28 January 2016
EMA/CHMP/107225/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

EXJADE

International non-proprietary name: deferasirox

Procedure No. EMEA/H/C/000670/X/0043

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

© European Medicines Agency, 2016. Reproduction is authorised provided the source is acknowledged.

Table of contents

1. Background information on the procedure 4
1.1. Submission of the dossier 4
1.2. Steps taken for the assessment of the product 5

2. Scientific discussion 6
2.1. Introduction 6
2.2. Quality aspects 7
2.2.1. Introduction 7
2.2.2. Active Substance 8
2.2.3. Finished Medicinal Product 8
2.2.4. Discussion on chemical, pharmaceutical and biological aspects 11
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects 11
2.2.6. Recommendations for future quality development 11
2.3. Non-clinical aspects 11
2.3.1. Introduction 11
2.3.2. Pharmacology 11
2.3.3. Pharmacokinetics 11
2.3.4. Toxicology 15
2.3.5. Ecotoxicity/environmental risk assessment 15
2.3.6. Discussion on non-clinical aspects 15
2.3.7. Conclusion on the non-clinical aspects 16
2.4. Clinical aspects 16
2.4.1. Introduction 16
2.4.2. Pharmacokinetics 17
2.4.3. Pharmacodynamics 32
2.4.4. Discussion on clinical pharmacology 34
2.4.5. Conclusions on clinical pharmacology 36
2.5. Clinical efficacy 37
2.5.1. Discussion on clinical efficacy 37
2.5.2. Conclusions on the clinical efficacy 37
2.6. Clinical safety 38
2.6.1. Discussion on clinical safety 40
2.6.2. Conclusions on the clinical safety 41
2.7. Risk Management Plan 41
2.8. Pharmacovigilance 50
2.9. Product information 50
2.9.1. User consultation 50

3. Benefit-Risk Balance 50

4. Recommendations 53

List of abbreviations

AUC	Area under the curve of blood/plasma concentration versus time
BCS	Biopharmaceutics Classification System
Cmax	Maximum blood/plasma concentration
CPP	Critical process parameter
CQA	Critical quality attribute
CV	Coefficient of variation
DT	Dispersible tablet
FCT	Film-coated tablet
FMEA	Failure mode effects analysis
GI	Gastrointestinal
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
NIR	Near infrared spectroscopy
PD	Pharmacodynamics
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative humidity
RTRT	Real time release testing
SAE	Serious adverse event
SmPC	Summary of product characteristics
SOC	System organ class
T½	Elimination half-life
TEAE	Treatment-emergent adverse events

1. Background information on the procedure

1.1. Submission of the dossier

The Marketing Authorisation Holder (MAH) Novartis Europharm Ltd submitted on 5 March 2015 an extension for a Marketing Authorisation to the European Medicines Agency (EMA) for EXJADE dispersible tablets 125 mg, 250 mg and 500 mg, through the centralised procedure falling under Article 19 of Commission Regulation (EC) No. 1234/2008, Annex I 2(c).

The MAH applied for a new pharmaceutical form (film-coated tablet) and three new strengths (90 mg, 180 mg and 360 mg).

EXJADE dispersible tablets are approved in the following indication:

EXJADE is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

EXJADE is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,
- in patients with other anaemias aged 2 years and older.

EXJADE is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

The indications for the new film-coated tablets are the same.

EXJADE was designated as an orphan medicinal product EU/3/02/092 on 13/03/2002 in the following indication: Treatment of chronic iron overload requiring chelation therapy.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008, Annex I 2.(a) Change of bioavailability, Annex I 2.(c) Change or addition of a new strength/potency and Annex I 2.(d) Change or addition of a new pharmaceutical form.

The application submitted is composed of administrative information and complete quality data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0199/2014 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP EMEA-001103-PIP01-10-M01 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 25/07/2002, 17/12/2003, 09/07/2008, 05/05/2009 and 19/05/2011. The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

Licensing status

EXJADE has been given a Marketing Authorisation in the EU on 28/08/2006.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Pierre Demolis.

- The application was received by the EMA on 5 March 2015.
- The procedure started on 26 March 2015.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 17 June 2015.
- The PRAC RMP Advice and assessment overview was adopted on 14 July 2015.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 September 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 October 2015.
- The PRAC RMP Advice and assessment overview was adopted on 06 November 2015.
- During the CHMP meeting on 19 November 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 December 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 15 January 2016.
- The PRAC RMP Advice and assessment overview was adopted on 14 January 2016 (Annex 8).
- During the meeting on 28 January 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension of the Marketing Authorisation to EXJADE, concerning a new pharmaceutical form and strengths: 90 mg, 180 mg, 360 mg film-coated tablets.

2. Scientific discussion

2.1. Introduction

Iron overload is the result of many disorders inducing an increased net entry of iron within the body and can lead *per se* to the development of organ damage and increased mortality. It can be classified as primary or secondary depending whether it results from a primary defect in the regulation of iron balance or is secondary to other genetic or acquired disorders. A known example of primary iron overload is hereditary hemochromatosis (HHC), in which iron is absorbed in excess because of increased iron transfer from the enteral cells to the blood. The secondary includes iron overload either due to, or associated with, ineffective erythropoiesis, chronic liver diseases, parenteral administration or ingestion of excessive amounts of iron. Thalassemia major and sideroblastic anemia are the two best studied examples of iron overload secondary to blood transfusions and ineffective erythropoiesis. Frequent blood transfusions lead to excessive accumulation of iron with a toxic accumulation in 3 to 10 years.

The aim of treatment of iron storage disease is to remove from the body the excess iron that has accumulated. In the case of patients without primary disorders of hematopoiesis (i.e. primary hemochromatosis), this is best achieved by phlebotomy, since regeneration of erythrocytes by the marrow utilizes iron, which is therefore withdrawn from various body pools. Phlebotomy is only occasionally feasible. Patients who have augmented iron stores because of ineffective erythropoiesis and those in whom the iron overload is the result of multiple transfusions require treatment with an iron chelating agent to achieve safe levels of body iron. This is a slow process because only a small proportion of body iron is available for chelation at any moment. By increasing the doses of chelators in an attempt to speed up iron removal, there is a risk of increasing the toxicity of iron chelators by chelating iron, which is needed for normal tissue metabolism. Therefore, while the slow process of decreasing tissue iron to safe levels is being achieved, a second goal is to make the iron as safe as possible by binding the toxic iron pools responsible for causing tissue damage. Iron chelation therapy reduces iron-related morbidity, reduces and retards liver diseases, diabetes and other endocrine failures, normalizes growth and sexual development, prevents, and in some cases reverses, cardiac insufficiency and improves quality of life. Consequently iron chelation therapy dramatically reduces mortality.

Deferoxamine mesylate was introduced about forty years ago on the basis of demonstrable clinical benefits on morbidity and mortality. Due to the challenges of administering deferoxamine by slow subcutaneous or intravenous infusion over 8 to 12 hours, five to seven nights per week, compliance is often poor, leading to less than optimal efficacy of this therapy in preventing complications. The oral iron chelator deferiprone is approved in Europe only for the treatment of iron-overloaded thalassemic patients who cannot adequately be treated with deferoxamine, or for whom deferoxamine is contraindicated (see SmPC Ferriprox).

EXJADE contains the active substance deferasirox, an orally active iron chelator for the treatment of chronic iron overload due to blood transfusions. Deferasirox is indicated for the treatment of chronic iron overload due to frequent blood transfusion in patients with beta thalassemia major aged 6 years and older. It is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) aged 2 to 5 years,

- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,

- in patients with other anaemias aged 2 years and older.

It is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non transfusion-dependent thalassaemia syndromes aged 10 years and older.

Deferasirox is an orally active chelator highly selective for iron III that promotes excretion of iron excess primarily in the faeces. The active ingredient known as deferasirox (EXJADE), also referred to ICL670, is a tridentate iron chelator, formulated as dispersible tablet 125, 250 and 500 mg. EXJADE is orally administered at an initial dose of 20 mg/kg, once daily, on an empty stomach, at least 30 minutes before eating. Starting doses of 10 or 30 mg/kg can also be used, depending on the frequency of the patient's transfusions.

The present submission is intended to support the registration of the film-coated tablet (FCT) formulation based on pharmacokinetic (PK) comparability with the approved dispersible tablet formulation. It is intended to be used for all currently approved deferasirox indications.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 90, 180 or 360 mg of deferasirox as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, crospovidone, povidone (K30), magnesium stearate, colloidal anhydrous silica, poloxamer 188

Coating material: hypromellose, titanium dioxide (E171), polyethylene glycol (4000), talc, FD&C blue #2/Indigo carmine aluminium lake (E132)

The product is available in PVC/PVDC/Aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

EXJADE 90, 180 and 360 mg film-coated tablets contain the same active substance, deferasirox, as that used to manufacture the already authorised dispersible tablets. The active substance is sourced from the same manufacturer, manufactured with the same process and released in accordance with the same active substance specifications. Therefore, the applicant presented no new information in the dossier to support this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of development was to produce film-coated tablets, equivalent to the already approved dispersible tablets with the overall aim of improving patient compliance. The dispersible tablets contain lactose and sodium lauryl sulfate which are thought to cause gastro-intestinal side effects. In addition, the dispersible tablets are chalky and unpalatable once added to the required large volume of water indicated in the SmPC. One requirement of the paediatric investigation plan (PIP) was to develop a more palatable orally available dosage form and this current line extension fulfils that request. In addition, the film-coated tablets contain a higher percentage of active substance which reduces the dose burden for patients.

Pharmaceutical development of the finished product contains QbD elements. The quality target product profile (QTPP) was defined as an orally available immediate release dosage form, which can be swallowed easily, with equivalent *in vivo* performance to dispersible EXJADE tablets, sufficiently stable, and that meets compendial and other relevant quality standards. Critical quality attributes (CQAs) were identified as appearance, aspect, size, identity, assay, content uniformity, impurity profile, disintegration and dissolution times and microbial limits.

Deferasirox is non-hygroscopic and practically insoluble in water. As a result, the active substance is micronized to reduce its particle size which is controlled by specification. The required polymorph is produced by the active substance manufacturing process carried out within the approved design space. It has good permeability and is thus BCS II, exhibiting dissolution limited biopharmaceutics.

The choice of excipients used in the film-coated tablet formulation was based on compatibility test results of binary mixtures with the drug substance. Excipients were chosen to optimize the dissolution profile and stability whilst minimizing adverse effects. In contrast to the existing dispersible tablets, the film-coated tablets do not contain lactose which will ensure better acceptance in lactose-intolerant patients. The film-coated tablets require less disintegrant as they are intended to be swallowed rather than dispersed. As a result, the percentage of active substance in the formulation increased resulting in smaller tablets which are easier to swallow. Sodium lauryl sulfate was replaced by poloxamer 188 to further reduce gastric irritation. Microcrystalline cellulose was added in order to improve flow properties and a wet granulation step introduced in order to increase bulk density. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

A first clinical bioequivalence trial carried out with film-coated tablets of the same strengths (125, 250, 500 mg) as the already approved dispersible tablets revealed that the new formulation has improved bioavailability. The content of active substance was thus reduced, resulting in the current 90, 180 and 360 mg tablets. The 360 mg tablet was shown to be clinically equivalent to its dispersible 500 mg counterpart. A biowaiver for the lower strengths was sought based on comparison of f_2 values of 4x90

mg tablets and 2x180 mg tablets vs 1x360 mg tablet. Since these were all >50 (range 63-99), then a biowaiver was considered justified.

Development of the dissolution method took into account the low aqueous solubility of the active substance. The dissolution method is considered sufficiently discriminatory and fit for purpose.

The formulation and manufacturing process development were evaluated through the use of risk assessment and iterative design of experiments (DoE) to identify the CQAs and critical process parameters (CPPs). A risk analysis was performed using the failure mode effect analysis (FMEA) method and Ishikawa diagrams in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies.

A first DoE using 500 mg tablets explored ranges of excipient content and process parameters (PPs) identified as potentially critical in the initial risk assessment.

Those parameters found to have significant impact on output only were set at optimum levels and those shown to impact on processability were carried forward into a pilot scale DoE using the revised 360 mg strength at the commercial manufacturing site. Other parameters which could potentially be affected by scale-up were also examined in this DoE but not as main effects. Critical and non-critical process parameters have been defined. The outcome of these studies was that appropriate ranges for CPPs were included in the final design space.

The primary packaging is PVC/PVDC/Aluminium blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: blending of deferasirox with intra-granular excipients; wet granulation and drying; blending of granules with extra-granular excipients; compression; film-coating. The process is considered to be a standard manufacturing process.

A design space, developed at pilot scale (half commercial scale in the commercial equipment), has been proposed. The applicant plans to verify this on commercial scale in two stages. The first has been completed and involved running the process in the “worst case scenario” corners of the design space in terms of their impact on processability and CQAs for each tablet strength. This will later be complemented by running the process at the other corners of the design space. This design space verification strategy is considered acceptable. The completed verification batches have to date resulted in finished product meeting the required specifications. A multi-variate statistical process control method was developed for the granulation step using on-line process parameters to develop a model. This will be refined during the second phase of verification and used to monitor the process henceforward.

Major steps of the manufacturing process have been validated by a number of studies. The first part of the design space verification protocol is considered sufficient to validate the entire process since it constitutes more than three consecutive commercial scale batches run within the design space. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The IPCs are adequate for this type of manufacturing process.

