report 10: 31 Dec 2023 Interim report 11: 31 Dec 2024 Final report of study results: 30 Jan 2026

3 Amendments and updates

Table 3-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	28-Jan-2014		Amendment 1 final	in response to PRAC request
2	02-May-2014		Amendment 2 draft Update	In response to PRAC request
3	14-Oct-2014		Amendment 2 final Update	In response to PRAC request
4	06-Jul-2015		Amendment 3 final Update	To allow enrollment of patients prescribed film coated tablets and response to FDA request
5	01-Dec-2015		Amendment 3.1 final Update	In response to PRAC request that the MAH should remove all mentions of tradename “Jadenu” in the protocol.
6	10-Jun-2020		Amendment 4 final Update	To allow baseline data collection within specified timeframes and to address inconsistencies between different sections of the protocol. Also in response to PRAC request regarding the reporting of overchelation as adverse events.

Amendment 1

Amendment rationale

This amendment was undertaken in response to the request received from Pharmacovigilance Risk Assessment Committee (PRAC) in Jan 2014, prior to the start of the study.

Following sections in the protocol have been revised per the request from PRAC in EU:

- Objectives and Endpoints
- Setting
- Data sources
- Study size
- Data analysis
- Quality control
- Limitations of the research methods
- Adverse event reporting

In addition, the following sections have been revised to align with the Novartis internal requirements:

- Milestones
- Study design
- Variables

- Data management

Changes to the protocol

- Section 3: In Table 3-1, Trial statistician was updated to [redacted]
- Section 6: Table 6-1 was amended to include milestones namely, protocol submitted to PRAC, FDA response regarding protocol finalization and PRAC second response regarding protocol finalization.
- Section 8: Table 8-1, objective to evaluate renal and hepatic safety parameters over time was revised as follows: "Absolute/relative changes from baseline of SGPT (ALT), SGOT (AST), total bilirubin, alkaline phosphatase, serum creatinine, creatinine clearance quarterly up to 5 years" and "Proportion of patients having hepatic and renal clinical events that are considered to be related to study drug up to 5 years from the start of deferasirox"
- Section 8: Table 8-1, objective to evaluate sexual development by gender was revised as follows "Changes from baseline to the last on-study value of all Tanner stage parameters."
- Section 8: Table 8-1, Evaluate all other safety parameters was revised as follows "Significant findings of safety data (ECG, vital signs, audiometry and ophthalmology examinations) will be documented as adverse events."
- Section 9.1 addition of the following text: "It is recommended that serum creatinine be assessed in duplicate before initiating therapy. Serum creatinine, creatinine clearance (estimated with the Cockcroft-Gault or MDRD formula in adults and with the Schwartz formula in children) should be monitored weekly in the first month after initiation or modification of therapy with deferasirox and monthly thereafter.
  It is recommended that serum transaminases, bilirubin and alkaline phosphatase be checked before the initiation of treatment, every 2 weeks during the first month and monthly thereafter."
- Section 9.1 Deletion of the "countries able to conduct the study" from feasibility assessment
- Section 9.2 Addition of the following text : "**Physician Selection:** This study will be carried out with specialist hematologists, internists, pediatricians or physicians working at specialized thalassemia centers, with a pediatric NTDT patient population and an interest in participating in such an observational study. These physicians were identified after detailed site selection visits at thalassemia centers located in countries with high prevalence of thalassemia. All sites have previously participated in thalassemia clinical research programs and have sufficient experience in treatment of these patients.
  Prior to study site selection, Novartis representatives reviewed the protocol with potential physicians at the center and an informed decision was taken by the physician whether or not to participate.
  It is anticipated that the physicians are following the treatment recommendations and local deferasirox prescribing information for patient assessment, which will be used as source data for the study as outlined in the suggested schedule of assessment in Section 9.3. This study does not alter the physician-patient relationship or the care or follow-up of the patients. The physicians remain free to choose their prescriptions and methods of follow-up."

- Section 9.2 Addition of the following text : "Population : Each physician participating in the study will approach all the eligible NTDT patients for the study who meet the criteria for inclusion and non-inclusion, and for whom they envision to be able to follow-up for a period of 5 years as needed for the study. In addition, patient database at the site will be reviewed to identify patients who may potentially qualify for the study. Furthermore, the source of patient recruitment could be referral from other practices, friends/family member referral, via advocacy groups, etc."
- Section 9.2: the Word "AND" has been added between all the Inclusion criteria.
- Section 9.3: A statement namely: "The key eligibility criteria will be checked via IWR" is added in the section on IWR (interactive web response system)
- Section 9.3: Table 9-1 is updated to Bilirubin, Proteinuria determination (urinalysis dipstick, urinary protein/urinary creatinine), End of Study/Study completion
- Section 9.4: A statement namely: "Every effort will be made to ensure all this available data in the patients' chart are captured in the eCRF" was added in the section for data collection schedule.
- Section 9.5: Addition of the following text: "Protocols for observational studies (or registry studies) to assess the natural history of a disease or to evaluate the safety of an established product (investigational drug) may not include formal sample size calculations. Data on global epidemiology of NTDT are scarce, see Section 9.2. Also the prevalence of NTDT patients with clinically significant iron overload constitutes a very small percentage of total number of NTDT patients.
  Given the small prevalence of the disease under consideration, data on the 40 patients would provide relevant data as described by the computation of probabilities to detect adverse events as shown below."
- Section 9.6 Data entry frequency was updated to "routinely".
- Section 9.7.4.2 one additional statement was added "In case of high number of SAEs, the number of SAEs adjusted by time of exposure (events per year or events per month) will also be tabulated."
- Section 9.7.4.3 was added Handling of missing values/censoring/discontinuations: "Missing values are not planned to be imputed. Missing day information for start date prior to chelation therapy or start date of history of blood transfusions will be imputed by the 15th of the month. If the month is missing it will be imputed by July."
- Section 9.7.4.3.1: Section on "Supportive analyses" was added "However, in case of a high number of missing values, sensitivity analyses using Complete Case Analysis approach will be performed. A Complete Case Analysis excludes cases with missing laboratory values (for main hepatic and renal parameters) so that only complete cases are available. The estimates obtained from the complete case analysis shall be compared with the overall data set to view the effect of missing values on the estimates."
- Section 9.7.5.2 Addition of the following text: "Proportion of patients having adverse events related to hepatic and renal functions that are considered to be related to study drug over the period up to 5 years from the start of deferasirox treatment will be calculated. For each laboratory parameters directly related to hepatic parameters: ALT, AST, total bilirubin, alkaline phosphatase and directly related to renal parameters: creatinine,

creatinine clearance; observed values (and changes from baseline) averaged at baseline, after first intake of study medication to day 30, day 31 to day 90 and per subsequent quarter will be summarized by descriptive statistics (n, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum).
In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots will be specified in the Report and Analysis Plan (RAP)."

- Section 9.7.5.2: Addition of the following statement: "The number of adverse events adjusted by time of exposure (events per year or events per month) will also be tabulated."
- Section 9.7.6.3 Addition of the following text and Table 9-2: "Similar to adverse events, the number of events related to lab abnormalities adjusted by time of exposure (events per year or events per month) will be tabulated."

Table 9-2 Criteria for clinically notable and extended laboratory ranges

Parameter	Criteria
ALT/AST	>5×ULN and >2×baseline value (extended range >10×ULN and >2×baseline value)
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)

- Section 9.8 was updated to include "field monitor" and "Novartis representative and designee."
- Section 9.8 addition of the following statement: "Retrospectively collected data in the medical charts will be reviewed for completeness and source document verified, by the field monitor and captured as per the monitoring plan."
- Section 9.9 was updated to add "small sample size" as a limitation of the research methods.
- Section 11: Following statement was added: "All adverse event reported by the patients will be recorded in the case report form."
- Throughout the protocol the term "Exjade" was changed to "deferasirox".

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Amendment 2 Update

Amendment rationale

This amendment will be undertaken in response to the requests received from Pharmacovigilance Risk Assessment Committee (PRAC) in the correspondence dated 3rd April 2014 and 10th July 2014

Following sections in the protocol have been revised per the request from PRAC in EU:

- Abstract
  - Milestones

- Setting
  - Physicians Selection
  - Population
  - Inclusion criteria
- Milestones
  - Annual 'Safety' reports have been changed to state 'Interim' reports

Changes to the protocol

Abstract – Annual 'Safety' reports have been changed to state 'Interim' reports.

Section 9.2, Setting - Physician Selection: The paragraph "It is anticipated that the physicians are following the treatment recommendations and local deferasirox prescribing information for patient assessment, which will be used as source data for the study as outlined in the suggested schedule of assessment in Section 9.3. This study does not alter the physician-patient relationship or the care or follow-up of the patients. The physicians remain free to choose their prescriptions and methods of follow-up" has been deleted.

Section 9.2, Setting – Population: The paragraph "Each physician participating in the study will approach all the eligible NTDT patients for the study who meet the criteria for inclusion and non-inclusion, and for whom they envision to be able to follow-up for a period of 5 years as needed for the study. In addition, patient database at the site will be reviewed to identify patients who may potentially qualify for the study" has been revised to "Each physician participating in the study will approach all the eligible NTDT patients for the study who meet the criteria for inclusion and non-inclusion. In addition, patient database at the site will be reviewed to identify patients who may potentially qualify for the study".

Section 9.2, Inclusion/Exclusion: The text, "treated (max 12 months)", has been deleted from Inclusion Criteria 1, the new text will be: "Male or female aged ≥ 10 but <18 years old with non-transfusion-dependent thalassemia syndromes inclusive of beta-thalassemia intermedia, HbE beta-thalassemia or alpha thalassemia intermedia (HbH disease) and chronic iron overload."

Amendment 3 Update

Amendment rationale

This Amendment was undertaken as a result of the development of a deferasirox film-coated tablet for oral administration and to allow the inclusion of patients who will be prescribed the film-coated tablet formulation. In addition, strength and dosing of the new formulation will be explained as well as the inclusion of text related to comments received from a Health Authority concerning the growth and development analyses and an update of the non-Serious AE text.

Changes to the protocol

Page 2: Change in authors

Section 2: Update list of abbreviations

Table 3-1: Change in the name of the Trial Lead Physician and changes in authors

Section 4: Update of abstract.

Table 5-1: Addition of amendment 3

Table 6-1: Update of Table

Section 7: Addition of Film Coated Tablet information:

Because of the chronic nature of chelation therapy and the importance of patient compliance, an improved deferasirox formulation for oral administration has been developed. The film coated tablet (FCT) to be used in this study contains the same active substance but has been strength-adjusted to achieve comparable exposure to the currently approved dispersible tablet.

Patients enrolled into this study will be permitted to use deferasirox dispersible tablets or the new film coated tablets. Patients will be allowed to change formulation under the advice and guidance of the Investigator.

Section 9.1 Addition of the following text: Deferasirox Dispersible tablets

Deferasirox dispersible tablet (DT) is currently marketed in three dosing strengths (125, 250, 500 mg) and is dosed based on body weight. The currently approved dose range is up to 40 mg/kg/day.

Deferasirox dispersible tablets prescribed by physicians in actual practice setting will be used in accordance with the local label.

Because of the chronic nature of chelation therapy and the importance of patient compliance, an improved deferasirox formulation for oral administration has been developed.

Deferasirox Film Coated Tablets (FCTs)

If approved in the country, the FCT may be used in this study. It contains the same active substance but has been strength-adjusted to achieve comparable exposure to the currently approved dispersible tablet. The FCT is available in three dose strengths (90 mg, 180 mg, and 360 mg) and is dosed based on body weight. The FCTs can be taken with or after a light meal.

Initial FCT is 14 mg.kg/d, 7d/wk. according to FCT prescribing information. Dose adjustments will be based on serum ferritin levels and the investigator's judgment. Dose adjustments based on safety are allowed at any time point in the study and will be in increments of 3.5-7 mg/kg/day. Throughout the study, the maximum dose of deferasirox, will be 28 mg/kg/day.

Table 7-1 Dose conversion between dispersible tablets and film coated tablets

Deferasirox dispersible tablets	Deferasirox film-coated tablets
Dose range: 10-40mg/kg; calculated and rounded to the nearest whole tablet size.	Dose range: 7-28mg/kg; calculated and rounded to the nearest whole tablet size.
Dose adjustment: increments of 5-10mg/kg	Dose adjustment: increments of 3.5-7mg/kg
Deferasirox DT therapeutic dose range: 10mg/kg 20mg/kg 30mg/kg 40mg/kg (max. recommended dose)	Deferasirox FCT therapeutic dose range: 7mg/kg 14mg/kg 21mg/kg 28mg/kg (max. recommended dose)
Calculated dose example for 50kg patient receiving deferasirox DT 30mg/kg: 30mg/kg * 50kg = 1500mg/day Three (3) 500mg tablets	Calculated dose example for 50kg patient receiving deferasirox FCT 21mg/kg: 21mg/kg * 50kg = 1050mg/day Three (3) 360mg tablets

Deferasirox Administration

The investigational study drug used in this trial is deferasirox (ICL670). It will be provided as dispersible tablets for oral use or as film coated tablets for oral use.

Deferasirox (company research code: ICL670) is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Two molecules of deferasirox form a complete complex with Fe^{3+}.

The high potency of deferasirox in mobilizing tissue iron and promoting iron excretion was demonstrated both in vitro and in vivo model systems (Nick 2003). Deferasirox is eliminated from the body by hepatic glucuronidation and biliary excretion.

Deferasirox was first approved for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adults and pediatric patients aged 2 years and older in the United States in November 2005 and is currently approved for this indication in more than 100 countries, including the European Union, Switzerland and Japan. Deferasirox has also been approved in more than 60 countries for the treatment of chronic iron overload in patients with non-transfusion dependent thalassemia aged 10 years and older.

Dispersible Tablets (DT)

Deferasirox is formulated as a dispersible tablet for oral suspension which facilitates administration of the appropriate quantity of drug substance to both pediatric and adult patients. The dispersible tablet is supplied as 125 mg, 250 mg and 500 mg tablets. Bioavailability studies indicate that absorption is highly variable when deferasirox is taken together with food. Therefore, it is recommended that deferasirox is taken on an empty stomach, at least 30 minutes prior to food intake preferably at the same time every day. The tablets are dispersed by stirring in a glass of water or apple or orange juice (100 to 200 mL) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be re-suspended in a small volume

of water or juice and swallowed. The tablets must not be chewed or swallowed whole. Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.

Film coated tablets (FCT)

Patients will swallow the required number of deferasirox FCT every day (not later than 12:00 PM) with or after a light meal.

It is recommended that the doses be timed such that they occur at almost the same time each day. For example, if the patient took the study medication at 10:00 AM on first day of treatment, the subsequent dose would also be taken at approximately 10:00 AM on the next day, and so on. However, all patients should take their deferasirox dose before 12:00 PM (noon). FCT should be swallowed whole with some water on an empty stomach or after a light meal. For patients who are unable to swallow whole tablets, FCT may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple). The dose should be immediately and completely consumed and not stored for future use.

Section 9.7.5: Addition of the following text;

Summary statistics of the height, weight and BMI standard deviation scores (SDS) for baseline, end of each year as well as end of study and change from baseline by gender and age category at baseline (10 - < 12, 12 - < 16, 16 - < 18) will be provided.

In addition, mean change from baseline for weight, height and BMI will be plotted by age category at the time of assessment for E2422, and the same analysis will be done for study ICL670A107E for the same age category patients as E2422. ICL670A107E is a registry study with the historical data from the four-year follow-up of the premarket clinical trial for children with β-thalassemia who are on a regular transfusion program.

Number and percentages of patients who are below, within and above the Marshal standards (Marshall and Tanner 1970) (mean age ± 2 SD) for each Tanner stages by gender will be provided.

The age of patients at time they reach the next Tanner stage will be flagged based on the Marshal standards and the listing will be provided.

Number and percentage of patients at different Tanner stages will be provided by gender and baseline age category (10 - < 12, 12 - < 16, 16 - < 18) at baseline, at the end of each year and at end of study.

Section 10 Adverse Event reporting: Amendments were made as follows:

All AEs, including SAEs occurring in association with exposure to the Novartis drug of interest, also have to be recorded in the Novartis safety database.

Adverse Drug Reactions (ADRs) occurring in association with exposure to Novartis drug other than the Novartis drug of interest, can be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or Novartis DS&E as a spontaneous report.

The following text was deleted " another Novartis drug, if applicable, also have to be notified for recording in the Novartis safety database."

The following text was added on page 47: Information on non-serious AEs is then transferred from the study database to Novartis DS&E by Novartis data management group/Quintiles on a periodic basis but not less frequently than once a month.

Section 13 References: The following references were added:

Marshall WA and Tanner JM. (1970). Variations in the pattern of pubertal changes in Boys. Archives of Disease in Childhood; 45: 13-23

Marshall WA and Tanner JM. (1969). Variations in the pattern of pubertal changes in Girls. Archives of Disease in Childhood; 44: 291-303

Amendment 3.1 Update

This summary of protocol amendment 3.1 update has been provided in protocol amendment 4.0 because it was missed in protocol amendment 3.1.

Amendment rationale

Request from EMA that MAH removes all tradename "Jadenu" in the protocol.

Changes to the protocol

- Page 2, Author: [redacted] was deleted and replaced with [redacted] in the author list.
- List of abbreviations: DT Dispersible Tablet was added to the list of abbreviations.
- Table 1.1 Responsible parties: [redacted] was deleted and replaced by [redacted].
- Throughout the protocol, Exjade was deleted and replaced with Deferasirox DT and Jadenu was deleted and replaced with Deferasirox FCT.

Amendment 4 Update

Amendment rationale

Amendment 4 was undertaken to implement the following:

- A timeframe around the baseline data collection.
- To clarify what will be considered as post-baseline safety assessment for inclusion in the safety set.
- To clarify the stopping rules in the context of a non-interventional study.
- To clarify the recommendation of monthly monitoring of serum ferritin to avoid overchelation, and to report as adverse events when it occurs.
- An editorial update of sensitivity analyses to supplementary analyses and clarify when the analysis will be performed.
- To modify the lower age group and the subgroup categories for sexual and growth analysis.

There has also been additional modifications as per the new protocol template.

The rationale of these modifications is detailed below.

- Addition of timeframe: The current version of the protocol defines baseline as "the point in time when the patient starts treatment with deferasirox (Section 7.1)". In addition, protocol

states that "data will be collected from the start of deferasirox treatment (baseline) and then on for up to five years (Sections 7.1, 7.3, 7.7)". Of note, there is no guidance in the protocol on timeframe prior to start date of deferasirox treatment during which baseline data may be collected. The current wording of the protocol has created confusion and inconsistencies in the way baseline data is collected. Investigators have applied their own interpretation on baseline data definition and have been reporting what is requested by the protocol as baseline, including data on or prior to the start date of deferasirox. The protocol is amended to correct this deficiency to allow a consistent approach, and to implement a timeframe around the baseline assessment data collection.

- Clarification has been provided on what will be considered as post-baseline safety assessment for inclusion in the safety set.
- Stopping rule: The protocol currently mandates stopping rules for deferasirox treatment based on serum ferritin levels, which in the context of a non-interventional study seems inappropriate since these cannot be enforced. In the study, patients are treated based on investigator judgement following local practices. The stopping rules remain in the protocol as a recommendation to investigators.
- In order to correct inconsistencies in the protocol regarding age categories and to align with the age group population defined in the study section 7.2, the analyses for growth and sexual development by age categories were reduced from 3 categories (10 -<12, 12-< 16, 16-<18 as in current protocol) to two categories (10-<=12, >12-<18). This modification is implemented considering that relatively small number of patient in the study, having three age subgroups will lead to small number of patients in each age category and to imprecise results. Furthermore, the 10-<=12 category (approximately half of the patients enrolled) represents an adequate group to assess the impact that deferasirox may have on growth and development.
- Table 3.1: Study protocol amendment and updates have been updated to include reasons for changes in protocol amendment 3.1 and 4.0.
- Table 7-2: Body Mass Index (BMI) was removed as it was never collected in CRF separately, but is calculated based on weight and height collected.
- Section 7.7.5.2.1: "Sensitivity analyses" has been changed to "Supplementary analyses" to align with ICH E9 addendum guidance and add clarification when this analysis will be conducted.
- Section 7.8: has been update with new protocol template text.
- Section 8: Informed consent procedure has been updated with new protocol template text.
- Section 10: Plans for disseminating and communicating study results have been updated with new protocol template text.
- Clear guidelines on how baseline data should be collected are provided.

Changes to the protocol

- Page 2: List of participating countries has been updated.
- Page 2: List of authors has been updated.
- Page 3: Marketing Authorization Holder contact person has been updated.
- Section 1: Table 1-1, Responsible parties have been updated.