Product specification

The finished product is released on the market based on the design space and a combination of traditional final product release testing and real time release testing (RTRT). The finished product release specification includes appropriate tests for this kind of dosage form and includes tests for appearance (as IPC), identity (NIR – RTRT and UV), identity of colourants (colour reaction and UV, skip testing), mean mass (as IPC), dissolution (Ph. Eur.), uniformity of dosage units (content uniformity by NIR – RTRT and Ph. Eur.), degradants (based on design space and HPLC), microbial enumeration (Ph. Eur., skip testing) and assay (NIR – RTRT and HPLC). The RTRT NIR methods for uniformity of dosage units and assay and the strategy for control of degradants will all be supplemented by traditional release tests carried out in parallel until a sufficient number of commercial scale batches have been manufactured to validate the correlation. A post-approval change management protocol (PACMP) has been submitted documenting the strategy and is considered acceptable. The supplementary methods can also be used as alternative methods should technical issues prevent use of the at-line RTRT methods.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results for three commercial scale and four pilot scale batches of each strength were provided. The traditional release methods were used in lieu of the NIR method which will only be implemented for commercial batches. The batches all complied with the specifications confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three pilot scale batches of each strength of finished product stored for up to 24 months under long term conditions (25 °C / 60% RH), up to 24 months under intermediate conditions (30 °C / 75% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) in line with the ICH guidelines were provided. The batches of EXJADE film-coated tablets are identical to and packed in the same primary packaging as those proposed for marketing. Samples were tested for appearance, assay, degradation products, dissolution and microbial quality. The analytical procedures used are stability indicating and are the same as those used for release testing. All results complied with the specification and no significant trends were observed to any of the measured parameters.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Batches were also exposed to extremes of temperature (between -20 and 50^{o}C) and ambient humidity, and to freeze/thaw cycles. Again, no changes were observed to any of the measured parameters.

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. The magnesium stearate used is of vegetable origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. A design space has been proposed which has been partially verified on commercial scale using the worst case scenario combination of set-points. A design space verification protocol has been submitted and is considered adequate to demonstrate the validity of the design space at commercial scale.

The product is intended to be released in the long term by RTRT. Until a sufficient number of commercial scale batches have been manufactured to demonstrate the correlation between RTRT methods and the standard release tests, these latter methods will be carried out in parallel and used to release product to the market. A PACMP has been submitted explaining steps which will be taken in order to demonstrate the relationship between the end-product specification and the RTRT.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical data submitted by the Applicant refers to 2 experimental pharmacokinetics studies testing 6 new formulations (3 tablets and 3 pellets).

2.3.2. Pharmacology

No new pharmacodynamic studies were submitted with the current application.

2.3.3. Pharmacokinetics

The Applicant provided relative bioavailability studies conducted in dogs to support deferasirox new formulation development compared to DT. All previous *in vitro* and *in vivo* studies, which investigated the absorption, pharmacokinetics, distribution, metabolism, and excretion (ADME) of deferasirox in laboratory species, including toxicokinetic (TK) studies performed during toxicity testing were included in the initial application.

Methods of analysis

Deferasirox was analysed in dog plasma using a specific liquid chromatography–tandem mass spectrometry method (LC-MS/MS) after solid phase extraction of the plasma samples. In both studies, the lower limit of quantification (LLOQ) was 0.670 µmol/L using 100 µL plasma. The concentration range was: 0.67 – 26.8 µmol/l and the curve was linear.

Absorption

Two PK studies (study 0900739 and study 1000323) conducted in dogs, at a single dose of 375 mg deferasirox were submitted. The goal of those studies was to investigate the PK of ICL670 after oral administration of new formulation variants in comparison to EXJADE DT in support of the choice of the pharmaceutical form.

Table 1: Pharmacokinetic parameters after single oral administration of 375 mg - Study 0900739

Species	**Assay**	**Route and dose (mg/kg)**		**Tmax (h)**	**Cmax (µM)**	**AUC_{0-48} (µM/h)**	**Relative biodisponibility (%) ***
male dog pre-treated with Pentagastrin 8/group	LC-MS/MS	Single oral dose, as suspension of tablets (form 1) or coated tablet formulation (form 2,3,4) 375 mg/dog	Form 1	1.75	92±24	442±164	100
			Form 2	1.75	92±18	454±52	113±35
			Form 3	4	40±32	423±659	101±151
			Form 4	2	37±24	210±124	48±30

*biodisponibility relative to form 1

Form 1: commercial EXJADE dispersible tablets 125 mg and 250 mg dose strengths;
Form 2: non-enteric coated tablet, HPMC as binder 375 mg dose strength
Form 3: enteric-coated tablet, HPMC as binder 375 mg dose strength
Form 4: enteric-coated tablets, Wet Granulation, PVP as binder 375 mg dose strength

In pentagastrin treated dogs, the ICL670 non-enteric coated tablet showed a similar exposure compared to marketed EXJADE DT.

Study 1000323 (see table 2) was a cross over pharmacokinetic study of ICL670 following single oral administration to Pentagrastrin-pretreated non naïve Beagle dogs. The study refers to pellets treated dogs in comparison with dogs treated with ICL670 suspension of EXJADE DT.

Table 2: Pharmacokinetic parameters after single administration

Species	Assay	Route and dose (mg/kg)		Tmax (h)	Tlast (h)	Cmax (µM)	AUC_{0-48} (µM/h)	Relative biodisponibility (%)	Clinical signs
Male Dog Pre-treated with pentagastrin 8/group	LC-MS/MS	Single dose, Oral as suspension of tablets (period 1) or pellet (period 2,3,4) 375 mg/dog	Period 1	1.75	24	74±15	311±77	100	No effect on dogs
			Period 2	1.75	8	80±14	349±126	115±28.1	Loose feces for dog D103
			Period 3	2	8	36±18	149±89	52±22.4	No effect on dogs
			Period 4	2	8	117±36	502±134	169±48.3	Loose feces and jelly-like excretion in dog D103

Period 1: suspension of EXJADE DT, formulation A (125 mg tablet and 250 mg tablet)
Period 2: enteric coated pellets, formulation B EXJADE LCM minitablets
Period 3: non-coated pellets, formulation C EXJADE LCM multiparticulates
Period 4: non-coated pellets, formulation D EXJADE LCM multiparticulates

Figure 1: Mean (± SD) concentrations (µM) of ICL670 in plasma of male Beagle dogs (n=8) following a single oral dose of 375 mg ICL670 administered as four different formulations.

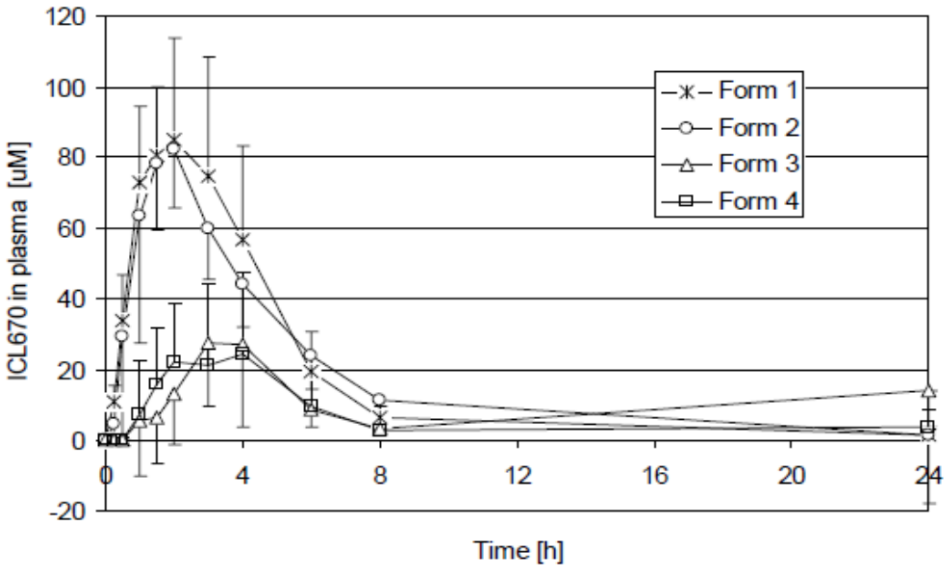
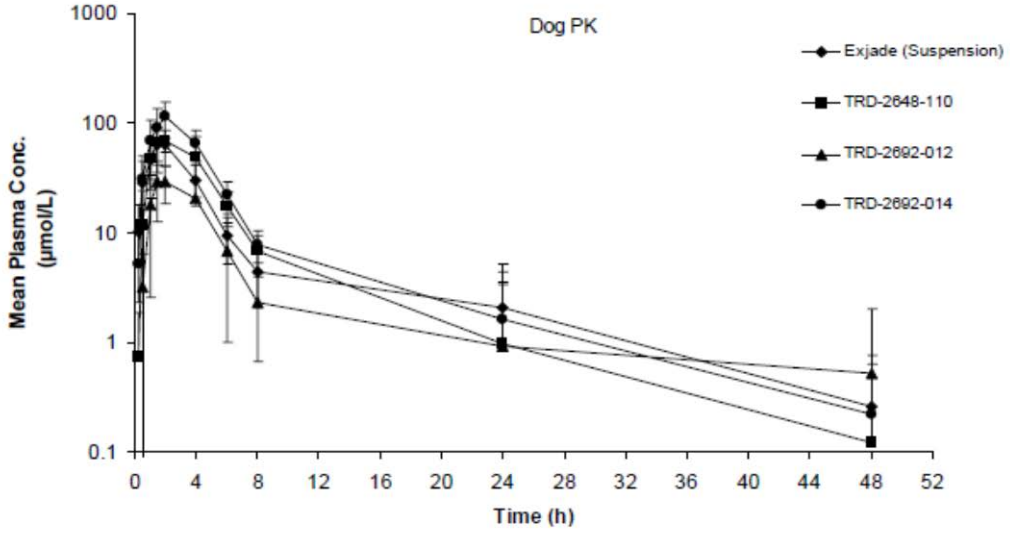


Figure 2: Mean (± SD) plasma concentration profiles of ICL670 following oral administration (375 mg/dog) in male Beagle dogs



The different formulations lead to a mean Cmax reached 2 hours post-dose. The maximal exposure and relative bioavailability was reached using formulation D in period 4 (non-coated pellets) and the minimal exposure and minimal bioavailability was obtained after treatment with non-coated pellet formulation C in period 3.

The inter-individual variability regarding Cmax and AUC was moderate and similar among formulations.

In comparison with EXJADE tablets the dosage of ICL670 as non-coated pellets, formulation D results in a higher relative bioavailability; the dosage of enteric coated pellets, formulation B results in similar bioavailability and the dosage of non-coated pellets, formulation C results in a lower relative bioavailability.

Distribution

No new studies were conducted for the current application.

Metabolism

No new studies were conducted for the current application.

Excretion

No new studies were conducted for the current application.

Pharmacokinetic drug interactions

No new studies were conducted for the current application.

Other pharmacokinetic studies

No new studies were conducted for the current application

2.3.4. Toxicology

No new toxicology studies have been submitted with this procedure.

2.3.5. Ecotoxicity / environmental risk assessment

Currently the recommended starting dose of deferasirox as EXJADE dispersible tablets for oral suspension is 20 mg per kg per day for transfusional iron overload, respectively 10 mg per kg per day for NTDT, and is available as 125, 250 and 500 mg dispersible tablets. The new strength-adjusted film-coated tablet will be dosed at a starting dose of 14 mg per kg per day for transfusional iron overload, respectively 7 mg per kg per day for NTDT and will be made available as 90, 180 and 360 mg film-coated tablets. Based on the fact that the recommended doses of EXJADE will decrease with the current line extension and consequently environmental exposure with deferasirox is not expected to increase, no updated environmental risk assessment was submitted.

2.3.6. Discussion on non-clinical aspects

No new pharmacodynamic studies were submitted with the current application, so no data are provided regarding pharmacology. The lack of pharmacodynamic studies is addressed by the available clinical efficacy information and comparability of the film-coated tablet with dispersible tablets submitted as part of the clinical studies (see clinical aspects).

In this application, regarding deferasirox film-coated tablet, relative bioavailability studies were performed in dogs to support new formulation development. Two PK studies were conducted in dogs, at a single dose of 375 mg deferasirox, the first one compared to tablets and the second one to pellets. The exposures were measured until 48 hours post-dose in both studies. The bioavailability relative to the DT was estimated for each formulation based on $AUC_{0\text{-}48h}$ values. The goal of those studies was to investigate the PK of ICL670 after oral administration of newly formulation variants in comparison to EXJADE DT to support the choice of a clinical disposable form. In pentagastrin treated dogs, the ICL670 non-enteric coated tablet showed a similar exposure compared to marketed EXJADE DT. Regarding the enteric coated tablet, a delayed time to reach maximal concentration and lower exposure was demonstrated, their bioavailability were about 2-fold lower compared to the marketed form. The study performed on pellet reported different result for non-coated and enteric one in terms

of exposure AUC, Cmax. Similar bioavailability results are obtained between enteric coated pellet and suspension of EXJADE. Some effects on feces are observed with pellets, coated or not.

Lack of non-clinical toxicology data is considered acceptable considering the available clinical safety and tolerance data.

The recommended doses of EXJADE will decrease with the current line extension and consequently environmental exposure with deferasirox is not expected to increase. Therefore, deferasirox formulated as FCT is not expected to pose a risk to the environment different from those already identified for DT and the current environmental risk assessment is still considered applicable.

2.3.7. Conclusion on the non-clinical aspects

No further need to update the non-clinical documentation for deferasirox is identified with the submission of the film coated tablets formulation. The non-clinical information included in the SmPC was not updated as a result of this procedure.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study no. / Type of study	Title	N	Deferasirox dose (formulation)	Food
[Study F2101] / pilot bioavailability study	A randomized, open-label, single-center, four-period, cross-over study evaluating the bioavailability of deferasirox (single dose) from three new formulations in comparison to the reference marketed deferasirox formulation in healthy subjects	20	1500mg (uncoated tablets) / 1500mg (DT)	fasted/ fasted
[Study F2102] / pivotal pharmacokinetic comparability study	A randomized, open-label, single-center, phase I, crossover study to evaluate the pharmacokinetic comparability of deferasirox new tablet formulation with the reference dispersible formulation in healthy subjects	32	1080mg (FCT) / 1500mg (DT)	fasted/ fasted
[Study F2103] / food effect study	A single-center, open-label, randomized, cross-over study to investigate the effect of food on the pharmacokinetics of new deferasirox tablet formulation in healthy subjects	25	1080mg (FCT)	fed/ fasted
[Study F2104] / dose proportionality study	A randomized, open-label, single-center, Phase I, four period cross-over study evaluating the bioavailability of new deferasirox granule formulation in comparison to the reference deferasirox (Exjade®) marketed formulation in healthy subjects	21	400, 800, 1200mg (G) / 1500mg (DT)	fasted/ fasted
[A2409 PK/PD analysis]	A one-year, open-label, single arm, multi-center trial evaluating the efficacy and safety of oral ICL670 (20 mg/kg/day) in patients diagnosed with transfusion-dependent iron overload: PK/PD analysis.	1744	20 mg/kg body weight/day (dispersible tablet formulation)	

DT= dispersible tablets (current formulation); FCT= film-coated tablets; G=granules; N= number of subjects exposed to deferasirox; PK/PD: pharmacokinetic/pharmacodynamic

2.4.2. Pharmacokinetics

Absorption

Bioavailability/ Bioequivalence

Study F2101

Design

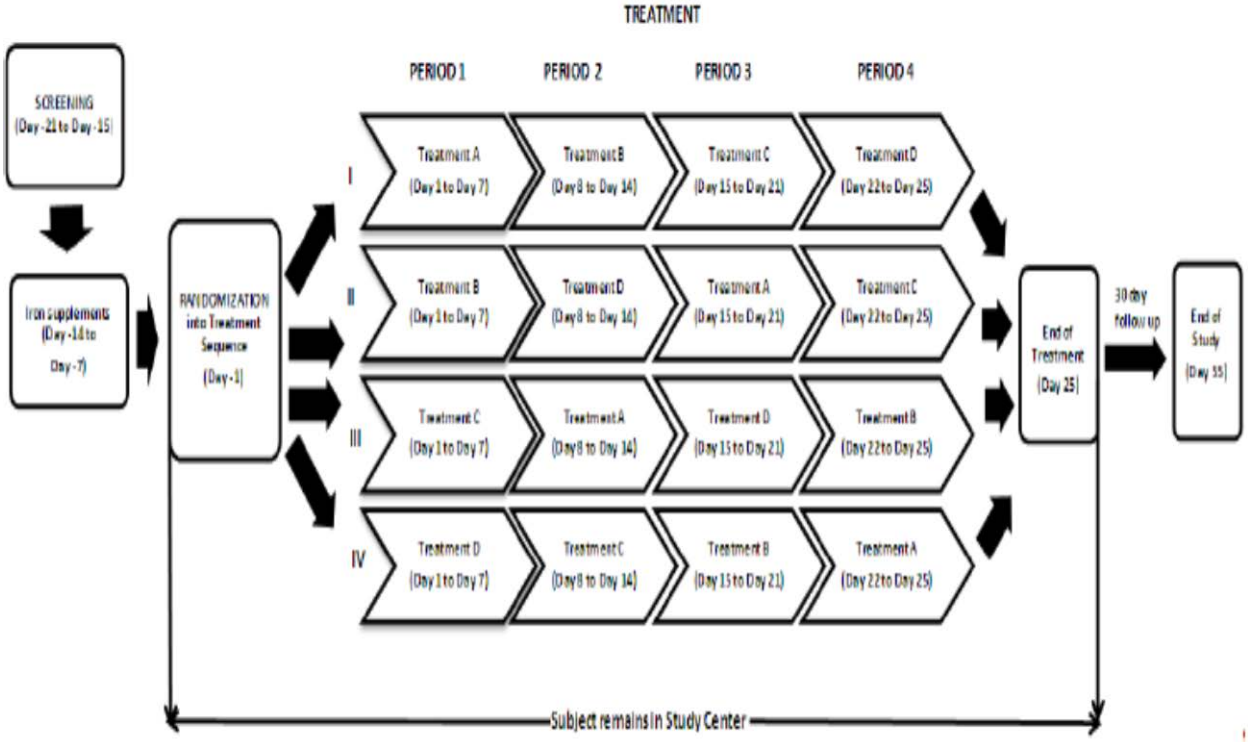
This study was designed to evaluate three new tablet formulations of deferasirox and was conducted in 20 healthy volunteers using a single oral dose of 1500 mg (3 x 500 mg) under fasted condition. The design was a single-center, open-label, four-period randomized, cross-over study with four treatment periods and four treatment sequences (Figure 4). The subjects were randomly assigned to one of the four treatment sequences (5 subjects per treatment sequence) to receive the following treatments with each of three deferasirox new tablet formulations as well as the DT; A) wet granulation with low surfactant, B) wet granulation with medium surfactant, and C) wet granulation with medium surfactant and modified release enteric coating. Randomization to one of four treatment sequences (in a 1:1:1:1 ratio) employed the Williams Square design, whereby each treatment followed the other treatment once. This open-label design did not need to control for bias reduction by stratification.

The study was conducted at Parexel Early Phase 1 Clinical Unit, Baltimore, MD, between the 18 Apr and 10 Jul 2011.

To counteract the potential iron loss due to deferasirox, subjects were also dosed with iron supplements for eight days prior to the start of deferasirox treatment. This supportive treatment was an iron supplement, ferrous sulfate 325-mg strength oral tablet, which was equivalent to 65 mg Fe^{++}.

Treatment periods were separated by a washout period of 6 days. Blood samples for the determination of deferasirox concentrations in plasma were determined on Days 1, 8, 15, and 22 at the following timepoints: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours post-dose.

Figure 3. F2101 Study design overview and by period.



A Williams Square design was utilized for randomization of the deferasirox treatment sequences (sequence no., variant name) in the following order: (a) Sequence I [A, B, C, D]; (b) Sequence II [B, D, A, C]; (c) Sequence III [C, A, D, B]; and (d) Sequence IV [D, C, B, A]. Deferasirox dosing occurred on the first day of each of the 4 open-label treatment periods. There was a 6-day washout between treatment periods.

Results

Following a single oral dose of 1500 mg deferasirox, mean C_{max} of deferasirox was achieved at 3 to 4 hours post-dose in all formulations tested including the reference formulation. Deferasirox bioavailability of all three new tablet formulations was greater than that of the reference DT formulation. Percent increase in C_{max} was comparable to that in AUC across the variants. The formulation with a low surfactant, Formulation A, was selected for further development of the FCT.

Geometric mean ratio (test/reference) and its 90% confidence intervals for primary pharmacokinetic parameters are listed in Table 3. Deferasirox pharmacokinetic parameters are listed in Table 4.

Table 3. Study F2101: Geometric mean ratio and 90 % CI for primary pharmacokinetic parameters.

Comparison	PK parameter	Geometric mean ratio (90% CI)
A:Reference (D)	AUClast	1.38 (1.179-1.620)
	AUCinf	1.36 (1.163-1.591)
	Cmax	1.39 (1.164-1.661)
B:Reference (D)	AUClast	1.43 (1.219-1.667)
	AUCinf	1.39 (1.196-1.626)
	Cmax	1.46 (1.226-1.741)
C:Reference (D)	AUClast	1.15 (0.986-1.348)
	AUCinf	1.13 (0.973-1.323)
	Cmax	1.11 (0.931-1.322)

Table 4. Study F2101: Deferasirox pharmacokinetic parameters by formulation.

PK variable	Formulation	N	Adjusted geometric mean	%CV geometric mean
AUClast (µmol×h/L)	A	19	1702.32	38.07
	B	20	1727.25	34.80
	C	20	1397.31	56.25
	Reference (D)	20	1211.68	47.86
AUCinf (µmol×h/L)	A	19	1758.47	38.36
	B	20	1772.96	35.73
	C	20	1442.81	54.23
	Reference (D)	20	1271.53	48.98
Cmax (µmol/L)	A	19	110.22	22.87
	B	20	115.11	22.99
	C	20	87.41	61.05
	Reference (D)	20	78.78	31.05
Tmax* (h)	A	19	3.983	1.5-6.1
	B	20	4.025	1.5-8.0
	C	20	3.517	1.5-24.1
	Reference (D)	20	3.000	1.5-8.0
T1/2 (h)	A	19	12.41	40.66
	B	20	12.74	31.81
	C	20	12.62	35.31
	Reference (D)	20	13.37	50.06

* Median and range are reported for Tmax
%CV = percent coefficient of variation

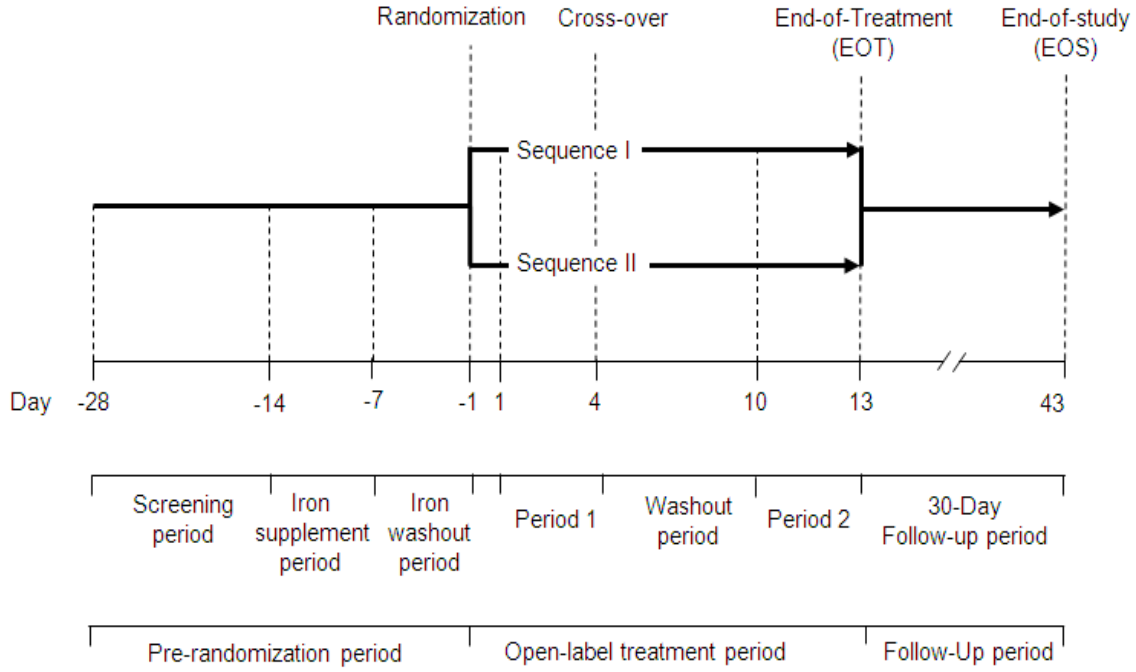
Study F2102

Design

The PK comparability study F2102 was designed to assess relative bioavailability of defersirox FCT versus defersirox DT formulation. The study was a single-center, open-label, randomized, cross-over study with two treatment periods and two treatment sequences (Figure 5) conducted in 32 healthy subjects. The subjects were randomly assigned to one of the two treatment sequences (16 subjects

per treatment sequence). The subjects received two single doses of deferasirox, 1080 mg (3 x 360 mg) deferasirox FCT, and 1500 mg (3 x 500 mg) deferasirox DT for oral suspension on Day 1 and Day 10. The study drug was administered to subjects under fasting conditions and treatment periods were separated by a washout period of 9 days.

Figure 4. F2102 Study design



All deferasirox was supplied by Novartis. The batch number, formulation, and treatment name of each investigational product are presented in Table 5.

Table 5. Study medication formulation and batch numbers.

Study drug, strength	Formulation	Batch number	Treatment name
Deferasirox, 360 mg	New oral film-coated tablet (FCT)	AEUS/2012-0106	FCT
Deferasirox, 500 mg	Commercial Dispersible tablet (DT)	S0325	DT

Date of manufacture of deferasirox FCT = April 2012, Expiry date: October 2013 Size batch 123457 FCT, purity 99.2%. Date of manufacture of deferasirox Dispersible tablet = November 2011, Expiry date: Nov 2016. Size batch 184192 dispersible tablets, purity 97%.

The supportive treatment was an iron supplement, ferrous sulfate 325-mg strength oral tablet, which was equivalent to 65 mg Fe++ (elemental iron). Natural ferrous sulfate, lot no. 11M840 with an expiration date of 31-Dec-2013, was manufactured by Rugby Laboratories Inc.

The study was conducted at the center of Pharmaceutical Product Development (PPD) Phase I Clinic, PPD Development (Texas, US) between 19 July and 27 September 2012.

Number of patients (planned and analyzed): 26 evaluable subjects were planned; 34 subjects were enrolled and randomized; and 32 Pharmacokinetic Analysis Set (PAS) subjects were analyzed: by treatment sequence, 16 PAS subjects in Sequence I and 16 PAS subjects in Sequence II.