- Section 2: Abstract, all changes described below in the protocol have been implemented in the abstract.
- Section 3: Table 3-1, "Study protocol amendments and updates" has been updated, by adding the missed information on amendment 3.1 and the new information regarding the present amendment 4.
- Section 3: Rational for and changes in protocol amendment 3.1 has been provided.
- Section 4: Table 4-1, Updated.
- Section 6: Table 6-1, Stopping rule has been updated as follows:

  In general, it is recommended that treatment should be stopped once a satisfactory body iron level has been achieved (LIC < 3 mg Fe/g dw or serum ferritin < 300 ng/mL). In the context of this non-interventional trial where no therapy protocol is imposed and patients are treated based on investigator judgment following local practice, investigators are advised to follow the stopping rules described above.
- Section 7.1: From the statement Retrospective data collection will be done for patients who have started deferasirox 12 months or less prior to enrollment "i.e. data will be collected from the start of deferasirox treatment (baseline) and then on for five years" was deleted and guidance on data collection is provided as below:

  The baseline is defined as the timeframe before the patient starts treatment with deferasirox.

  In patients who have protocol specified assessments performed prior to the date of first deferasirox treatment, the baseline data will be collected if it is within the following timeframe prior to the date of starting deferasirox treatment (see also table 7-2):
  - 1.5 months for all laboratory assessments
  - 6 months for vital signs, weight, height, LIC, ECG, ECHO, CMR, ocular and audiometry assessments
  - 12 months for pubertal assessments (Tanner stage).

  Post baseline data will be collected from the start date of deferasirox and then on for five years.
- Section 7.1: Film coated tablet: The paragraph on stopping rule has been updated as follows:

  In general, it is recommended that treatment should be stopped once a satisfactory body iron level has been achieved (LIC < 3 mg Fe/g dw or serum ferritin < 300 ng/mL). In the context of this non-interventional trial where no therapy protocol is imposed and patients are treated based on investigator judgment following local practice, investigators are advised to follow the stopping rules described above.
- Section 7.1: added "It is recommended that serum ferritin be monitored monthly in order to assess the patient's response to therapy and to avoid overchelation".
- Section 7.1: Feasibility Assessment has been updated with the final number of countries in which feasibility was conducted. Additionally, the statement that "This assessment was based on the assumption that the country would have Health Authority approval by 01 December 2015 (the date of last patient first visit)" was deleted as it is no longer relevant.

- Table 7-2: BMI was removed as it was never collected but calculated based on weight and height. Table 7-2 has also been updated with timeframe for baseline data collection. Additionally, assessments that are considered a safety assessment are specified.
- Section 7.3: Study flow and visit schedule has been updated as below.

  From the statement Retrospective data collection will be done for patients whom have started deferasirox 12 months or less prior to enrollment, "i.e. data will be collected from the start of deferasirox treatment (baseline) and then on for five years" has been removed and guidance on data collection has been provided as follows:

  The baseline is defined as the timeframe before the patient starts treatment with deferasirox.

  In patients who have protocol specified assessments performed prior to the date of first deferasirox treatment, the baseline data will be collected if it is within the following timeframe prior to the date of starting deferasirox treatment (see also table 7-2):
  - 1.5 months for all laboratory assessments
  - 6 months for vital signs, weight, height, LIC ECG, ECHO, CMR, ocular and audiometry assessments
  - 12 months for pubertal assessments (Tanner stage).

  Post baseline data will be collected from the start date of deferasirox and then on for five years.
- Section 7.6: Approvers for any change to a final locked database has been updated.
- Section 7.7: Data analysis: From the statement Retrospective data collection will be done for patients whom have started deferasirox 12 months or less prior to enrollment, "i.e. data will be collected from the start of deferasirox treatment (baseline) and then on for five years" has been removed and guidance on data collection has been provided as follows:

  The baseline is defined as the timeframe before the patient starts treatment with deferasirox.

  Post baseline data will be collected from the start date of deferasirox and then on for five years.
- Section 7.7.1.2 Clarification added to the safety set definition by providing the criteria to determine post-baseline safety assessments for the different safety data domains.
- Section 7.7.4.3 Revised handling of missing values to be imputed will be described in the SAP. Supportive analyses moved to Section 7.7.5.2.1.
- Section 7.7.5.2.1: Supportive analysis: "Sensitivity analyses" has been changed to "Supplementary analyses" to align with ICH E9 addendum guidance.
- Section 7.7.5.3: The age categories have been updated to 10-<=12, >12-<18; (12 - < 16 and 16 - < 18 removed).
- Section 7.7.5.4: The age categories have been updated to 10-<=12, >12-<18; (12 - < 16 and 16 - < 18 removed).
- Section 7.7.6.1: Clarified definition of pre-treatment period for patients who started study medication 12 months or less prior to enrollment.

- Section 8: Informed consent procedure has been updated per new protocol template by adding as statement that "The physician must keep the original informed consent form signed by the patient (a signed copy is given to the patient)".
- Section 9: Adverse event reporting. Added: "Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy and to avoid overchelation. If serum ferritin falls below 300 ng/mL treatment with deferasirox should be stopped. Patients should be closely monitored for clinical or laboratory events potentially related to overchelation and report those as an adverse event", and removed "Serum ferritin reaching levels below 500 ng/mL and indicating that the patient has reached therapeutic goal should not be reported as an Adverse Event".
- Editorial changes have been made throughout the protocol.

IRB/IEC/HA

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

4 Milestones

Table 4-1 Planned dates of study milestones

Milestone	Planned (P) / Actual (A) date
Protocol submitted to PRAC	25 Jul 2013 (A)
Protocol submitted to FDA	30 Aug 2013 (A)
FDA response regarding protocol finalization	9 Oct 2013 (A)
PRAC response regarding protocol finalization	11 Oct 2013 (A)
Registration in the EU PAS register	30 Nov 2013 (A)
PRAC 2nd response regarding protocol finalization	15 Jan 2014 (A)
PRAC 3rd response regarding protocol finalization	3 Apr 2014 (A)
PRAC 4th response regarding protocol finalization	10 Jul 2014 (A)
Start of data collection	13 Aug 2014 (A)
End of data collection	30 Jul 2025(P)
Interim report 1	31 Dec 2014 (A)
Interim report 2	31 Dec 2015 (A)
Interim report 3	31 Dec 2016 (A)
Interim report 4	31 Dec 2017 (A)
Interim report 5	31 Dec 2018 (A)
Interim report 6	31 Dec 2019 (A)
Interim report 7	31 Dec 2020 (P)
Interim report 8	31 Dec 2021 (P)
Interim report 9	31 Dec 2022 (P)
Interim report 10	31 Dec 2023 (P)
Interim report 11	31 Dec 2024 (P)
Final report of study results	30 Jan 2026 (P)

5 Rationale and background

Non-transfusion-dependent thalassemia (NTDT) is a broad spectrum of different forms of thalassemia which include β-thalassemia intermedia, hemoglobin E (HbE) β-thalassemia, and hemoglobin H (HbH) disease α-thalassemia. Generally, patients with NTDT do not require regular RBC transfusions for survival, but may require occasional transfusions due to infection or pregnancy or may require more regular transfusions later in life due to splenomegaly or other complications (Weatherall D, Blood Reviews 2012).

Beta-thalassemia is prevalent in Mediterranean countries, the Middle East, Central Asia, India, Southern China, the Far East as well as countries along the north coast of Africa and in South America. The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world and 1 in 10,000 people in the European Union (Galanello R and Origa R, Orphanet Journal of Rare Diseases 2010).

Hemoglobin H disease is commonly seen in Southeast Asia and it occurs sporadically in most other tropical regions. The frequency of α-thalassemia reaches 25% in regions of Southeast Asia and Hb H, Hb H–CS (Constant Spring), and homozygous α-thalassemia affect at least a million people worldwide (Weatherall D and Clegg J, Bull World Health Organ 2001). Due to immigration patterns, patients with alpha and beta thalassemia may be found in many countries outside of the endemic regions.

Thalassemia intermedia encompasses a wide clinical spectrum and it arises from defective gene function leading to the partial suppression of beta-globin protein production. Mildly affected patients are completely asymptomatic until adult life, experiencing only mild anemia and maintaining hemoglobin levels between 7 and 10 g/dl. These patients require only occasional blood transfusions, if any. Patients with more severe thalassemia intermedia generally present between the ages of 2 and 6 years, and although they are able to survive without regular transfusion therapy, growth and development can be retarded (Taher A, et. al., Blood Cells, Molecules, and Diseases 2006).

HbE beta (β)-thalassemia is a common form of β-thalassemia that exhibits a heterogeneous clinical presentation and variable clinical course. It results from co-inheritance of β-thalassemia and the structural variant HbE G→A substitution in codon #26 of the β-globin gene (Olivieri N, Blood Reviews 2012). About half of the patients have thalassemia intermedia, and many patients can have the thalassemia major phenotype (Fucharoen S and Winichagoon P, Current Opinion in Hematology 2000). Iron overload in non-transfused patients is common, secondary to increased gastrointestinal absorption of iron (Pakbaz Z, et. al., Pediatr Blood Cancer 2007)

Hemoglobin H (HbH) disease is the most severe non-fatal form of α-thalassemia syndrome, caused by molecular defects of the α-globin genes in which α-globin expression is decreased. The majority of patients with HbH have compensated hemolytic anemia with average hemoglobin levels of more than 9 g/dL. In general, patients with HbH rarely require blood transfusion (outside of hemolytic episodes activated by high fever or acute infections) (Fucharoen S and Viprakasit V, ASH Hematology 2009).

Ineffective erythropoiesis, due to excess production of either free alpha (α)-globin chains or beta (β)–globin chains, is the hallmark of both beta- and alpha-thalassemias. The combination of ineffective erythropoiesis, anemia, and hypoxia, leads to a compensatory increase in serum

levels of erythropoietin (EPO), as well as a decrease in serum levels of hepcidin, which promotes an increase in intestinal iron absorption and an increased release of recycled iron from the reticuloendothelial system (Rivella S, Blood Reviews 2012). This in turn results in depletion of macrophage iron, relatively lower levels of serum ferritin, and increased liver iron concentration (Origa R, et. al., Haematologica 2007) with subsequent release into the circulation of labile plasma iron and non-transferrin-bound iron which can cause target-organ damage (Taher A, et. al., Br J Haematol 2009). In addition to iron overload due to increased interstitial iron absorption, these patients may also accumulate iron from occasional or more frequent transfusions (Musallam K, et. al., Blood Reviews 2012).

The clinical consequences of iron overload in patients with NTDT are multifactorial and include hypothyroidism and hypogonadism, osteoporosis, thromboembolism and pulmonary hypertension (Taher A, et. al., Br J Haematol 2010). A recent study by Musallam and colleagues demonstrated that in patients with NTDT, an increase of 1 mg Fe/g dry weight liver iron concentration (LIC) was independently and significantly associated with higher odds of the aforementioned complications (Musallam K, et. al., Haematologica 2011). Iron accumulation in NTDT patients primarily occurs in hepatocytes, resulting in the risk of developing liver fibrosis, cirrhosis and potentially hepatocellular carcinoma (Restivo G, et. al., Br J Haematol 2010; Borgna-Pignatti C et. al., Br J Haematol 2004; Taher A, et. al., Br J Haematol 2009). In addition, the risk of some complications increases with age (Taher A, et. al., Br J Haematol 2010).

Growth retardation and pubertal delay are common complications in patients with thalassemia intermedia. Giardina and colleagues reported that 21% of thalassemia intermedia patients in their retrospective study had abnormal linear growth and 49% had a pubertal delay (Giardina, et. al., The Genetic Resource: Special issue, 1997). In addition, a short stature was found in 51%, failure of puberty in 2% and secondary amenorrhea in 6.4% of the thalassemia patients without transfusions (Karamifar H, et. al., Int J of Biomed Science 2006).

An analysis from clinical data on 378 patients with hemoglobin E β-thalassemia showed that 75% of patients had growth retardation and some patients presented with delay in sexual development (Fucharoen S, et. al., Current Opinion in Hematology 2000). The mechanism of short-stature in these patients seems to be complex and has been attributed to growth hormone (GH) deficiency, hypothyroidism, diabetes mellitus, zinc deficiency and low hemoglobin levels.

Iron load was also stated as the main contributor to hypothalamic-pituitary-gonadal (H-P-G) dysfunction and GH dysfunction in many patients with thalassemia (Borgna-Pignetti C, et. al., J. Pediatr 1985).

Serum ferritin (SF) has been traditionally used to assess transfusional iron overload with a well-established correlation to liver iron concentration (LIC), a more direct measurement of liver tissue iron. However, SF levels have recently been reported to underestimate LIC in patients with NTDT as compared to regularly transfused patients (Origa R, et. al., Haematologica 2007; Pakbaz Z, et. al., Pediatr Blood Cancer 2007; Taher A, et. al., Haematologica 2008). Magnetic resonance imaging (MRI) is a sensitive and specific tool for non-invasively assessing hepatic iron overload (Clark P and St. Pierre T, Magnetic Resonance Imaging 2000; St Pierre T and Clark P, et. al., Blood 2005).

NTDT patients whose LIC levels ≥5 mg Fe/g dry weight (or serum ferritin level >800 ng/mL) are at higher risk of developing iron-related morbidity (Musallam K, et. al., Blood Cells Mol Dis. 2013; Blood Reviews 2012). The use iron chelation therapy in NTDT has been documented in previous reports and small uncontrolled studies (Olivieri 1992; Rombos 2000; Pootrakul 2003; Taher et. al., Blood 2010) and recommended by Thalassemia International Federation (Guidelines for the Management of NTDT, 2013).

Out of three available chelators, deferasirox is the only drug that has been evaluated in a randomized clinical study in patients with NTDT (No CICL670E2209, the THALASSA study).

In this study, deferasirox compared with placebo, at starting doses of 5 and 10 mg/kg/day with dose escalations up to 20 mg/kg/day in patients with high levels of iron overload (LIC ≥5 mg Fe/g dw and SF >300 ng/mL) significantly reduced LIC and SF levels after one year of treatment. Based on the results of this study deferasirox has been recently approved by FDA and EU for the treatment of iron overload in this population (Taher A, et. al., Blood 2012).

In addition, the 1-year extension study of THALASSA showed that NTDT patients receiving deferasirox for up to 2 years continue to respond with decreases in LIC and serum ferritin. More patients reached LIC <5 and <3 mg Fe/g dw during the extension indicating that with appropriate dosing and treatment deferasirox continues to effectively remove iron (Taher A, et. al., poster 3258; ASH 2012).

Both adults and pediatric population (21 patients) under 18 years were included in the efficacy and safety analysis. Diarrhea, rash and nausea were the most frequent study drug-related AEs. Both diarrhea and rash were more frequent in the 10 mg/kg/day deferasirox, group than in the 5 mg/kg/day deferasirox group or the placebo groups, but no difference between groups was observed for nausea. There were no deaths, and the incidence of SAEs was comparable between treatment groups. Eight patients experienced AEs resulting in study discontinuation (Taher A, et. al., Blood 2012).

Renal function, assessed by measuring serum creatinine, creatinine clearance and Urinary Protein Creatinine Ratio (UPCR), was only mildly affected by deferasirox, which was reflected by a small number of patients developing abnormal values, that resolved spontaneously or after drug interruption. There were no progressive changes in mean serum creatinine, creatinine clearance, or UPCR.

Both ALT and AST parameters were decreased slightly over time in patients on deferasirox and these were more evident in the higher dose group. Shifts from below ULN at baseline to above ULN occurred in about a third of the patients with normal baseline values, and there were no relevant differences between deferasirox- and placebo-treated patients. No patients receiving deferasirox demonstrated an increase in ALT >5 x ULN and >2x baseline, although this did occur in one patient on placebo 10mg/kg/day.

The safety profile over 2 years of deferasirox treatment did not differ from that observed in the core 1-year study (Taher A, et. al., poster 3258; ASH 2012). Moreover, findings from sub-analysis of the THALASSA study confirm that the safety profile of deferasirox remains consistent as patients with NTDT approach the lower iron burden of LIC <3 mg Fe/g dw. The exposure-adjusted AE incidence in the patients not achieving LIC<3 did not differ from those reaching LIC<3. Increases in serum creatinine observed in three patients (>33% increase from

baseline and >ULN on two consecutive occasions) receiving deferasirox, treatment were reversible on dose interruption. These results suggest that the target of LIC <3 mg Fe/g dw may be reached with appropriate deferasirox treatment without increased risk of over chelation (Taher A, et. al., poster 391, EHA 2013).

Overall, the frequency and severity of AEs was comparable between treatment groups and deferasirox had a favorable safety profile with a low rate of discontinuation due to adverse events. These results are consistent with previous experience.

For pediatric patients, gastrointestinal (GI) disorders (nausea, abdominal discomfort) and skin and subcutaneous tissue disorders (rash) were the only AEs that were suspected to be related to deferasirox. Nausea occurred in two deferasirox-treated patients and one placebo-treated patient. Abdominal discomfort occurred in one placebo-treated patient. Rash occurred in three deferasirox-treated patients, and in one placebo-treated patient.

There were no AEs leading to discontinuation in pediatric patients. The number of severe AEs was comparable between all pediatric patients and adults treated with deferasirox.

Moreover, pediatric patients did not have any severe GI, cardiac disorders, eye disorders, hepatobiliary disorders, infections and infestations, metabolism and nutrition disorders, nervous system disorders, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders. Only two deferasirox-treated pediatric patients had a dose adjustment or interruption treatment due to an AE.

Renal function assessment showed that none of the deferasirox- or placebo-treated pediatric patients showed an >33% increase in serum creatinine above ULN on two consecutive occasions.

None of the deferasirox-treated pediatric patients had creatinine clearance values below 60 mL/min on two consecutive occasions and none of the deferasirox-treated pediatric patients had UPCR > 1mg/mg on 2 consecutive occasions.

Hepatic function assessment showed that only one deferasirox-treated pediatric patient had at least one episode of AST increased from normal to >ULN and ≤5xULN. Four placebo-treated pediatric patients had at least one episode of AST increased from normal to >ULN and ≤5xULN. Two deferasirox-treated pediatric patient had at least one episode of ALT increased from normal to >ULN and ≤5xULN. Four placebo-treated pediatric patients had at least one episode of ALT increased from normal to >ULN and ≤5xULN.

In summary, the study confirmed that AE and clinical laboratory evaluation for patients under 18 years of age was consistent with that of the adult study population and the safety analysis confirmed that deferasirox was safe and well tolerated and no new safety concerns emerged in this study.

The effect of deferasirox on growth and development was studied in the four-year extension of the phase III trial, Study CICL670A107, in pediatric patients with β-thalassemia major and transfusional iron overload (Cappellini MD, et. al., Blood 2011). Height, weight, growth, and pubertal stage (female breast development, male testes volume and pubic hair) were analyzed annually. The study results indicated that growth and sexual development were not impaired and progressed normally during long-term deferasirox treatment, thus suggesting that iron chelation with deferasirox abates the inhibitory effects of iron overload. However, this positive

effect of deferasirox has been not studied in NTDT pediatric patients and therefore it requires confirmation.

Because of the chronic nature of chelation therapy and the importance of patient compliance, an improved deferasirox formulation for oral administration has been developed. The film coated tablet (FCT) to be used in this study contains the same active substance but has been strength-adjusted to achieve comparable exposure to the currently approved dispersible tablet.

The purpose of this observational study is to provide further data, in addition to that obtained from the THALASSA trial, for the assessment of the safety of deferasirox in NTDT pediatric patients with documented iron overload as defined in a local product label. In addition, the assessment of growth in this patient population and sexual development of children between age ≥ 10 to <18 will be performed.

Patients enrolled into this study will be permitted to use deferasirox dispersible tablets or the new film coated tablets. Patients will be allowed to change formulation under the advice and guidance of the Investigator.

The study represents a key component of the active surveillance program for deferasirox. The monitoring of pediatric patient safety in actual practice settings will provide additional knowledge about the incidence and management of important ADRs.

A post-authorization safety study (PASS) is defined in Directive 2001/83/EC (DIR) Art 1(15) as any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

Non-interventional study (NIS)' in this context is used synonymously with 'observational study', i.e., does not involve any kind of intervention, experimental or otherwise. In these studies, interviews, questionnaires and blood samples may be performed as normal clinical practice.

6 Research question and objectives

This observational study will evaluate the long term safety of deferasirox therapy in pediatric patients ≥ 10 to <18 years at enrollment with NTDT in actual practice setting.

Table 6-1 Objectives and Endpoints

Objectives	Endpoints	Analysis
Primary		
Evaluate the long term safety of deferasirox	Proportion of patients having SAEs that are considered to be related to study drug up to 5 years from the start of deferasirox treatment	Section 7.7.4
Secondary		

Evaluate the incidence of serum creatinine and SGPT (ALT) increases in actual practice setting	The proportion of patients having (up to 5 years from the start of deferasirox treatment): Serum creatinine > 33 % above baseline and above the age adjusted ULN in at least two consecutive post-baseline measurements at least 7 days apart from each other. SGPT (ALT) above 5 x ULN in at least two consecutive post-baseline measurements at least 7 days apart from each other	Section 7.7.5.1
Evaluate renal and hepatic safety parameters over time	Absolute/relative changes from baseline of SGPT (ALT), SGOT (AST), total bilirubin, alkaline phosphatase, serum creatinine, creatinine clearance quarterly up to 5 years. Proportion of patients having hepatic and renal clinical events that are considered to be related to study drug up to 5 years from the start of deferasirox.	Section 7.7.5.2
Evaluate growth by gender	Absolute change in BMI, weight and height from baseline to EOS Proportion of patients falling behind in growth based on height, weight and BMI	Section 7.7.5.3
Evaluate sexual development by gender	Mean age at assessment for each Tanner stage Changes from baseline to the last on-study value of all Tanner stage parameters.	Section 7.7.5.4
Evaluate long term efficacy of deferasirox as measured by serum ferritin and LIC	Absolute/relative change in SF and LIC from baseline to EOS Proportion of patient achieving a SF <300 ng/mL Proportion of patients achieving LIC <3 mg Fe/g dw Proportion of patients reinitiating deferasirox after discontinuation due to a “stopping rule” *	Section 7.7.5.5
Evaluate all other safety parameters	Significant findings of safety data (ECG, vital signs, audiometry and ophthalmology examinations) will be documented as adverse events.	Section 7.7.6

*Stopping rule: In general, it is recommended that treatment should be stopped Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 ng/mL).