Results

The bioavailability (AUC_{last} and AUC_{inf}) of the oral FCT administred at 1080 mg dose demonstrated comparability to the commercial DT, administered at 1500 mg, with geometric mean ratios of 1.00 (90% CI: 0.932- 1.078) and 0.98 (0.916-1.059), respectively. Yet, following the single 1500-mg dose DT formualtion (i.e. the reference), deferasirox Cmax was observed at a median time of 3 h post-dose with Cmax averaging 81.54 µmol/L vs. a median time of 2 h post-dose with Cmax averaging 105.83 µmol/L following the single 1080-mg dose delivered as an oral FCT. This yielded peak deferasirox concentrations 30% higher (geometric mean ratio, 1.30; 90% CI: 1.203-1.400) with the oral FCT than the commercial DT for oral suspension.

Although C_{max} did not meet the standard bioequivalence criteria, individual C_{max} values from Study F2102 and Study F2103 (food effect study) are within the range of historical Cmax values observed with the DT formulation. Figure 7 includes Cmax data from (1) previous clinical pharmacology studies in healthy subjects given 20 mg/kg deferasirox DT (Study A2120, Study A2121, Study A2122), (2) FCT treatment in Study F2102, and (3) FCT treatment under fasted conditions in Study F2103.

The arithmetic mean concentration-time profiles of deferasirox are shown in linear scales in Figure 6. Deferasirox primary pharmacokinetic parameters, and statistical analyses are shown in Table 6. Deferasirox secondary pharmacokinetic parameters are listed in Table 7.

The PK exposure (AUC and Cmax) in the new oral FCT exhibited less variability, compared with that observed with the DT. Inter-subject variability (CV%) with FCT and DT were 44% vs. 49% for AUC and 28% vs. 32% for Cmax, respectively (Figure 8).

Figure 5. Study F2102: arithmetic mean (SD) concentrations time profiles of deferasirox by treatment.

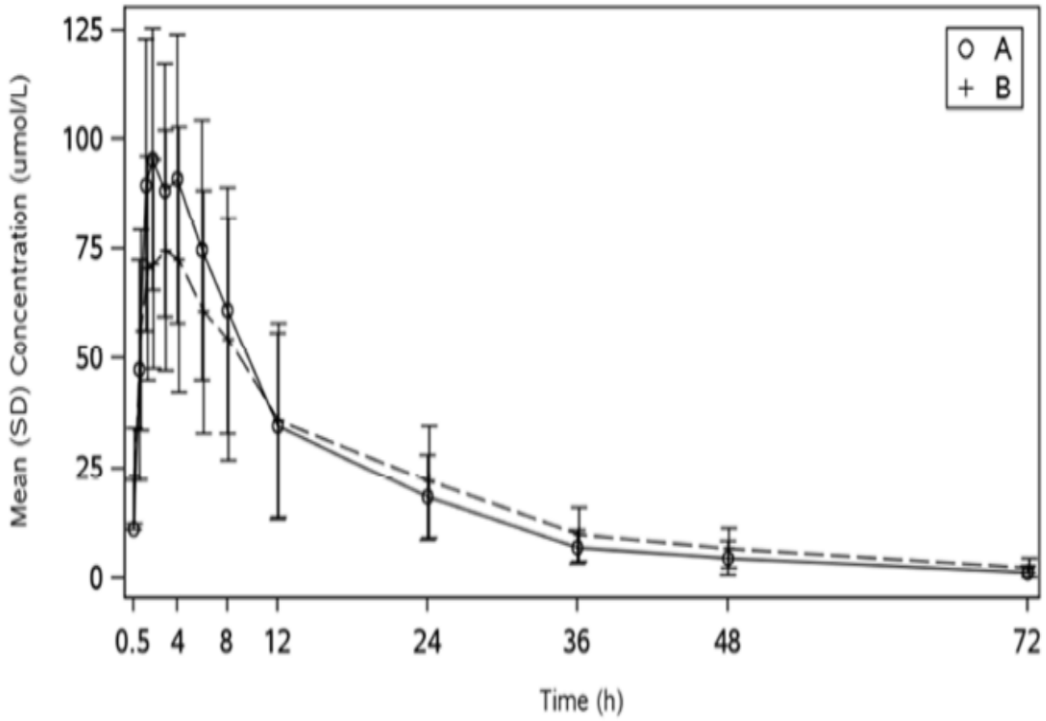


Figure 6. Deferasirox C_{max} comparison: historical healthy volunteer data with 20 mg/kg DT vs. FCT studies 2102 and 2103.

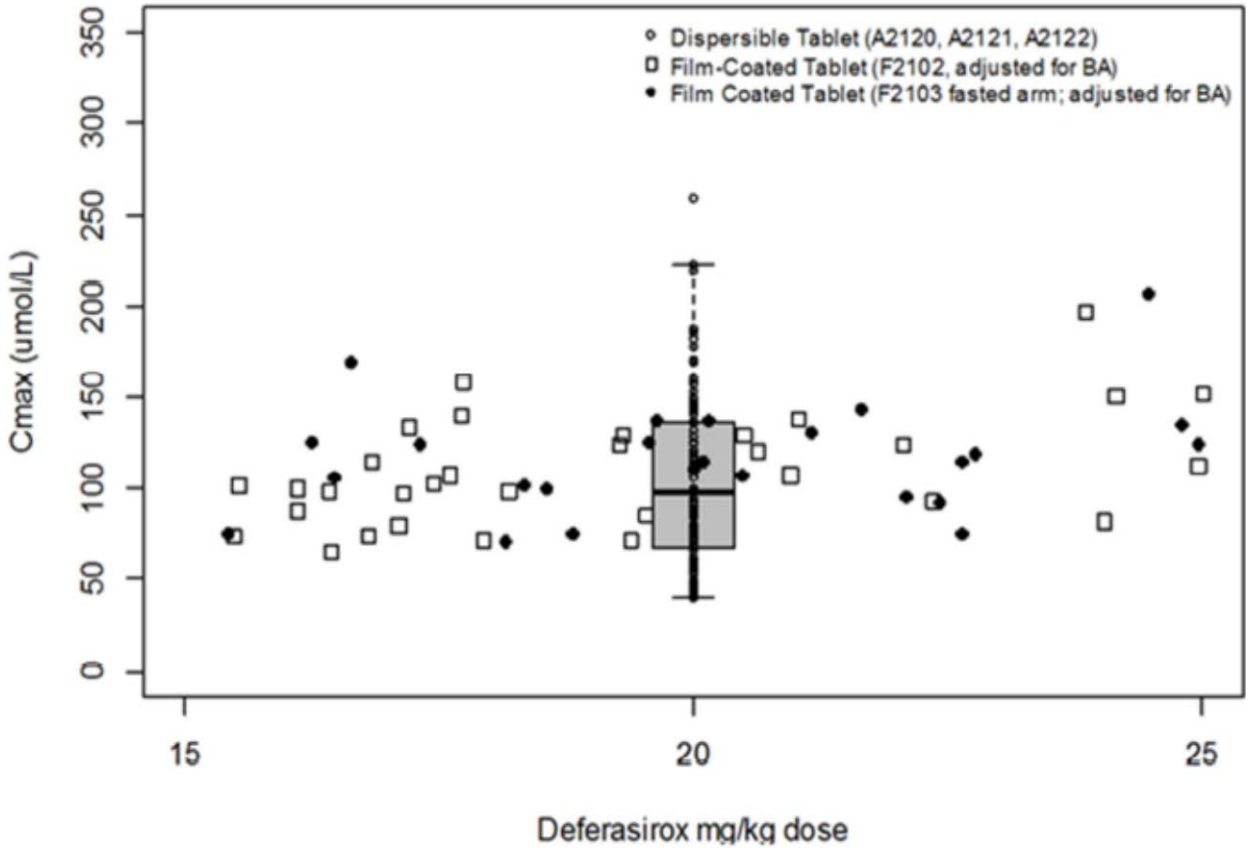


Table 6. Treatment comparison of primary pharmacokinetic results: geometric mean ratio and 90% CI.

PK variable (unit)	Treatment	N	Adjusted geometric mean	Geometric mean ratio (90% CI)*	
AUClast (µmol × h/L)	DT	32	1270.79		
	FCT	32	1273.78	1.00	(0.932–1.078)
AUCinf (µmol × h/L)	DT	32	1327.01		
	FCT	32	1307.04	0.98	(0.916–1.059)
Cmax (µmol/L)	DT	32	81.54		
	FCT	32	105.83	1.30	(1.203–1.400)

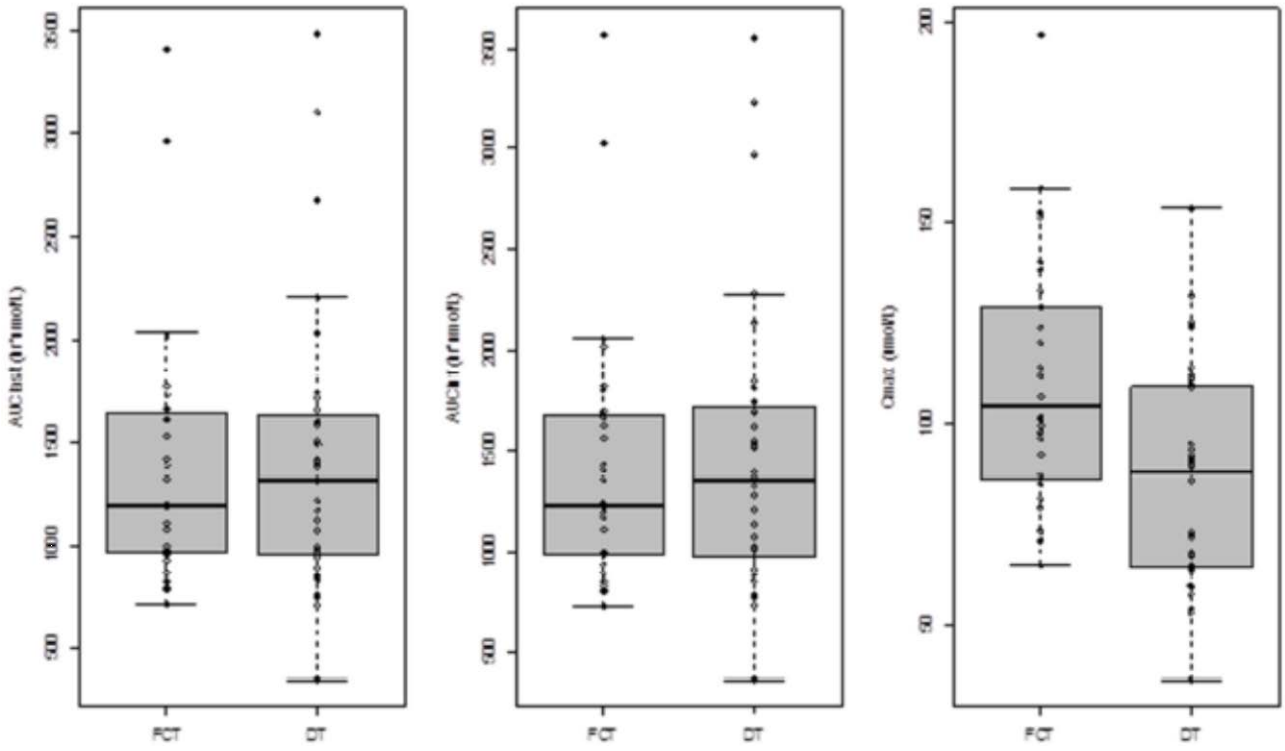
FCT = Film-coated tablet: single dose of 1080-mg deferasirox oral film-coated tablets (3 tablets × 360 mg); DT = Dispersible tablet/reference: single dose of 1500-mg deferasirox dispersible tablets for oral suspension (3 tablets × 500 mg); CI = confidence interval; * Comparisons were based on FCT vs. DT

Table 7. Secondary pharmacokinetic parameters by treatment.

Secondary pharmacokinetics derived from plasma levels		FCT N=32	DT N=32
Tmax (h)	N	32	32
	Median	2.00	3.00
	Range	1.50–6.03	1.00–8.00
T1/2 (h)	N	32	32
	Geometric mean	12.48	15.64
	CV% geometric mean	30.69	29.47

FCT = Film-coated tablet: single dose of 1080-mg deferasirox oral film-coated tablets (3 tablets × 360 mg)
DT = Dispersible tablet/reference: single dose of 1500-mg deferasirox dispersible tablets for oral suspension (3 tablets × 500 mg)

Figure 7. Inter-subject variability in PK parameters in Study F2102



Influence of food

Study F2103

The study was single-center, open-label, randomized, three-period, six sequence crossover evaluating the effect of food on deferasirox pharmacokinetics in healthy subjects. Twenty-five (25) healthy subjects received a single dose of 1080 mg (360 mg x 3) FCT under fasted, low-fat breakfast, or high-fat breakfast conditions. Low-fat or high-fat breakfast had approximately 250 kcal or 1000 kcal with a fat content of 6.2% or 58.6%, respectively. A single dose of 1080 mg deferasirox FCT was administered with either a low-fat breakfast, high-fat breakfast, or under fasted conditions on study Days 1, 10, and 19. The treatment periods were separated by an 8-day washout period. The study was conducted between the 08-Jul-2013 to 05-Nov-2013. Iron supplement, ferrous sulfate 325-mg oral tablet; (equivalent to 65 mg elemental iron); was also given.