In the context of this non-interventional trial where no therapy protocol is imposed and patients are treated based on investigator judgment following local practice, investigators are advised to follow the stopping rules described above.

7 Research methods

7.1 Study design

This study is a registry of pediatric patients with non-transfusion dependent thalassemia conducted in response to a post-approval commitment to the US FDA for an observational study in this population in order to assess long-term exposure and safety of deferasirox. (PMR 1994-4: “Establish a registry of children (aged 10 to <18 years old at enrollment) with NTDT and treated with deferasirox for documented iron overload. Study CICL670E2422 will follow at least 40 children for up to 5 years to assess and analyze the long-term safety of treatment with deferasirox, including an assessment of growth, compared to children on a regular transfusion program receiving deferasirox (based on historical data)”).

This study is non-interventional and does not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. However, a minimum of quarterly visits are suggested. Patients

will be treated with deferasirox in accordance with the local (country-specific) deferasirox prescribing information.

The definition of non-interventional study is provided in Article 21 of Directive 2001/20/EC: "A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular strategy is not decided in advance by a study protocol but falls within the current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data". In this context it is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice (EMEA 2008).

The study will take place in actual practice setting and will monitor patients treated with deferasirox according to the local (country-specific) prescribing information. The study will be based on primary data collection directly from healthcare professionals.

The enrollment is defined as the patient's entry into the study; which is the point at which informed consent form is signed. Data will be collected on a minimum of 40 eligible pediatric patients who signed informed consent. These patients should be aged ≥ 10 to <18 years at enrollment, are diagnosed with non-transfusion dependent thalassemia and require to be treated with deferasirox or started deferasirox treatment 12 months or less prior to enrollment. These patients will be followed for up to 5 years from the start of deferasirox treatment. Retrospective data collection will be done for patients whom have started deferasirox 12 months or less prior to enrollment.

The baseline is defined as the timeframe before the patient starts treatment with deferasirox.

In patients who have protocol specified assessments performed prior to the date of first deferasirox treatment, the baseline data will be collected if it is within the following timeframe prior to the date of starting deferasirox treatment (see also table 7-2):

- 1.5 months for all laboratory assessments
- 6 months for vital signs, weight, height, LIC, ECG, ECHO, CMR, ocular and audiometry assessments
- 12 months for pubertal assessments (Tanner stage).

Post baseline data will be collected from the start date of deferasirox and then on for five years.

Investigational treatment

Deferasirox dispersible tablets

Deferasirox dispersible tablet is currently marketed in three dosing strengths (125, 250, 500 mg) and is dosed based on body weight. The currently approved dose range is up to 40 mg/kg/day.

Deferasirox dispersible tablets prescribed by physicians in actual practice setting will be used in accordance with the local label.

Initial deferasirox dose 10 mg/kg/d, 7 d/wk in accordance with the deferasirox prescribing information. Dose titration of deferasirox may be performed based on LIC levels as measured by magnetic resonance imaging (MRI) and/or SF levels and safety markers in steps of 5–10 mg/kg/d as defined by local label requirements.

Deferasirox Film Coated Tablets (FCTs)

Because of the chronic nature of chelation therapy and the importance of patient compliance, an improved deferasirox formulation for oral administration has been developed.

If approved in the country, FCT may be used in this study. It contains the same active substance but has been strength-adjusted to achieve comparable exposure to the currently approved dispersible tablet. FCT is available in three dose strengths (90 mg, 180 mg, and 360 mg) and is dosed based on body weight. The FCT can be taken with or after a light meal. Initial FCT dose is 14 mg.kg/d, 7d/wk according to FCT prescribing information. Dose adjustments will be based on serum ferritin levels and the investigator's judgement. Dose adjustments based on safety are allowed at any time point in the study and will be in increments of 3.5-7 mg/kg/day. Throughout the study, the maximum dose of FCT will be 28 mg/kg/day.

Table 7-1 Dose conversion between dispersible tablets and film coated tablets

Deferasirox dispersible tablets	Deferasirox film-coated tablets
Dose range: 10-40mg/kg; calculated and rounded to the nearest whole tablet size.	Dose range: 7-28mg/kg; calculated and rounded to the nearest whole tablet size.
Dose adjustment: increments of 5-10mg/kg	Dose adjustment: increments of 3.5-7mg/kg
Deferasirox DT therapeutic dose range: 10mg/kg 20mg/kg 30mg/kg 40mg/kg (max. recommended dose)	Deferasirox FCT therapeutic dose range: 7mg/kg 14mg/kg 21mg/kg 28mg/kg (max. recommended dose)
Calculated dose example for 50kg patient receiving deferasirox DT 30mg/kg: 30mg/kg * 50kg = 1500mg/day Three (3) 500mg tablets	Calculated dose example for 50kg patient receiving deferasirox FCT 21mg/kg: 21mg/kg * 50kg = 1050mg/day Three (3) 360mg tablets

Deferasirox Administration

The investigational study drug used in this trial is deferasirox (ICL670). It will be provided as dispersible tablets for oral use or as film coated tablets for oral use.

Deferasirox (company research code: ICL670) is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Two molecules of deferasirox form a complete complex with Fe^{3+}.

The high potency of deferasirox in mobilizing tissue iron and promoting iron excretion was demonstrated both in vitro and in vivo model systems (Nick 2003). Deferasirox is eliminated from the body by hepatic glucuronidation and biliary excretion.

Deferasirox was first approved for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adults and pediatric patients aged 2 years and older in the United States in November 2005 and is currently approved for this indication in more than 100 countries, including the European Union, Switzerland and Japan. Deferasirox has also been approved in more than 60 countries for the treatment of chronic iron overload in patients with non-transfusion dependent thalassemia aged 10 years and older.

Dispersible Tablets (DT)

Deferasirox is formulated as a dispersible tablet for oral suspension which facilitates administration of the appropriate quantity of drug substance to both pediatric and adult patients. The dispersible tablet is supplied as 125 mg, 250 mg and 500 mg tablets. Bioavailability studies indicate that absorption is highly variable when deferasirox is taken together with food. Therefore, it is recommended that deferasirox is taken on an empty stomach, at least 30 minutes prior to food intake preferably at the same time every day. The tablets are dispersed by stirring in a glass of water or apple or orange juice (100 to 200 mL) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be re-suspended in a small volume of water or juice and swallowed. The tablets must not be chewed or swallowed whole. Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.

Film coated tablets (FCT)

Patients will swallow the required number of deferasirox FCT every day (not later than 12:00 PM) with or after a light meal.

It is recommended that the doses be timed such that they occur at almost the same time each day. For example, if the patient took the study medication at 10:00 AM on first day of treatment, the subsequent dose would also be taken at approximately 10:00 AM on the next day, and so on. However, all patients should take their deferasirox dose before 12:00 PM (noon). FCT should be swallowed whole with some water on an empty stomach or after a light meal. For patients who are unable to swallow whole tablets, FCT may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple). The dose should be immediately and completely consumed and not stored for future use.

It is expected that the stopping rule for treatment discontinuation will be followed by physicians and reintroduction of deferasirox therapy will take place if the LIC and/or SF levels increase above the thresholds as per local label requirements. (Stopping rule: In general it is recommended that treatment should be stopped once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 ng/mL). In the context of this non-interventional trial where no therapy protocol is imposed and patients are treated based on

investigator judgment following local practice, investigators are advised to follow the stopping rules described above)

It is recommended that serum creatinine be assessed in duplicate before initiating therapy. Serum creatinine, creatinine clearance (estimated with the Cockcroft-Gault or MDRD formula in adults and with the Schwartz formula in children) should be monitored weekly in the first month after initiation or modification of therapy with deferasirox, and monthly thereafter.

It is recommended that serum transaminases, bilirubin and alkaline phosphatase be checked before the initiation of treatment, every 2 weeks during the first month and monthly thereafter.

It is recommended that serum ferritin be monitored monthly in order to assess the patient's response to therapy and to avoid overchelation.

Treatment

Since the study is non-interventional, deferasirox treatment duration is at the discretion of the physician. The maximum duration of deferasirox treatment observed will be 5 years.

Patient numbering and screening

Each patient is identified in the study by a subject ID with a maximum length of 9 digits, which is a combination of his/her site ID (the first 4 digits of the subject ID) and subject number (the last 5 digits of the subject ID) when the patient is first enrolled. The site ID is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned the subject ID by the physician. At each site, the first patient is assigned subject number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned the subject number 2, the third patient is assigned the subject number 3). Once assigned, the subject number must not be reused for any other subject and the subject number for that individual must not be changed, even if the patient is re-screened.

Definition of End of Study

The study will end when each of the patient enrolled in the study will have either withdrawn from the study or completed 5 years from the start of deferasirox treatment whichever occurs earlier.

Termination of Study

This study can be terminated at any time for any reason by Novartis.

The physician may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The physician will be responsible for informing IRBs and/or ECs of the early termination of the study.

Feasibility Assessment

The operational feasibility of study CICL670E2422 was conducted in 28 countries in Europe, North America, and Asia. This feasibility was conducted in order to assess the number of pediatric patients between the ages of 10 and 18 years with non-transfusion-dependent thalassemia syndromes, inclusive of beta-thalassemia intermedia, HbE beta-thalassemia or

alpha thalassemia intermedia (HbH disease) and chronic iron overload treated (max 12 months) or planned to be treated with deferasirox, who would be eligible to enter this observational registry study of a 5 years duration to assess deferasirox's effects on growth and development.

Countries were requested to consider if the study was aligned with their medical practices and any potential issues with inclusion / exclusion criteria.

7.2 Setting

Physician Selection:

This study will be carried out with specialist hematologists, internists, pediatricians or physicians working at specialized thalassemia centers, with a pediatric NTDT patient population and an interest in participating in such an observational study. These physicians were identified after detailed site selection visits at thalassemia centers located in countries with high prevalence of thalassemia. All sites have previously participated in thalassemia clinical research programs and have sufficient experience in treatment of these patients.

Prior to study site selection, Novartis representatives reviewed the protocol with potential physicians at the center and an informed decision was taken by the physician whether or not to participate.

Population:

A minimum of 40 patients who currently are (maximum of 12 months) or are planned to be treated with deferasirox, will be enrolled in this registry. At least 20 patients will be enrolled for the two age categories (10 to ≤12 and >12 to <18).

Each physician participating in the study will approach all the eligible NTDT patients for the study who meet the criteria for inclusion and non-inclusion. In addition, patient database at the site will be reviewed to identify patients who may potentially qualify for the study.

Furthermore, the source of patient recruitment could be referral from other practices, friends/family member referral, via advocacy groups, etc.

A least 40 patients will be sufficient to evaluate the safety of deferasirox in the pediatric NTDT population. According to the Guidelines for the treatment of NTDT, data on the global epidemiology of the thalassemias, especially NTDT, are scarce. Some 23,000 children are born with transfusion-dependent β-thalassemia major each year, while a smaller ill-defined number have the NTDT form β-thalassemia intermedia. The prevalence of non-transfusion-dependent thalassemia patients with clinically significant iron overload is assumed to be 2 - 14% of the total number of transfusion-dependent thalassemia patients).

In NTDT, a combination of increased intestinal iron over-absorption and occasional transfusions results in an iron accumulation rate which is much slower than in patients with transfusion dependent thalassemias. As a result, patients with NTDT tend to present with some degree of iron overload later in their life compared to transfusion dependent patients. This fact limits the pool of patients who could potentially meet the eligibility criteria and be enrolled in to the study. Furthermore, the feasibility which was conducted in major thalassemia countries

confirmed the limited number of pediatric patients with NTDT who can be treated with deferasirox.

Patients will be enrolled if they meet the following criteria.

Inclusion criteria:

Patients eligible for inclusion in this study must meet all of the following criteria:

1. Male or female aged ≥ 10 but <18 years old with non-transfusion-dependent thalassemia syndromes inclusive of beta-thalassemia intermedia, HbE beta-thalassemia or alpha thalassemia intermedia (HbH disease) and chronic iron overload

   AND
2. Patients currently treated for a maximum of 12 months or patients planned to be treated with deferasirox

   AND
3. Written informed consent obtained prior to any screening procedures. The consent form will be signed by the patient's legal guardian.

Exclusion Criteria

1. Patients treated with deferasirox in an interventional clinical study.

7.3 Variables

Treatment

Treating the Patient

The study being non-interventional, the patient will be treated at the physician's discretion and according to the local country-specific deferasirox prescribing information.

The starting dose of deferasirox, subsequent dose adjustments and treatment interruption will be at the physician's discretion and according to the local country-specific prescribing information and will be recorded on the Dosage Administration Record eCRF together with the reasons for the dose changes and interruptions.

Drug Compliance

The compliance will be assessed by caregiver interviews. The caregiver will be asked how many doses, if any, of deferasirox treatment was missed in the last treatment period.

Drug Accountability

Not applicable since commercial drug is used.

IWR (Interactive Web Response System)

The physician or designated staff will contact the IWR and provide the requested identifying information for the patient to register them into the IWR. Once assigned, the Patient Number

must not be reused for any other patient and the Patient Number for that individual must not be changed, even if the patient is re-screened.

The key eligibility criteria will be checked via IWR.

If the patient fails to be enrolled in the trial for any reason, the reason will be entered into the Screening Log.

IWR must be notified within 2 days that the patient was not enrolled.

Visit schedule and assessments

Study flow and visit schedule

This study is non-interventional and does not impose a therapy protocol, diagnostic/therapeutic interventions or a strict visit schedule. The frequency of assessments will be according to the physician's judgment and in accordance with the local country- specific deferasirox prescribing information. If the data is available, it is suggested that the treating physician complete the appropriate eCRFs at a minimum of every 3 months. Below is the recommended assessment schedule.

Retrospective data collection will be done for patients whom have started deferasirox 12 months or less prior to enrollment.

The baseline is defined as the timeframe before the patient starts treatment with deferasirox.

In patients who have protocol specified assessments performed prior to the date of first deferasirox treatment, the baseline data will be collected if it is within the following timeframe prior to the date of starting deferasirox treatment (see also table 7-2):

- 1.5 months for all laboratory assessments
- 6 months for vital signs, weight, height, LIC ECG, ECHO, CMR, ocular and audiometry assessments
- 12 months for pubertal assessments (Tanner stage).

Post baseline data will be collected from the start date of deferasirox and then on for five years.

Table 7-2 Suggested Schedule of Assessments

	At Baseline / Enrollment	At each visit	Discontinuation / End of Study
Obtain Inform Consent	X		
Demographics	X		
IRW	X		
Inclusion / Exclusion Criteria	X		
Medical History	X*		
Previous Iron Chelation History	X*		
Transfusion / RBC History	X*		
Physical Exam[4]	X	X	X
Height[4]	X[1]	X	X
Weight[4]	X[1]	X	X
Vitals[4]	X	X	X

	At Baseline / Enrollment	**At each visit**	**Discontinuation / End of Study**
Sexual development assessment (Tanner stage) [4]	X[2]	X	X
ECG[4]	X[1]	X	X
ECHO[4]	X[1]	X	X
CMR[4]	X[1]	X	X
Ocular Exam[4]	X[1]	X	X
Audiometry[4]	X[1]	X	X
LIC	X	X	X
Laboratory Assessments:			
Hematology[4]	X[3]	X	X
Biochemistry[4]	X[3]	X	X
Hepatitis Viral[4]	X[3]	X	X
Serum Ferritin	X[3]	X	X
Serum Creatinine[4]	X[3]	X	X
ALT/AST[4]	X[3]	X	X
Bilirubin[4]	X[3]	X	X
Alkaline Phosphatase[4]	X[3]	X	X
Urea[4]	X[3]	X	X
Creatinine Clearance[4]	X[3]	X	X
Proteinuria determination (urinalysis dipstick, urinary protein/urinary creatinine) [4]	X[3]	X	X
Serum pregnancy test[4]	X[3]	X	X
Urinary pregnancy test[4]	X[3]	X	X
Transfusions	X*	X	X
Concomitant Medication	X*	X	X
Adverse Events	X	X	X
Dose administration Record (DT)	X	X	X
Dose administration Record (FCT)	X	X	X
End of Study/Study completion			X

*For patients already treated with deferasirox, transfusion, concomitant medications and concomitant diseases will be collected at enrollment.

[1]Baseline assessments will be collected if performed within 6 months prior to the start date of deferasirox treatment.

[2]Baseline pubertal assessment (Tanner stage) will be collected if performed up to 12 months prior to the start date of deferasirox treatment.

[3]Baseline assessments will be collected if performed within 1.5 months prior to the start date of deferasirox treatment.

[4]Assessments considered to be safety assessment.

Screening examination

Eligibility screening

The physician will review the patient medical file to assess whether he or she is eligible for participation in the surveillance study.

Information to be collected on screening failures

None.

Patient demographics and other baseline characteristics

The following baseline information will be collected where available within the timeframe provided in table 7-2:

- Date of birth, gender, race, and ethnicity
- Medical history and disease characteristics
- History of previous iron chelation
- History of transfusion in the 12 months prior to the start of deferasirox treatment
- Baseline laboratory assessments such as serum creatinine (SrCr), creatinine clearance, SF, urea, SGOT (AST), SGPT (ALT), alkaline phosphatase, bilirubin and proteinuria.
- Baseline vital signs, weight, height, sexual development assessment, ECG, echocardiography, cardiac magnetic resonance (CMR), and LIC.

For patients already treated with deferasirox, transfusion, concomitant medications and concomitant diseases will be collected at enrollment.

Treatment period

This study is a non-interventional study and therefore does not impose a treatment period. Patients will be treated with deferasirox according to the physician's judgment and in accordance with the local country-specific deferasirox prescribing information. The daily dose of deferasirox will be recorded by the physician and/or study personnel, this will include the initial dose of deferasirox and subsequent changes in dose. The maximum treatment duration of deferasirox treatment observed will be 5 years.

Compliance will be recorded by the physician from information provided retrospectively by the parent/caregiver.

Effectiveness

According to the general prescribing information for deferasirox, measurements of SF should be performed monthly to assess response to therapy and to evaluate for the possibility of overchelation of iron. All available SF values will be recorded.

Premature withdrawal

Patients must be withdrawn from the study if any of the following occurs:

- Consent withdrawal

- Deferasirox treatment permanently stopped, except due to stopping rule.
- Patient participating in an interventional clinical trial

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the physician at any time.

For patients who are lost to follow-up, the physician should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Follow up period

Data will be collected on each patient for up to 5 years from the start of deferasirox treatment. There is no follow-up period after the 5 years unless the patient discontinued due to an adverse event (in this case refer to Section 9).

Assessment types

Safety

Patient safety will be monitored by reviewing medical and laboratory records and collecting available data on:

- SrCr, creatinine clearance, SF, urea, SGOT (AST), SGPT (ALT), alkaline phosphatase, bilirubin and proteinuria,
- LIC, CMR, echocardiography, ECG, vital signs,
- cardiac events potentially related to cardiac iron overload,
- height, weight, BMI,
- sexual development according to Tanner stage,
- audiometry and ophthalmology examination findings,
- concomitant medication at time of renal or hepatic AE,
- adverse event (AE)

For details on AE collection and reporting, refer to Section 9.

Laboratory evaluations

All local laboratories contributing to the study should provide the sponsor with a copy of the laboratory's certification and a tabulation of the normal ranges and standard deviations from control values for each of the parameters being evaluated. These laboratory references should be forwarded to the sponsor prior to study start and updated promptly if any information changes during the course of the study.

Data on the following parameters will be collected when available:

- serum creatinine
- creatinine clearance (the method used by the site to check the creatinine clearance will also be collected)
- serum ferritin

- urea
- SGOT (AST)
- SGPT (ALT)
- alkaline phosphatase
- bilirubin
- proteinuria (the method used by the site to check the proteinuria will also be collected)

Renal biopsy

Information on renal biopsies will be collected when available.

Cardiac parameters

Information on blood pressure, pulse, ECG, echocardiography and CMR will be collected when available.

Information on cardiac events that meet the definition of Serious Adverse Event must be reported as described in Section 9.

A list of cardiac events potentially related to cardiac iron overload is provided below:

- Sudden cardiac death
- Cardiac arrhythmias
- Congestive heart failure
- Cardiomyopathy
- Pulmonary hypertension

Liver iron concentration

Information on LIC and the method of its assessment will be collected when available.

Auditory and ophthalmology

The Prescribing Information recommends annual audiometry and ophthalmology examinations. The examination dates and findings (normal or not) will be collected on the audiometry and ophthalmology eCRF. Information about the examination must be present in the source documentation at the study site. Findings that meet the definition of an adverse event must also be recorded in the AE eCRF.