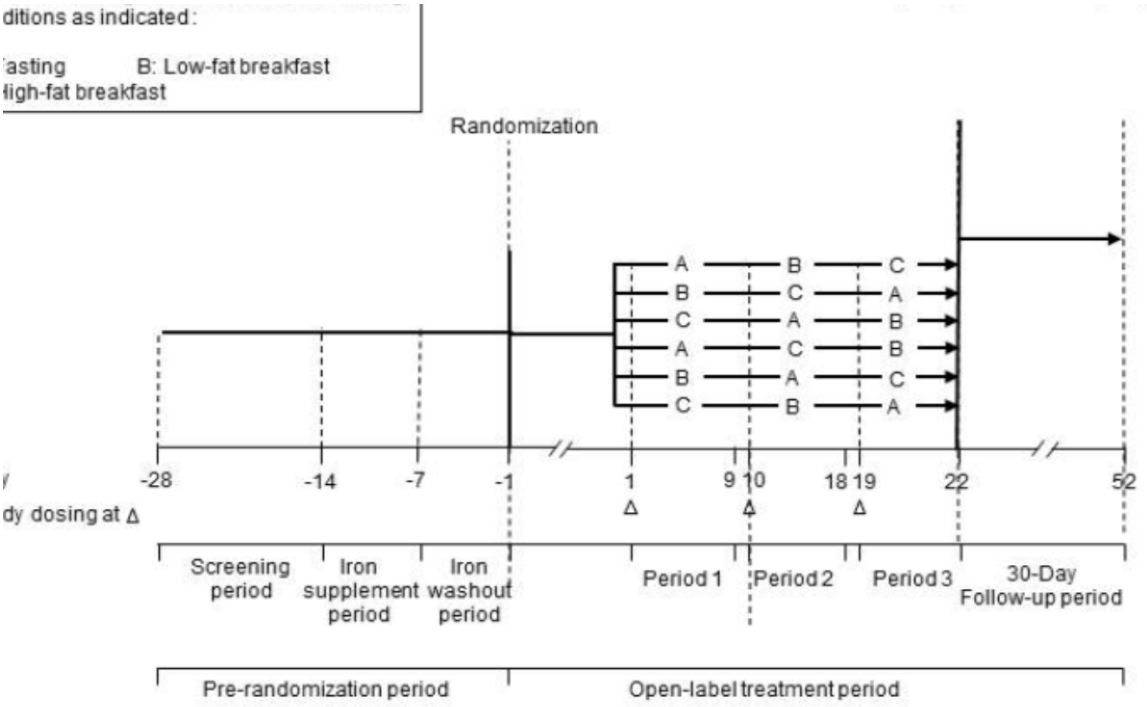
Subjects were randomly assigned to one of the six Treatment Sequences in a ratio of 1:1:1:1:1:1. Four subjects were assigned to each Treatment Sequence to ensure three evaluable subjects in each Treatment Sequence to obtain at least 18 evaluable subjects. The dosing per treatment was as follows:

• **Treatment A**: 3 x 360 mg FCTs for a total of 1080 mg, taken with a glass of water (240 mL) after overnight fasting for at least 10 hours.

• **Treatment B**: three 360 mg FCTs for a total of 1080 mg, with a glass of water (240 mL), within 30 minutes after the start of the low-fat breakfast (whole wheat English muffin, packet jelly (0.5 ounces), and fluid ounces skim milk) consisted of 6.2% fat.

• **Treatment C**: On the day of Treatment C dosing, the subjects swallowed three 360 mg FCTs for a total of 1080 mg, with a glass of water (240 mL), within 30 minutes after the start of the high-fat breakfast (eggs fried in 2 teaspoons, slices of bacon, slices white toast with one teaspoon butter, ounces hash browns fried in 2 teaspoons butter, and fluid ounces whole milk) consisted of 58.6% fat. The entire breakfast had to be consumed by the subject prior to dosing.

Figure 8. F2103 Study design.



A total of 28 subjects were randomized and included in Safety Set. Of these 28 subjects, 25 received at least one dose of deferasirox, and 24 subjects completed both end of treatment and end of study visit and included in Pharmacokinetic Analysis Set.

Plasma deferasirox concentrations were determined on Days 1 through 4, 10 to 13 and 19 to 22 of Treatment Periods 1, 2 and 3 at the following time points: 0 (pre-dose) and at 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, and 72 hours post-dose.

Subjects who completed at least one period with test treatment (i.e. Single dose of 1080 mg deferasirox (3 x 360 mg film-coated tablets) under fasted conditions) and a period with reference treatment (i.e. under fed conditions, with low-fat or high-fat breakfast) with evaluable PK data, allowing at least one comparison between the test treatment and the reference treatment were included into the statistical analysis of the PK data. Each primary PK parameter (AUClast, AUCinf and Cmax) were analyzed separately using a linear mixed effect model with log-transformed PK parameters as the dependent variable, fitting terms for treatment, sequence and period as fixed effects, and subject nested within sequence as random effect.

Results

When a single dose of deferasirox was administered within 30 minutes after a low-fat breakfast compared to fasted conditions, the extent of absorption (AUC) was comparable, whereas the peak concentration (Cmax) was reduced by 16% on average. The estimated geometric mean ratios for AUC_{last} and AUC_{inf} were 0.89 (90% CI: 0.84, 0.94) and 0.89 (90% CI: 0.84, 0.95), respectively. The estimated geometric mean ratio for Cmax was 0.84 (90% CI: 0.77, 0.90). When a single dose of deferasirox administered within 30 minutes after a high-fat breakfast compared to fasted conditions, the overall food effect on the extent of absorption was an increase of 18% in AUC_{inf} and 29% in C_{max}. In fact, the estimated geometric mean ratios for AUC_{last} and AUC_{inf} were 1.17 (90% CI: 1.11, 1.24) and 1.18 (90% CI: 1.11, 1.25), respectively. The estimated geometric mean ratio for Cmax was 1.29

(90% CI: 1.20, 1.39). Deferasirox primary pharmacokinetic parameters and statistical analyses are shown in Table 8.

When deferasirox was administered under a fasting condition (with water), after a low-fat breakfast, and after a high-fat breakfast, the median Tmax (range) were 3 h (1.5 to 8.0 h), 4 h (3.0 to 8.0 h), and 4 h (1.5 to 8.0 h), respectively. Low-fat meal and high fat meal appeared to slightly delay the T_{max}. The elimination kinetics (lambda_z and half-life) of deferasirox were comparable across treatments. The geometric mean terminal elimination half-life (T1/2) ranged from 12.3 to 13.0 h, after administration of deferasirox under fed or fasted conditions.

Table 8. Summary of statistical analysis of primary PK parameters for plasma deferasirox.

					Treatment comparison 90% CI		
PK parameter (unit)	Treatment	n*	Adjusted geometric mean	Comparison (s)	Geometric mean ratio	Lower	Upper
AUCinf (µmol/L*hr)	A	25	1570	-	-	-	-
	B	22	1390	B/A	0.890	0.835	0.948
	C	25	1840	C/A	1.18	1.11	1.25
AUClast (µmol/L*hr)	A	25	1520	-	-	-	-
	B	24	1340	B/A	0.886	0.835	0.940
	C	25	1780	C/A	1.17	1.11	1.24
Cmax (µmol/L)	A	25	113	-	-	-	-
	B	24	94.1	B/A	0.835	0.774	0.901
	C	25	145	C/A	1.29	1.20	1.39

Model is a linear mixed model of the log transformed PK parameters with sequence, period and treatment as fixed effects, and subject nested within sequence as random effect. Results were back transformed to get adjusted geo-mean, GM ratio, and 90% CI.

Distribution

Not applicable

Elimination

Not applicable

Dose proportionality and time dependencies

Dose proportionality

Study F2104

Methods

The study was a randomized, open-label, single-center, four-period, four sequence crossover, single-dose Phase I bioavailability study comparing a deferasirox granule formulation to the commercial dispersible tablet (reference) formulation. The granule formulation (400-mg deferasirox granules in bottles) was administered at single doses of 400 mg, 800 mg (2 × 400 mg), and 1200 mg (3 × 400 mg). The reference formulation (3 x 500 mg DT for oral suspension) was administered at a single dose of 1500 mg. the second objective was to evaluate the dose-proportionality of deferasirox pharmacokinetics with the granule formulation in healthy subjects under fasted conditions.

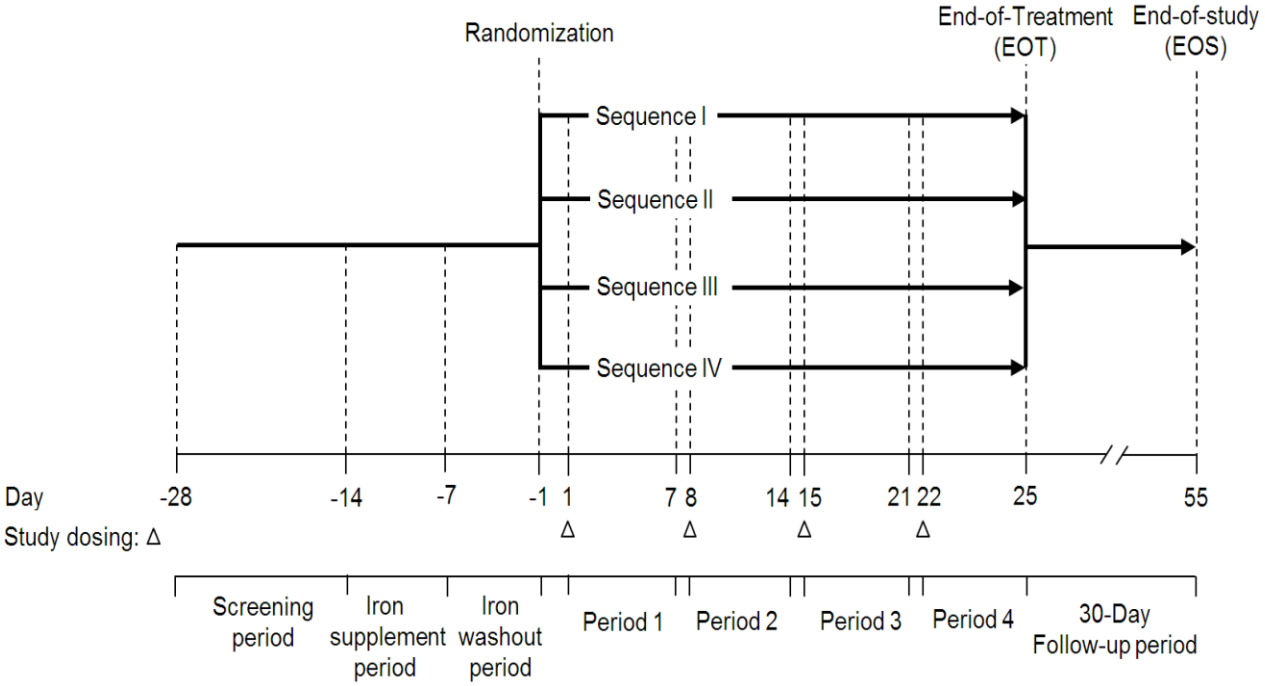
Dosing occurred on the first day of each treatment period. There was a 6-day washout between each dose.

Randomization to a treatment sequence employed a Williams Square design.

The treatment duration was 8 days of iron supplementation followed by 4 single doses of deferasirox on days 1, 8, 15 and 22: Ferrous sulfate was to be administered as supportive treatment of 325-mg oral tablet -equivalent to 65 mg elemental iron.

The sample size planned was 20 subjects to be randomized in order to get at least 16 evaluable subjects for the statistical analysis.

Figure 9. F2104 Study design.



A = Single dose of 1500 mg (3 deferasirox dispersible tablets of 500 mg)
B = Single dose of 400 mg (1 bottle with 400-mg deferasirox granules)
C = Single dose of 800 mg (2 bottles of 400-mg deferasirox granules)

D = Single dose of 1200 mg (3 bottles of 400-mg deferasirox granules)

Blood collection: 3 mL lithium-heparin blood: Days 1 to 4, Days 8 to 11, Days 15 to 18, and Days 22 to 25 at the following time points: 0 (pre-dose), 0.5 h, 1.0 h, 1.5 h, 2.0 h, 3.0 h, 4.0 h, 6.0 h, 8.0 h, 12.0h, 24.0 h, 36.0 h, 48.0 h, and 72.0 h post-dose.

Only subjects who completed at least one treatment period with the granule formulation (400-mg, 800-mg and 1200-mg) and the treatment period for the reference formulation (1500-mg DT) with evaluable PK data were included into the statistical analysis of the pharmacokinetic data. The bioavailability of three doses of the granule formulation (400 mg, 800 mg, 1200 mg) was compared to that of the commercial formulation at a dose of 1500 mg. Each dose-normalized PK parameter was analyzed separately using a linear mixed model with the dose-normalized log-transformed PK parameters as the dependent variable and fitting sequence, period and treatment as fixed effects, and subject-within sequence as random effect. Dose proportionality was examined using a power model (PK parameter=a Dose^{b} × error) for 3 granule formulation doses (400 mg, 800 mg, 1200 mg).

Results

The study was conducted between the 12th July 2012 and the 30th October 2012.

Numbers analyzed were: 39 subjects were enrolled of which 21 subjects were included in the pharmacokinetic analysis set (PAS).

As compared to the reference formulation, the bioavailability (based on dose normalized AUClast and AUCinf) of deferasirox was 7% to 8%, 20% to 21%, and 25% greater with the 400-mg granules, 800-mg granules, and 1200-mg granules treatment groups. Dose-normalized C_{max} was also increased by 65%, 62%, and 47% with the 400-mg granules, 800-mg granules, and 1200-mg granules treatment groups, respectively, as compared to the DT. This expected increase was the reason for adjusting the strength of the granule formulation.

Without dose-normalization, AUCinf and AUClast at the 1200-mg granule deferasirox treatment were equivalent to that of 1500-mg DT, although Cmax was higher by 18%. The geometric mean ratios for AUC_{inf}, AUC_{last} and C_{max} were 1.00, 1.00 and 1.18 for 1200-mg granules treatment group, respectively, when compared to the DT (reference).

Deferasirox primary pharmacokinetic parameters by treatment are listed in Table 9. Geometric mean ratio (test/reference) and its 90% confidence intervals for primary pharmacokinetic parameters are listed in Table 10.

Table 9. Primary pharmacokinetic parameters – descriptive statistics for AUC_{last}, AUC_{inf}, and C_{max} by treatment.

Primary PK derived from plasma levels	deferasirox DT N=21	deferasirox 400-mg granules N=21	deferasirox 800-mg granules N=20	deferasirox 1200-mg granules N=20
AUClast (µmol×h/L)				
Mean	1682.76	471.30	1039.28	1634.23
SD	668.915	162.149	379.119	584.537
CV (of the mean), %	39.75	34.40	36.48	35.77
Geometric mean	1551.71	447.50	984.67	1535.75
CV (of the geometric mean), %	44.34	33.44	33.73	38.15
Median	1466.98	427.10	921.03	1520.21
Range	621.1–3028.6	249.7–848.2	506.3–2201.7	704.6–2861.5
AUCinf (µmol×h/L)				
Mean	1750.16	490.80	1097.22	1711.48
SD	733.313	172.926	465.582	647.660
CV (of the mean), %	41.90	35.23	42.43	37.84
Geometric mean	1604.32	465.06	1027.38	1600.12
CV (of the geometric mean), %	45.86	34.05	36.65	39.44
Median	1483.41	444.76	943.80	1568.13
Range	635.4–3168.1	256.9–883.9	517.9–2690.0	719.5–3204.4
Cmax (µmol/L)				
Mean	96.00	44.05	80.30	110.70
SD	32.011	18.231	21.822	34.146
CV (of the mean), %	33.34	41.39	27.18	30.85
Geometric mean	91.19	40.16	77.64	105.64
CV (of the geometric mean), %	33.83	48.33	26.94	32.47
Median	89.80	43.80	76.25	111.00
Range	49.9–176.0	17.4–74.8	51.1–123.0	61.8–168.0

CV% = coefficient of variation (%) = sd/mean*100; CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100; DT = dispersible tablet (the reference single dose of 1500 mg (3 deferasirox tablets of 500 mg); SD = standard deviation

Source: Table 14.2-2.1

Table 10. Treatment comparison of dose-normalized primary pharmacokinetic variables by treatment: geometric mean ratio and 90% CI.

PK variable (unit)	Deferasirox treatment	Adjusted geometric mean	Geometric mean ratio (90% CI)*	
AUClast (µmol×h/L)	1500-mg DT	1.04		
	400-mg granules	1.12	1.08	(0.988–1.182)
	800-mg granules	1.25	1.21	(1.101–1.321)
	1200-mg granules	1.30	1.25	(1.144–1.373)
AUCinf (µmol×h/L)	1500-mg DT	1.09		
	400-mg granules	1.16	1.07	(0.977–1.176)
	800-mg granules	1.30	1.20	(1.092–1.319)
	1200-mg granules	1.35	1.25	(1.134–1.369)
Cmax (µmol/L)	1500-mg DT	0.06		
	400-mg granules	0.10	1.65	(1.474–1.851)
	800-mg granules	0.10	1.62	(1.447–1.823)
	1200-mg granules	0.09	1.47	(1.313–1.654)

The analysis of dose proportionality of PK parameters after a single dose of granule deferasirox formulation (400, 800 and 1200 mg in healthy subjects is summarized in Table 11.

Following a single dose of granule deferasirox (400, 800, and 1200 mg), AUC and Cmax values increased with increasing doses of deferasirox granules. The estimated proportionality coefficients (beta) for AUClast, AUCinf and Cmax were 1.13 (90% CI 1.07, 1.19), 1.13 (90% CI 1.07, 1.20) and 0.90 (90% CI 0.79, 1.01), respectively. Despite the study was not powered to assess dose-proportionality, the 90% CI for the slope for AUClast and AUCinf after a single dose of granule deferasirox (400, 800, and 1200 mg) was within the target region of 0.80-1.20. For Cmax, the lower bound (0.79) of the 90% CI was slightly below the pre-defined interval. Thus, AUC was considered to increase dose proportionally across the three dose levels and Cmax was considered approximately dose-proportional between 400 and 1200-mg single doses tested in healthy subjects.

Table 11. Overview of dose proportionality analysis

PK variable (unit)	Dose range (mg)	Estimate of the beta	(90% CI (lower - upper)*
AUClast (µmol×h/L)	400 to 1200	1.13	(1.068–1.194)
AUCinf (µmol×h/L)	400 to 1200	1.13	(1.070–1.198)
Cmax (µmol/L)	400 to 1200	0.90	(0.794–1.012)

Results were based on the power model: ln (PK parameter) = ln(a) + beta*ln(Dose) + error.
* The 90% CI for the slope is to be within the target region of [0.80–1.20] to conclude dose-proportionality for a dose range of 400 mg to 1200 mg.

Time dependency

Not applicable. Pharmacokinetics after repeated doses of the FCT has not been investigated.

Intra- and inter-individual variability

Not applicable

Pharmacokinetics in target population

No new dedicated clinical Pharmacology studies with deferasirox FCT were conducted in the target patient population.

Special populations

No additional studies on special populations were submitted.

Pharmacokinetic interaction studies

N/A

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

N/A

Primary and Secondary pharmacology

N/A

Relationship between plasma concentration and effect

To investigate the expected clinical impact of increased C_{max} observed with the FCT and the granules on either efficacy or safety, a retrospective exposure-response analysis [A2409 PK/PD analysis] was conducted on a large clinical trial database. The data were from study A2409 (efficacy and safety study over 52 weeks) which included 1744 patients diagnosed with transfusion dependent iron overload who received one year deferasirox treatment.

Patient Population

The target patient pool consisted of patients with a serum ferritin level of ≥ 1000 ng/mL or patients presenting with a serum ferritin level <1000 ng/mL but with history of multiple transfusions (>20 transfusions or 100 mL/kg of packed red blood cells) and LIC >2 mg Fe/g dry weight.

deferasirox doses

The initial recommended daily dose of deferasirox DT was 20 mg/kg/day body weight for patients, who had received blood transfusions with a frequency of about 2 to 4 units/month of packed red blood cells. An initial daily dose of 10 mg/kg/day or 30 mg/kg/day was permitted for patients receiving less or more frequent blood transfusions, respectively. Average daily dose for all patients was 22.22 mg/kg (SD: 5.921), with the majority of these patients having no dose interruptions (77.6%), or only one dose interruption (15.1%).

Efficacy parameter

Change in serum ferritin from baseline was the defined primary endpoint of the study. It was collected at Baseline (Week 1 Day 1) and at Week 12 and Week 28.

Safety parameters

- Approximately one third of β-thalassemia patients treated with deferasirox had ≥ 2 consecutive dose-dependent increases in serum creatinine that were >33% above baseline mostly within the normal range. Since, the effect of deferasirox on renal laboratory values is well documented, renal laboratory parameters (serum creatinine and creatinine clearance) were the safety parameters used in this analysis.

These parameters were collected at Baseline and Week 4, Week 12 and Week 28.

Creatinine clearance was calculated from the laboratory reported values of serum creatinine using Cockroft-Gault formula for adults and Schwarz's formula for pediatric (<16 years) patients.

- Other laboratory parameters such as liver function tests (ALT) did not show any relationship to exposure, in exploratory analyses.

Pharmacokinetic data

PK data were collected in a large sub-group of patients (N = 1112) at pre-dose (Ctrough) and 2 hr post-dose (C2h) on Visit 3 (Day 1), Visit 6 (Week 12) and Visit 10 (Week 28) and EOS. Blood collection for PK analysis was only performed in patients who had been on deferasirox treatment without dose adjustment or treatment interruption for at least 4 days prior to scheduled PK sampling.

The plasma concentration-time profile that yields AUC in the steady state includes Ctrough, which is highly associated with AUC. Thus, Ctrough,ss at Week 12 and Week 28 are considered as surrogate markers for AUC. Similarly, steady state concentrations collected at 2 hr post-dose (C2h,ss at Week 12 and Week 28) are used as a surrogate marker for Cmax.

Concentrations at 2 h post dose are within the range of deferasirox Cmax, which is achieved between 1.5 to 4.3 h in patients for the dose range of 5-30 mg/kg in various studies.

The PK/PD analyses in this report use C2h collected on Day 1, and Ctrough,ss and C2h,ss collected on both Week 12 and Week 28. Analyses were performed on the parent compound deferasirox. Data from iron complex were not included in the statistical analysis.

Objectives

The analysis focused on investigating the relationship between PK parameters (C2h and Ctrough) and 1) renal laboratory changes (serum creatinine and creatinine clearance), and 2) the efficacy parameter (serum ferritin).

Results

The pharmacokinetic-pharmacodynamics relationship for deferasirox has been evaluated using a large clinical trial in the target population (n= 1112). Efficacy (serum ferritin change from baseline) and safety (serum creatinine and creatinine clearance change from baseline) endpoints could be acceptable as valid indicators of deferasirox treatment. Similarly, for PK parameters, it's acceptable that pre-dose or trough concentrations at steady state (Ctrough,ss at Week 12 and Week 28) were used as a surrogate marker for AUC and concentrations collected at 2 hours (C2h at Day 1, C2h,ss at Week 12 and Week 28) were used as a surrogate for C_{max}.

In this study patients received the EXJADE dispersible tablets and not the new formulation (FCT). Nevertheless, since the PK/PD relationship is driven by the active substance and not the pharmaceutical form, conclusions from the provided analyses are expected to be also valid for the FCT formulation.

A covariate analysis using a proportional odds model was performed to determine the relative impact of each PK parameter on renal function. Specifically, the probability of worsening in renal function was estimated with a proportional odds model including exposure and C_{max} as potential explanatory variables. The analysis showed that Ctrough had a strong impact on creatinine clearance change in categories ($p<0.0001$) but C2h,ss had minimal impact ($p=0.2544$) after adjusting for Ctrough,ss. Furthermore, a C2h,ss increase by 1.7-fold would provide an odds ratio of worsening from baseline in creatinine clearance categories of 1.146 (0.906, 1.449).

The relationship between PK parameters at steady state (Ctrough,ss and C2h,ss) and efficacy (as described by serum ferritin) was further investigated by using a linear mixed model of log-transformed serum ferritin values (using observations at week 12 and 28) with patient included in model as a random effect.
After log-transformation, baseline creatinine levels, C2h,ss and Ctrough,ss were included as predictors in the model. As shown in Table 12, the results of this analysis showed that at steady state, Ctrough has a statistically significant impact ($p<0.001$) on the changes in serum ferritin while C2h has no statistically significant impact ($p=0.130$). In particular, after adjusting for Ctrough,ss, an increase in C2h,ss by 70% would lead to a change of -1.28 % (90% CI: - 2.65%, 0.12%) in the percent change from baseline in serum ferritin.

Table 12. Analysis of serum ferritin values versus steady state PK parameters –Week 12 and Week 28 (Safety set)

Parameter	Estimate	Standard error	T value	Pr >|t|	Lower 90% CI	Upper 90% CI
log (baseline ferritin)	0.89	0.02	55.70	<0.001	0.86	0.91
log (C2h,ss)	-0.02	0.02	-1.51	0.130	-0.05	0.00
log (Ctrough,ss)	-0.07	0.01	-6.68	<0.001	-0.08	-0.05

Pr: probability; T: T-test value

A similar conclusion could be drawn regarding the relationship of AUC and C_{max} to efficacy (serum ferritin change from baseline). A log-linear mixed model was used with AUC and Cmax as covariates in an attempt to distinguish between the two PK parameters. At steady state, Ctrough has a statistically significant impact ($p<0.001$) on the changes in serum ferritin while C2h has no statistically significant impact ($p=0.130$). In particular, after adjusting for Ctrough,ss, an increase in C2h,ss by 70% would lead to a change of -1.28% (90% CI: -2.65%, 0.12%) in the percent change from baseline in serum ferritin which is clinically insignificant.

Based on these results, it is agreed that higher C_{max} in patients with a same or similar AUC will not result in clinically significant changes in renal laboratory values or serum ferritin changes from baseline, as AUC is the key parameter for assessing deferasirox safety and efficacy. Therefore, the observed differences (mean increase of 30%) in C_{max} between the DT and the FCT are not expected to be clinically relevant.

2.4.4. Discussion on clinical pharmacology

Deferasirox is available in the EU as a dispersible tablet (DT) for once daily administration at strengths of 125 mg, 250mg and 500 mg. The pharmacokinetics of deferasirox has been well characterized in healthy volunteers and in iron-overloaded patients.

The new FCT formulation has been developed as equivalent formulation to the DT. Based on the improved bioavailability of the FCT, three strengths of the FCT as 90 mg, 180 mg and 360 mg (which are compositionally proportional) were developed based on dose-adjusted approach and PK comparability to the approved dispersible tablet formulation.