Transfusion requirements

Blood transfusion requirements will be collected if available.

7.4 Data sources

Initiation of the participating sites will be performed by Novartis and/or a designated CRO. Before study initiation, a Novartis representative (or designee) will review the protocol and eCRF with the physicians and their staff.

Sites enrolling patients in this study will record data on eCRFs provided by Novartis (or designee) which will capture, check, store and analyze the data.

CROs (if utilized) will follow their own internal SOPs that have been reviewed and approved by Novartis.

Concomitant or prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Safety data will be transferred to Novartis at a frequency as defined in Section 9 of this protocol and/or CRO contract. Clinical data will be transferred to Novartis after closure of the study.

Data collection schedule

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study. Every effort will be made to ensure all this available data in the patients' chart are captured in the eCRF. The treating physician is asked to complete if possible at every patient visit the appropriate eCRF.

For patients who discontinue prematurely, the reason for discontinuation should be determined.

7.5 Study size

This is a non-interventional study which plans to enroll a minimum of 40 patients. No formal sample size calculation based on the primary endpoint of long-term safety is performed.

Protocols for observational studies (or registry studies) to assess the natural history of a disease or to evaluate the safety of an established product (investigational drug) may not include formal sample size calculations. Data on global epidemiology of NTDT are scarce, see Section 7.2. Also the prevalence of NTDT patients with clinically significant iron overload constitutes a very small percentage of total number of NTDT patients.

Given the small prevalence of the disease under consideration, data on the 40 patients would provide relevant data as described by the computation of probabilities to detect adverse events as shown below. Statistical computations were performed (see table below) to evaluate probabilities to detect at least one patient with an AE given 40 patients and different scenarios of AE incidence rates (Hanley and Lippman-Hand 1983). This table shows a reasonable chance to detect adverse events occurring with an incidence of 5% or higher.

Probability to observe at least one AE for different incidence rates:

Incidence rate of an adverse event	Probability that at least one patient out of 40 experiences the adverse event
3%	0.70
4%	0.80
5%	0.87
6%	0.92
10%	0.99

Incidence rate of an adverse event	Probability that at least one patient out of 40 experiences the adverse event
15%	1.00

7.6 Data management

Data will be entered routinely into the study database by the physician/study coordinator.

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy.

Electronic data queries stating the nature of the problem and requesting clarification will be created for all other discrepancies and missing values and sent to the investigational site via the EDC system. Designated physician site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions, cause of death and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After this action has been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Data Management, Therapeutic Area Head, Biostatistics Development Unit Head.

7.7 Data analysis

This is a non-interventional pediatric study that does not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Data will be collected on all eligible pediatric patients aged ≥ 10 to <18 years at enrollment with non-transfusion dependent thalassemia treated with deferasirox and will be followed for up to 5 years from the start of deferasirox treatment. Retrospective data collection will be done for patients who have started deferasirox 12 months or less prior to enrollment.

The baseline is defined as the timeframe before the patient starts treatment with deferasirox.

Post baseline data will be collected from the start date of deferasirox and then on for five years.

The data will be analyzed by Novartis and/or a designated CRO.

Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, 25^{th}-percentile, median, 75^{th} percentile and maximum. Categorical variables will be summarized by absolute and relative frequencies.

In addition to the statistical methods outlined below, further details and any additional, exploratory analyses that may be performed will be described in the Statistical Analysis Plan (SAP).

7.7.1 Analysis sets

7.7.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of deferasirox during the study.

7.7.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of deferasirox during the study and have at least one post-baseline safety assessment. For post-baseline safety assessments, if a patient has any assessment taken a day after treatment start date for examination based assessments, e.g. laboratory, the patient will be included. For AE/ Death patients with an AE start date/ death date on or after the start date of treatment will be considered as having as least one post-baseline safety assessment and will be included in the safety set.

7.7.2 Patient demographics/other baseline characteristics

Demographics and other baseline data and disease characteristics will be summarized descriptively using the FAS.

7.7.3 Treatments (study treatment, concomitant therapies, compliance)

Using the Safety Set, data on deferasirox dose and exposure (duration of exposure, total patient-years exposure, reason for dose increase or decrease, average dose, number of interruptions and reason) and concomitant therapies will be summarized descriptively.

7.7.4 Primary objective

The primary objective is to evaluate the long term safety of deferasirox as determined by adverse events.

7.7.4.1 Variable

The primary variable is the proportion of patients having SAEs that are considered to be related to study drug over the period of up to 5 years from the start of deferasirox treatment.

7.7.4.2 Statistical hypothesis, model, and method of analysis

Counts and frequencies of patients with any drug related SAEs will be provided descriptively on Safety Set overall and by preferred term and system organ class.

In case of high number of SAEs, exposure-adjusted adverse event incidence will also be tabulated.

7.7.4.3 Handling of missing values/censoring/discontinuations

Details on imputation of missing data will be described in the SAP.

7.7.5 Secondary objectives

7.7.5.1 To evaluate the incidence of serum creatinine and ALT increases in actual practice setting

Counts and frequencies will be provided on Safety Set for patients with:

- Serum creatinine > 33 % above baseline and the age adjusted ULN (as per local normal ranges) in at least two consecutive post-baseline measurements at least 7 days apart from each other;
- SGPT (ALT) above 5 x ULN in at least two consecutive post-baseline measurements at least 7 days apart from each other.

7.7.5.2 To evaluate renal and hepatic safety parameters over time

Proportion of patients having adverse events related to hepatic and renal functions that are considered to be related to study drug over the period up to 5 years from the start of deferasirox treatment will be calculated.

For laboratory parameters directly related to hepatic parameters: ALT, AST, total bilirubin, alkaline phosphatase and directly related to renal parameters: serum creatinine, creatinine clearance; observed values (and changes from baseline) averaged at baseline, after first intake of study medication to day 30, day 31 to day 90 and per subsequent quarter will be summarized by descriptive statistics (n, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum).

In addition to the above mentioned tables and listings, other exploratory analyses, for example, figures plotting time course of raw or change in laboratory tests over time or box plots, will be specified in the Statistical Analysis Plan (SAP).

7.7.5.2.1 Supportive analyses

However, in case of a high number of missing values, supplementary analyses using Complete Case Analysis approach will be performed. A Complete Case Analysis excludes cases with missing laboratory values (for main hepatic and renal parameters) so that only complete cases are available. The estimates obtained from the complete case analysis shall be compared with the overall data set to view the effect of missing values on the estimates. If the number of patients to be included in this analysis is low, the analysis will not be conducted.

7.7.5.3 To evaluate growth by gender

The time-course of weight, height and BMI and its absolute or relative changes from baseline, as appropriate will be summarized on Safety Set using descriptive statistics.

All individual trajectories for weight, height and BMI will be superimposed on a graph with CDC US growth chart percentiles (5th, 25th, 50th, 75th, 95th), available for patients from 10 to 20 years.

In addition, weight, height and BMI will be flagged according to these percentile categories [0-5^{th}); [5^{th} - 25^{th}); [25^{th} - 50^{th}); [50^{th}- 75^{th}); [75^{th} - 100^{th}] and shift tables will be provided to compare baseline to the last available value on study.

Summary statistics of the height, weight and BMI standard deviation scores (SDS) for baseline, end of each year as well as end of study and change from baseline by gender and age category at enrollment (10 - < =12, >12 - < 18) will be provided.

In addition, weight, height and BMI will be plotted by age category at the time of assessment for E2422, and the same analysis will be done for study ICL670A107E for the same age

category patients as E2422. ICL670A107E is a registry study with the historical data from the four-year follow-up of the premarket clinical trial for children with β-thalassemia who are on a regular transfusion program.

7.7.5.4 To evaluate sexual development by gender

Shift tables for Tanner stages to compare baseline to the last on-study value will be provided. Descriptive statistics will be also provided for age at assessment for each Tanner stage.

Number and percentages of patients who are below, within and above the Marshal standards (Marshall and Tanner 1970) (mean age ± 2 SD) for each Tanner stages by gender will be provided.

The age of patients at time they reach the next Tanner stage will be flagged based on the Marshal standards and the listing will be provided.

Number and percentage of patients at different Tanner stages will be provided by gender and baseline age category (10 - < =12, >12 - < 18) at enrollment, at the end of each year and at end of study.

7.7.5.5 To evaluate long term efficacy of deferasirox as measured by serum ferritin and LIC

The time-course of serum ferritin and LIC and its absolute/relative changes from baseline will be summarized on FAS using descriptive statistics quarterly.

Counts and frequencies will be provided on FAS for patients:

- achieving a SF <300 ng/mL at any time during study;
- achieving LIC <3 mg Fe/g dw at any time during study;
- restarting deferasirox treatment after temporary interruption due to one of the two criteria mentioned above (SF <300 ng/mL or LIC <3 mg Fe/g dw at any time during study).

7.7.6 Safety data

Analyses will be done on Safety Set.

7.7.6.1 Analysis set and grouping for the analyses

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

- pre-treatment period: from day of patient's informed consent to the day before first dose of study medication except for patients who started their study medication 12 months or less prior to enrollment. For these patients, the pre-treatment period will include any day before the first dose of study medication.
- on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
- post-treatment period: starting at day 30+1 after last dose of study medication

7.7.6.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged (also tabulated for post-treatment period).

The incidence of treatment-emergent adverse events will be summarized by system organ class and or preferred term, severity (mild/moderate/severe), type of adverse event and relation to study treatment. A table will be also provided for incidence of treatment-emergent adverse events per total patient-years exposure.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by preferred term.

Additionally, AEs with suspected relationship to study drug, requiring dose adjustment, leading to drug interruption/discontinuation will be specifically tabulated and listed, as well as cardiac AEs of special interest ("Sudden cardiac death", "Cardiac arrhythmias", "Congestive heart failure", "Cardiomyopathy", "Pulmonary hypertension").

The number of adverse events adjusted by time of exposure (events per year or events per month) will also be tabulated.

7.7.6.3 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using the low/normal/high classifications based on laboratory normal ranges and for selected parameters by notable/extended ranges (see Table 7-3 below).

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- shift tables using normal/notable/extended ranges to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding normal/notable/extended ranges.

For each hematology/iron metabolism parameter, observed values (and changes from baseline) will be summarized by descriptive statistics (n, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum).

Creatinine clearance estimated using the Schwarz formula for patients < 18 years old and Cockcroft-Gault formula for patients ≥ 18 years old will be displayed using relative change from baseline by categories.

Similar to adverse events, the number of events related to lab abnormalities adjusted by time of exposure (events per year or events per month) will be tabulated.