The MAH submitted four clinical pharmacology studies in healthy subjects. Methodology used is adequate and in compliance with acceptance selectivity and sensitivity criteria. Pharmacokinetic parameters such as AUCinf, AUClast, Cmax, T1/2 and Tmax of deferasirox in plasma were estimated using non-compartmental analysis in line with current guidelines by a linear mixed effects model. In all pharmacokinetic studies, the amount of drug used was selected to be approximately equivalent to the clinically relevant recommended starting dose of 20 mg/kg of the dispersible tablet. The dose of 1080 mg used for the FCT formulation is estimated to be in the range of 15-25 mg/kg of the dispersible tablet formulation. The design, number of subjects, strengths and dosing used is acceptable. The washout period (between 6 to 9 days depending on study) is considered adequate (with expected half-life for deferasirox between 8 and 16h) to allow the complete elimination of the drug before subsequent dosing and to minimize the possibility of a carry-over effect.

EXJADE film-coated tablets demonstrate higher bioavailability compared to the EXJADE dispersible tablet formulation. After adjustment of the strength, the film-coated tablet formulation (360 mg strength) was equivalent to EXJADE dispersible tablets (500 mg strength) with respect to the mean area under the plasma concentration time curve (AUC) under fasting conditions. The C_{max} was increased by 30% (90% CI: 20.3% - 40.0%). However a clinical exposure/response analysis revealed no evidence of clinically relevant effects of such an increase.

Deferasirox (dispersible tablet formulation) is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox (dispersible tablet formulation) is about 70% compared to an intravenous dose. The absolute bioavailability of the film-coated tablet formulation has not been determined. Bioavailability of deferasirox film-coated tablets was 36% greater than that with dispersible tablets. (See SmPC section 5.2.) The PK exposure (AUC and Cmax) of the new oral FCT was found to exhibit less variability, compared with that observed with the DT. Inter-subject variability (CV%) with FCT and DT were 44% vs. 49% for AUC and 28% vs. 32% for Cmax, respectively.

Based on the improved bioavailability of the FCT observed in the pilot study, a dose-adjusted approach was taken in study F2102 (pivotal PK comparability study). The study followed a two-period randomized cross-over design in 32 healthy subjects, and compares the relative bioavailability of the highest dose strength of deferasirox (360 mg) FCT at 1080 mg dose and the marketed DT (500 mg) at 1500 mg dose under fasted conditions, in accordance with EMA CHMP guidance (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr 2010). The bioavailability (AUClast and AUCinf) of two formulations (1080 mg FCT and 1500 mg DT) were equivalent based on the reference bioequivalence criteria of 80-125%, with geometric mean ratios of 1.00 (90% CI: 0.932- 1.078) and 0.98 (0.916-1.059), respectively. However, the peak concentration of the FCT was 30% higher, with Cmax averaging 105.83 µmol/L vs. Cmax averaging 81.54 µmol/L for the DT.

Study F2103 (food effect study) compared pharmacokinetics of deferasirox FCT (3 x 360 mg) under both fed (immediately after a high fat or a low fat breakfast) and fasted conditions in 25 healthy subjects. The results indicated that AUCs was increased by 18% (90% CI: 1.11, 1.25) and the Cmax by 29% (90% CI: 1.20, 1.39) when the new FCT formulation of deferasirox was taken after a high-fat meal. Whereas, AUC was reduced in average by 11% (90% CI meet the bioequivalence criteria 80-125%) and the Cmax was reduced by 16% (90% CI: 0.77, 0.90), when deferasirox was taken with

low-fat meal. Deferasirox absorption was slightly prolonged with a median Tmax being from 3 to 4 hours. Otherwise the corresponding elimination half-life under fed conditions was similar to that under fasting conditions. Overall, systemic availability of the new FCT formulation deferasirox under fed conditions was only slightly modified and so the food effect is not expected to be clinically relevant. However, taking into account the difference in Cmax under fasted conditions between the formulations, i.e. Cmax with the FCT is 30% higher than with the DT, it is not recommended to take the FCT with a high-fat meal due to potential additive effect.

In summary the food-effect study involving administration of the film-coated tablets to healthy volunteers under fasting conditions and with a low-fat (fat content <10% of calories) or high-fat (fat content >50% of calories) meal indicated that the AUC and C_{max} were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and C_{max} were increased (by 18% and 29%, respectively). The increases in C_{max} due to the change in formulation and due to the effect of a high-fat meal may be additive and therefore, it is recommended that the film-coated tablets should be taken either on an empty stomach or with a light meal. The information is reflected in the SmPC sections 5.2.

The dose-proportionality of deferasirox PK has been characterized in study F2104. The study was conducted on 21 healthy subjects and using the granule formulation. Following a single dose of granule deferasirox, the increase in mean deferasirox exposure (AUC), and peak concentration (Cmax) is dose proportional in the dose range of 400 to 1200 mg. Indeed, the estimated proportionality coefficients (beta) and the 90% confidence interval for AUClast 1.13 (90% CI 1.07, 1.19), AUCinf 1.13 (90% CI 1.07, 1.20) and Cmax 0.90 (90% CI 0.79, 1.01) were within the target region of 0.80 - 1.20. Consequently, pharmacokinetics of the FCT is expected to be dose-proportional since basic PK characteristics are considered same or similar between the granules and the FCT given that the composition is identical except that the granules are uncoated.

An additional PK/PD analysis [Study A2409] included in this submission used a statistical model to assess the influence of Cmax and other PK parameters on efficacy and safety. The pharmacokinetic-pharmacodynamics relationship for deferasirox has been evaluated using a large clinical trial in the target population (n= 1112). Efficacy (serum ferritin change from baseline) and safety (serum creatinine and creatinine clearance change from baseline) endpoints are acceptable as valid indicators of deferasirox treatment. Similarly, for PK parameters, it is considered acceptable that pre-dose or trough concentrations at steady state (Ctrough,ss at Week 12 and Week 28) were used as a surrogate marker for AUC and concentrations collected at 2 hours (C2h at Day 1, C2h,ss at Week 12 and Week 28) were used as a surrogate for C_{max}. These results support the notion that total drug exposure, AUC, is the key parameter predicting safety and efficacy of deferasirox. The available safety and efficacy and exposure data for deferasirox across age groups support the conclusion that a modest increase in C_{max} is not clinically meaningful; total drug exposure, AUC, is the key parameter predicting safety and efficacy of deferasirox.

2.4.5. Conclusions on clinical pharmacology

Clinical pharmacology data available support the comparability of the two formulations. Relevant information has been included in the SmPC.

Results concerning the consequences of the higher C_{max} of the new formulation are reassuring. However these need to be considered in the light of clinical efficacy and safety data (see later sections).

2.5. Clinical efficacy

No data on clinical efficacy were submitted.

2.5.1. Discussion on clinical efficacy

This application cross-refers to the existing efficacy data generated with the dispersible tablet formulation for which pharmacology data on bioavailability and comparability are discussed under the clinical pharmacology section.

Iron chelation is a physicochemical process, and the dose-dependent efficacy of chelation therapy has been previously demonstrated for deferasirox as well as for other chelators such as deferoxamine.

Following the pharmacology data available showing higher bioavailability of the film-coated tablet as compared to the current formulation when switching from dispersible tablets to film-coated tablets, the dose of the film-coated tablets should be 30% lower than the dose of the dispersible tablets, rounded to the nearest whole tablet; therefore the starting dose for film-coated tablets should usually be 14 mg/kg/day. Starting doses of 7 or 21 mg/kg can also be used, depending on the frequency of the patient's transfusions. Adjustment steps are 3.5 - 7 mg/kg and a maximum dose 28 mg/kg/day (See section 4.2 of the SmPC).

Based on the results from PK/PD analysis (Study A2409) using a statistical model to assess the influence of Cmax and other PK parameters on efficacy, the moderately higher C_{max} values (30% increase) observed with the new film-coated tablet formulation are not expected to be clinically relevant and efficacy of the new dosage form are expected to be comparable to the current dispersible tablet (See Clinical Pharmacology section).
Over the years, the MAH has received reports on certain features of the current deferasirox formulation being undesirable with a potential impact on compliance. Indeed, the chalky texture of the dispersion is described as unpalatable, and this is compounded by the volume that must be consumed (100-250 mL), and the fact that it must be taken on an empty stomach. This is especially true for young children where the features of the drug are reported to reduce adherence to treatment. Novartis developed the film-coated tablet deferasirox formulation in order to improve palatability and convenience of the drug, and potentially improve adherence to treatment. Results from Study CICL670F2201 are expected to bring more information on the benefits of the new deferasirox formulation (film-coated tablet) in comparison to the commercially approved dispersible tablet (See RMP).

2.5.2. Conclusions on the clinical efficacy

The available data on clinical pharmacology support cross reference of clinical efficacy to the original submission.

The CHMP considers the following measures necessary to address issues related to efficacy:

- The MAH shall submit the results of a Phase II safety study investigating the benefits of the new deferasirox formulation (film-coated tablet) in comparison to the commercially approved dispersible tablet: final study report due September 2016.

2.6. Clinical safety

Patient exposure

The overall exposure in the four clinical pharmacology studies is summarized in the table below.

In Study F2104, one subject missed the 800 mg and 1200 mg doses of granules due to a protocol deviation.

Table 13: Overall exposure in the clinical pharmacology studies

Table 1-2 Overall exposure in the clinical pharmacology studies

Study	Number of subjects	Dosage
F2101	19	4 doses of 1500 mg deferasirox (dispersible tablet and three swallowable tablet variants)
F2102	32	1 dose of 1080 mg FCT, 1 dose of 1500 mg DT
F2103	24	3 doses of 1080 mg FCT
F2104	20	1 dose of 400 mg granules, 1 dose of 800 mg granules, 1 dose of 1200 mg granules, 1 dose of 1500 mg DT

Source: Individual CSRs of PK studies

Adverse events

In subjects receiving FCT, the most commonly adverse events were diarrhoea, dyspepsia and headache. These events were described as common with the dispersible tablets.

In study F2102 most TEAE were mild. 2 subjects had TEAEs moderate in severity. One event of headache and one of dizziness were considered moderate in intensity in patients treated with FCT.

In study 2103, the majority of TEAEs were mild in nature, except the AE vomiting which was moderate.

No grade 3-4 adverse events were observed in healthy volunteers taking the FCT.

The MAH provided interim results of a confirmatory clinical safety (study F2201). Study ICL670F2201 is an open-label, randomized, multicenter, two arm, Phase II study in male and female patients aged ≥ 10 years with transfusion-dependent thalassemia and myelodysplastic syndrome (MDS). The randomization is stratified by prior deferasirox treatment and by underlying disease. The study has a treatment duration of 24 weeks. Overall safety is the primary objective of this study and will be addressed by measuring the frequency and severity of adverse events (AEs) and changes in laboratory values, of deferasirox film coated tablet (FCT) and deferasirox dispersible tablet (DT). In addition, safety is also addressed by assessing adverse events of special interest (AESI) including selected gastrointestinal AEs of diarrhea, constipation, nausea, vomiting, and abdominal pain.

In order to assess longer term safety over multiple months, the data cut off was set to include any patient who completed at least 3 months on treatment by the interim cut-off date (25-Mar-2015) and/or at least one Week 13 safety assessment performed by the cut-off date.

At the time of the interim data cut-off, 65 of 173 patients were enrolled in the study (DT: 32 patients; FCT: 33 patients). Of these patients, 15 patients in each arm had completed at least 3 months of treatment and were included in the interim analysis.

As expected, gastrointestinal AEs were the most frequent AEs observed in this study. The number of patients experiencing GI AEs was similar in both arms.

These events are not reported more frequently in the new formulation of FCT than in patients on DT in this interim analysis data set. It can also be acknowledged that the selected GI AEs was numerically lower in the FCT arm than in the DT arm.

As regard drug-related AEs, increased urine protein/creatinine ratio have been noted in both formulations. As regard severe AEs, two patients in the DT group experienced SAEs (dehydration, renal impairment, and viral infection) whereas no patient in the FCT group.

The safety profile of FCT when the tablet is crushed deserved to be discussed.

FCT would allow patients who have difficulty in swallowing whole tablets, to take crushed tablets with soft food such as apple sauce and yogurt. However, Novartis did not collect any clinical data on the tolerability of the crushed tablet.

Data on the GI tolerability of the crushed FCT formulation, particularly in the youngest population are to be provided.

Serious adverse event / deaths / other significant events

One patient in the FCT group experienced severe gastro-intestinal AE (abdominal pain).

No deaths occurring within 30 days of the last dose were reported in the pharmacokinetic studies with FCT.

No deaths occurring within 3 months of study F2201 were reported in interim report.

Laboratory findings

No data.

Safety in special populations

The safety profile of two paediatric patients treated with FCT looks comparable to the known safety profile of deferasirox DT.

Safety related to drug-drug interactions and other interactions

No new data submitted.

Discontinuation due to adverse events

No dose interruptions due to AE were observed in the FCT arm of in the Interim report of study F2201.

Post marketing experience

In the USA, deferasirox FCT were approved by the FDA on 30 March 2015 under the invented name Jadenu and launched on 1st April 2015. Between April and September, approximately 60% of patients (1,820 patients) had switched from dispersible tablets (DT) to FCT and about 1,180 patients were prescribed FCT.