Table 7-3 Criteria for clinically notable and extended laboratory ranges

Parameter	Criteria
ALT/AST	>5×ULN and >2×baseline value (extended range >10×ULN and >2×baseline value)
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)

7.7.6.4 Other safety data

Data from electrocardiogram, vital signs, renal biopsies, ocular and auditory examination will be listed, summarized and flagged as appropriate. Any significant findings after start of study will be documented as adverse events and reported as such.

Summary statistics of the number of transfusions, average amount RBC (in mL/kg/day) transfused per patient as well as average iron intake rate (in mg/kg/day) will be provided.

7.7.7 Interim analysis

No formal interim analyses will be done. However, interim safety outputs will be generated on yearly basis for interim updates.

7.7.8 Sample size

See Section 7.5.

7.8 Quality control

Data quality assurance

The Field Monitor will assure database quality by reviewing the data entered into the eCRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

Data quality management

Novartis Data Management will assure database quality processes are followed including review of the data entered into the CRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

Data recording and document retention

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the eCRF must be traceable to these source documents in the patient's file. The physician must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).The physician must give Novartis (or designee) access to all

relevant source documents to confirm their consistency with the eCRF entries. No information in source documents about the identity of the patients will be disclosed.

Site monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study.

The field monitor will assure compliance monitoring.

Before study initiation, at a site initiation visit or at a physician's meeting, a Novartis representative or designee will review the protocol and eCRFs with the physicians and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol, the adherence to Good Clinical Practice, and the progress of enrollment. Key study personnel must be available to assist the field monitor during these visits.

The physician must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

Retrospectively collected data in the medical charts will be reviewed for completeness and source document verified, by the field monitor and captured as per the monitoring plan

Data Collection

As the study will be using Electronic Data Capture (EDC), the designated physician staff will enter monthly all the available data to date required by the protocol into the Electronic Case Report Forms (eCRF) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated physician site staff will not be given access to the EDC system until they have been trained. The Principal Physician is responsible for assuring that the data entered into the eCRF is complete, accurate, and that entry is performed in a timely manner. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the physician staff before transfer to Novartis (or designated CRO) via a secure network. After database lock, the physician will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

7.9 Limitations of the research methods

Limitations of the research methods are:

- No planned visit schedule
- Small sample size

7.10 Other aspects

Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the physician, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

8 Protection of human subjects

Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

Responsibilities of the physician and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the physician is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent

with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2008), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (European Medicines Agency 2010).

Informed consent procedures

The physician must keep the original informed consent form signed by the patient (a signed copy is given to the patient).

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to treating physicians or other involved medical professionals in a separate document a proposed informed consent form that complies with the Declaration of Helsinki principle and regulatory requirements and is considered appropriate for this study.

9 Management and reporting of adverse events/adverse reactions

All adverse events (AEs) – including serious adverse events (SAEs) and safety endpoints (where relevant) – must be collected and recorded in the study database, irrespective of causal association. All AEs, including SAEs occurring in association with exposure to the Novartis drug of interest, also have to be recorded in the Novartis safety database.

Adverse Drug Reactions (ADRs) occurring in association with exposure to Novartis drug other than the Novartis drug of interest, can be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or Novartis DS&E as a spontaneous report.

All adverse reactions identified for non-Novartis products should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder; these will not be recorded in the Novartis safety database.

Adverse event reporting

An Adverse Event is any untoward medical occurrence in a patient administered deferasirox that does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Novartis drug, whether or not related to the medicinal product(s).

Drug of interest includes the drug under evaluation if specified as part of the research objective, given at any time during the study. Medical conditions/diseases present before starting the drug of interest are only considered adverse events if they worsen after starting the drug of interest.

Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy and to avoid overchelation. In general, it is recommended that treatment should be stopped once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 ng/mL). During periods of treatment with high doses and when serum ferritin levels are close to the target range, it is recommended to closely monitor for clinical and/or laboratory findings (i.e. renal and/or hepatic event) potentially related to overchelation and report those as an adverse event. In those cases, concomitant report of adverse event of organ dysfunction (i.e. renal and/or hepatic event) and adverse event of serum ferritin decreased should be considered.

Adverse events occurring after the signing the informed consent or after the start of treatment with deferasirox whichever is the earlier, should be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them.

Adverse event monitoring should be carried out for 5 years from the start of deferasirox treatment or continued for at least 30 days following the last dose of deferasirox if the patient is withdrawn prematurely from the study.

Abnormal laboratory values or test results occurring after signing the informed consent form or after the start of treatment with deferasirox whichever is the earlier, constitute adverse events only if they induce clinical signs or symptoms, or require therapy, (e.g., any hematologic abnormality that requires transfusion or hematological stem cell support) or changes in study medication(s) are considered clinically significant and should be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events eCRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. All adverse event reported by the patients will be recorded in the case report form. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

All adverse events must be recorded on the Adverse Events case report/case record form (eCRF) with the following information:

- the severity grade (mild, moderate, or severe)
- its relationship to the drug(s) of interest (suspected/not suspected)

- its duration (start and end dates or if continuing at final exam)
- whether it constitutes a serious adverse event (SAE)
- action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued
- whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

The start and end dates of deferasirox treatment is recorded on the Dose Administration Record eCRF. Any change, interruption or discontinuation of dose requires assessment of attribution to an adverse event.

Any adverse event which is fatal is recorded as a serious adverse event with attribution listing the cause of death, as per the Serious Adverse Event eCRF.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements, as stated below.

Laboratory test abnormalities

Abnormal laboratory values or test results that constitute adverse events or underlying conditions should not be reported separately in addition to the respective adverse events or underlying diagnosis.

Additionally, laboratory abnormalities that are considered clinically significant due to induction of clinical signs or symptoms, or requiring concomitant therapy (e.g. any hematologic abnormality that requires transfusion or cytokine treatment) or changes in study medication(s), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse events should be followed until they have returned to normal or an adequate explanation of the abnormality is found.

Laboratory abnormalities, that do not meet the criteria of clinical significance, as judged by the physician, should not be reported as adverse events.

A severe event does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per physician's discretion.

A dose hold of medication for the lab abnormality may be required by the local prescribing information and should not contribute to designation of a lab parameter abnormality as a SAE.

In addition, all reports of the following special scenarios are also considered an adverse event irrespective if a clinical event has occurred:

1. Drug-drug or drug-food interaction
2. Drug exposure during pregnancy
3. Drug use during lactation or breast-feeding,
4. Lack of effectiveness
5. Overdose
6. Drug abuse and misuse
7. Drug maladministration or accidental exposure

8. Dispensing errors / Medication errors
9. Off-label use
10. Withdrawal or rebound symptoms

Any treatment of any adverse event should be recorded on the Adverse Event eCRF. Some examples of treatment to be recorded are: no action taken (i.e., further observation only); drug of interest dosage adjusted/temporarily interrupted; drug of interest permanently discontinued due to this adverse event; treatment medication adjusted; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

Information about common adverse effects already known about the medicinal product can be found in the Package Insert. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

Information on all AEs is included in the individual patient eCRFs which must be updated and committed in the study database on a periodic basis but not later than once a month. Information on non-serious AEs is then transferred from the study database to Novartis DS&E by Novartis data management group/ Quintiles on a periodic basis but not less frequently than once a month.

Serious adverse event reporting

An SAE is defined as an event which:

1. Is fatal or life-threatening
2. Results in persistent or significant disability/incapacity
3. Constitutes a congenital anomaly/birth defect
4. Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    a. Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    b. Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
    c. Social reasons and respite care in the absence of any deterioration in the patient's general condition
    d. Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
5. Transmission of infectious agent via medicinal product

To ensure patient safety, every SAE, regardless of causality assessment, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study

participation (defined as time of last dose of the drug of interest taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the treating physician or other involved health care professional suspects a causal relationship to the drug of interest.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the treating physician or other involved health care professional receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The treating physician or other involved health care professional must assess the relationship to the drug of interest, complete the SAE Report Form and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety & Epidemiology (DS&E) Department. The telephone and telefax number of the contact persons in the local department of DS&E, specific to the site, are listed in the treating physician or other involved health care health care professional folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Package Insert, a local DS&E Department associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

Pregnancies

To ensure patient safety, any occurrence of a pregnancy in a patient on the drug of interest must be reported to Novartis within 24 hours of learning of its occurrence. Any SAE experienced during pregnancy must be reported on the SAE Report Form. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Pregnancy Form and reported by the treating physician or other involved health care professional to the local Novartis DS&E Department. In case of any congenital abnormality, birth defect or maternal and newborn complications, the possible relationship to the Novartis drug of interest should be reported.

10 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

For applicable non-interventional PASS (in the EU or mandated by an EU Health Authority outside the EU), the final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

None

12.2 Annex 2 – ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload

Study reference number:
CICL670E2422

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	12
1.1.2 End of data collection[2]	☒	☐	☐	12
1.1.3 Study progress report(s)	☒	☐	☐	12
1.1.4 Interim progress report(s)	☒	☐	☐	12
1.1.5 Registration in the EU PAS register	☒	☐	☐	12
1.1.6 Final report of study results.	☒	☐	☐	12

Comments:
This is a non-interventional study

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	17
2.1.2 The objective(s) of the study?	☒	☐	☐	18
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	23
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:
This is a non-interventional study

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	20
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:
This is a non-interventional study

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	23
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	20
4.2.2 Age and sex?	☒	☐	☐	20
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	20
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	23

Comments:
This is a non-interventional study

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	32
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective				

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:
This is a non-interventional study

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	18
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:
This is a non-interventional study

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☒	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:
This is a non-interventional study

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	27
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	30
8.1.3 Covariates?	☒	☐	☐	25
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	27
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	30
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	25
8.3 Is a coding system described for:				

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	30
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	30
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:
This is a non-interventional study

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☐	☒	☐	

Comments:
This is a non-interventional study, no formal sample size calculation based on the primary endpoint is performed.

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	32
10.3 Are descriptive analyses included?	☒	☐	☐	32
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:
This is a non-interventional study

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	36
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	36
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:
This is a non-interventional study

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐ ☐	☒ ☒	☐ ☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	22
12.3 Does the protocol address other limitations?	☒	☐	☐	37

Comments:
This is a non-interventional study

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	50
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	50

Comments:
This is a non-interventional study

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	48

Comments:
This is a non-interventional study

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	44
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	44

Comments:
This is a non-interventional study

Name of the main author of the protocol: [redacted]

Date: 11/13/2013

Signature: [redacted]

Digitally signed by [redacted]
DN: SERIALNUMBER=650429 + CN=[redacted] OU=PH, OU=people, DC=novartis, DC=com
Reason: I attest to the accuracy and integrity of this document.
Date: 2013.11.14 10:12:31 -5:00

12.3 Annex 3 – Additional information

NA