On 22 October 2015, a Supplemental New Drug Application (sNDA) was approved by the FDA for the addition of crushing instructions to the US Prescribing Information. Due to the very recent sNDA approval, only very few patients are expected to have received crushed FCT. Nevertheless, a review was performed on the data retrieved from the Novartis safety database for the period 01.11.2014 to 31.10.15, corresponding to the latest Periodic Safety Update Report. Outputs for identified and

potential risks (renal disorders, gastrointestinal haemorrhage and ulceration, hearing loss, increased transaminases/hepatitis/hepatic failure, lens opacities, Stevens-Johnson syndrome, other severe skin reactions, peripheral blood cytopenias) were reviewed, as well as outputs for medication errors, for paediatric cases of the ages 2-6 years and for the entire System Organ Class Gastrointestinal Disorders. These outputs were searched to identify cases coded for crushed film-coated deferasirox tablets or for cases coded for Jadenu which were reviewed for information regarding crushing of film-coated tablets. No cases were identified.

2.6.1. Discussion on clinical safety

The submission was based on exposure data from studies conducted in 60 healthy volunteers where subjects in phase I studies received only 1 to 3 doses of 1080 mg of FCT and no exposure data in a long term is available. Moreover, deferasirox is often used in children whereas healthy volunteers are adult patients.

Only results of studies F2102 and F2103 have an informative value on the comparison of the two formulations therefore, confirmatory clinical safety results have been requested in patients receiving FCT during several months (study F2201). In the interim report, there is no apparent new safety signal emerging from limited data on comparison of the 2 formulations from this study, however the number of patients for whom the clinical data are exploitable and particularly the number of patients <18 years of age (DT: 5 patients; FCT: 2 patients), is too low for any conclusion to be made.

No grade 3-4 adverse events were observed in healthy volunteers taking the FCT. However, such data are insufficient to draw reliable conclusions on the safety profile of this new formulation in patients. Supplementary data are needed and more specifically, a special attention should be taken to the renal safety of FCT (both in a short and long term).

It was noted that even in healthy volunteers treated with one to three doses of deferasirox, gastrointestinal side effects have been observed with the new formulation. Therefore the film coated tablet could not be associated with a better gastro-intestinal tolerability at this stage of the assessment. In addition further data have been requested in terms of tolerability of the crushed formulation in view of the side effects already observed with the dispersible tablet (oesophagitis, stomatitis and mouth ulceration, gastric ulcers and haemorrhage).
As expected, gastrointestinal AEs are the most frequent AEs observed, and the number of patients experiencing GI AEs was similar in both arms. It can also be acknowledged that the selected GI AEs was numerically lower in the FCT arm than in the DT arm but due to the small sample set it cannot be stated that the GI tolerability is better for the FCT than the DT. Therefore an improved gastro-intestinal tolerability of the film coated tablet cannot be claimed since more definitive data need to be provided by the final study report planned to be submitted post-approval.

As regard drug-related AEs, increased urine protein/creatinine ratio, have been noted in both formulations. Renal disorders have already been identified as important risk in the RMP. The applicant plans to submit the final CSR of study F2201 in September 2016 (see RMP and annex II). This additional PV activity has been added to characterize the safety of this new formulation (FCT) as missing information (See RMP).

Although no conclusion can be drawn due to the low number of patients for whom the clinical data are exploitable and particularly the number of patients <18 years of age (DT: 5 patients; FCT: 2 patients), the safety profiles of patients treated with deferasirox FCT and deferasirox DT look comparable.

There is no apparent new safety signal emerging from these limited data.

Regarding the GI tolerability of the crushed FCT formulation, no data exist on the tolerability of the crushed formulation particularly used in the youngest population. Novartis provided a review of data from their safety database corresponding to the period covered by the latest PSUR (01.11.2014 to 31.10.15). No cases were identified by the MAH in which the FCT were reported to have been crushed for patient administration during this period. However, addition of FCT crushing instructions were only approved by the FDA on 22nd October 2015, therefore this way of administration is not covered by the report.

After reviewing these first data since the recent launch in the US, no safety signal seems to emerge regarding the use of crushed FCT but these preliminary observations were based on limited data and cannot totally rule out the remaining uncertainties with crushed tablet (especially in youngest patients). In order to document the safety profile of crushed formulation especially in the youngest population, the MAH is therefore asked to document the safety profile in patients taking the crushed FCT formulation from reports obtained in the post-marketing setting particularly for children < 10 years. (See RMP).

In addition, the applicant has taken advantage of the on-going amendment of the PASS protocol EMEA/H/C/PSP/0010.4.A.1 aiming at *assessing the safety of deferasirox in the treatment of pediatric patients with nontransfusion-dependent iron overload,* to provide relevant safety data of the FCT formulation for the pediatric population (between 10-17 years-old).

The safety in the youngest children (particularly <6 yrs) is not known (missing information – see RMP), for the new formulation (FCT) especially when the tablets are crushed. Therefore, the MAH proposed an additional PV activity to characterise the paediatric safety profile.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been assessed and relevant information included in the Summary of Product Characteristics (See SmPC section 4.4, 4.8.)

2.6.2. Conclusions on the clinical safety

The safety profile of the film coated tabled is in line with the already known characteristics of the currently approved formulation.

The CHMP considers the following measures necessary to address issues related to safety (See Annex II):

- The MAH shall conduct an observational cohort study in paediatric non-transfusion-dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate, in order to assess the long-term exposure and safety of deferasirox dispersible and film-coated tablets, based on a CHMP-agreed protocol; final study report due June 2021.
- The MAH shall conduct a study to assess the safety of deferasirox film-coated tablets in the paediatric population (especially when the tablets are crushed); final study report due June 2021.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.2 is acceptable. PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 10.2 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome]) Increased liver transaminases Gastrointestinal haemorrhage and ulcers; esophagitis Hearing loss Lens opacities, retinal changes and optic neuritis Stevens-Johnson syndrome Interaction with food Interaction with aluminium-containing antacids Induction of CYP3A4 Inhibition of CYP1A2 UGT inducers Inhibition of CYP2C8 Interaction with cholestyramine
Important potential risks	Hepatic failure Peripheral blood cytopenias Compliance with posology and biological monitoring Medication errors Severe cutaneous adverse reactions (TEN and DRESS)
Missing information	Long term safety in paediatric patients aged 2 to less than 6 years of age Long term safety in paediatric NTDT patients aged 10 to 17 years Safety in pregnant women Safety of FCT formulation

Pharmacovigilance plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status(planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Study CICL670A2301 (non-interventional, 3) International sentinel site surveillance of patients with transfusional	Evaluate the long-term safety of deferasirox treatment in adult and paediatric patients' ≥ 2 years old with chronic transfusional iron overload in actual practice setting.	Increased serum creatinine, increased liver transaminases, long term safety in paediatric patients aged 2 to less than 6 years of age.	Ongoing	Jun-2016 (final report)

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status(planned, started)	Date for submission of interim or final reports (planned or actual)
hemosiderosis treated with deferasirox in actual practice setting.				
Study CICL670A2426 (non-interventional, 3) Prescription Event Monitoring (PEM) study.	To examine the safety and use of deferasirox prescribed in general practice in England for the treatment of chronic iron overload due to frequent blood transfusions.	Increased serum creatinine, increased liver transaminases.	Ongoing	Jun-2015 (final report)
Study CICL670AFR01T (non-interventional, 3) Follow-up study under real conditions of treatment on patients treated with EXJADE (ESCAPADE Study)	Real life study of patients treated with deferasirox for post-transfusional hemosiderosis.	Increased serum creatinine, increased liver transaminases.	Ongoing	Jun-2015 (5-year study; final report)
Study CICL670A2411 (non-interventional, 3) A 5-year observational study (registry) of children aged 2 to less than 6 years at enrolment with transfusional hemosiderosis treated with deferasirox.	To evaluate the long-term safety of deferasirox in an unselected population of paediatric patients aged 2 to less than 6 years of age at enrolment with chronic iron overload related to blood transfusions used in the treatment of transfusion-dependent anaemias.	Hearing loss, lens opacities, retinal changes, and optic neuritis, Long term safety in paediatric patients aged 2 to less than 6 years with transfusional iron overload.	Ongoing	Feb-2016

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status(planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Study CICL670A2425 (non-interventional, 3) Physician and patient survey to assess awareness of appropriate dosing and biological monitoring.	To assess awareness of appropriate dosing and biological monitoring	Compliance with posology and biological monitoring	~~Proposal submitted to CHMP Jul 2013~~ Started	Jun-2015
Study CICL670E2422 (non-interventional, 1) An observational, multicenter study to evaluate the safety of deferasirox in the treatment of pediatric patients with nontransfusion-dependent iron overload.	To evaluate long term safety of deferasirox DT and FCT in pediatric NTDT patients aged 10 to 17 years-old.	Long term safety in paediatric NTDT patients aged 10 to 17 years-old and safety of FCT formulation.	~~Planned~~ Started	Planned final CSR: Jun-2021 (Annual progress reports)
Study CICL670F2201 (interventional, 1) A randomized, openlabel, multicenter, two arm, Phase II study to investigate the benefits of the –new deferasirox formulation (film-	Safety study to investigate the benefits of the new deferasirox formulation (film-coated tablet) in comparison to the commercially approved dispersible tablet (EXJADE)	This study is key to benefit risk Safety of FCT formulation	Started	Planned final CSR September-2016

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status(planned, started)	Date for submission of interim or final reports (planned or actual)
coated tablet)				
Physician survey to assess the awareness and appropriate use of both formulations. (non-interventional, 3) This survey aims to recruit overall a sample of prescribers from five countries: France, Germany, Italy, Spain, and United Kingdom.	To assess the awareness and appropriate use of both formulations	Medication errors	Planned	Eighteen months after the last launch in participating countries
A PASS study to assess the safety of deferasirox film-coated tablets in the paediatric population (1)	To obtain additional data on the safety profile of FCT formulation, especially when the tablets are crushed, and to further characterize the pediatric safety profile.	Safety of FCT formulation	Planned	Protocol submission: Q3 2016 Final study report : Jun-2021

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional pharmacovigilance activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified risks		
Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders, [acquired Fanconi's syndrome])	This item is appropriately communicated through current labelling: SmPC Section 4.2 Posology and method of administration, 4.3 Contraindications, and 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Increased liver transaminases	This item is appropriately communicated through current labelling: SmPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Gastrointestinal hemorrhage, ulcers, and esophagitis	This item is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and precautions for use, and 4.5 Interaction with other medicinal products and other forms of interaction. Relevant terms are included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Hearing loss	This item is appropriately communicated through current labelling: SmPC Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in SmPC	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.8 Undesirable effects.	
Lens opacities, retinal changes, and optic neuritis	This item is appropriately communicated through current labelling: SmPC Section 4.4 Special warnings and precautions for use, 5.3 Preclinical safety data. Relevant terms are included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Stevens-Johnson syndrome	This item is appropriately communicated through current labelling: SmPC Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Important Potential risks		
Hepatic failure	This item is appropriately communicated through current labelling: SmPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Peripheral blood cytopenias	This item is appropriately communicated through current labelling: SmPC Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Compliance with posology and biological monitoring	SmPC Section 4.2 Posology and method of administration and 4.4 Special warnings and	Educational materials for physicians and patients regardless of the indication.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	precautions for use.	
Medication errors	SmPC Section 4.2 Posology and method of administration	Educational materials for physicians and patients for both formulations and all indications, desribing the deferasirox new formulation and appropriate dosing. Introduction notification letter to pharmacists explaining the switch between formulations. Introduction notification letter to prescribers which includes a prescriber´s guide and a patient´s guide. A specific letter to prescribers and pharmacists regarding the timelines for stopping supply of EXJADE dispersible tablet on the respective local markets across EU.
Severe cutaneous adverse reactions (TEN and DRESS)	This item severe skin reactions including TEN and DRESS is communicated through labelling SmPC section 4.4 Special warnings and precautions for use.	None
Identified interactions		
Interaction with food	This item is appropriately communicated through current labelling: SmPC Sections 4.2 Posology and method of administration, 4.5 Interaction with other medicinal products and other forms of interaction and 5.2 Pharmacokinetic properties.	None
Interaction with aluminum-containing antacids	SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction.	None
Induction of CYP3A4	This item is appropriately	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	communicated through current labelling: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction.	
Inhibition of CYP1A2	This item is appropriately communicated through current labelling: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction.	None
UGT inducers	This item is appropriately communicated through current labelling: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction.	None
Inhibition of CYP2C8 enzyme	This item is appropriately communicated through current labelling: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction.	None
Interaction with cholestyramine	This item is appropriately communicated through current labelling: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction.	None
Missing information		
Long term safety in pediatric patients aged 2 to less than 6 years of age	This item is appropriately communicated through current labelling: SmPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use.	None
Long term safety in pediatric NTDT patients aged 10 to 17	This item is appropriately communicated through current	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
years	labelling: SmPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use.	
Safety in pregnant women	This item is appropriately communicated through current labelling: SmPC Section 4.6 Fertility, Pregnancy and lactation; and Section 5.3 Preclinical safety data.	None
Safety of FCT formulation	This item is appropriately communicated through current labelling: SmPC Section 4.2 and 5.2 and Patient Leaflet.	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the EXJADE dispersible tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

No new data on clinical efficacy were submitted as part of this application.

EXJADE was approved as an efficient oral iron chelator able to reverse iron overload and maintain normal values in patients suffering from various transfusion dependent conditions; the initial approval

was based on a non-inferiority against deferoxamine as second line treatment in beta-thalassemic patients with infrequent transfusions. Iron chelation is a physicochemical process, and the dose-dependent efficacy of chelation therapy has been previously demonstrated for deferasirox as well as for other chelators such as deferoxamine. This application for a film coated tablet formulation cross-refers to the existing efficacy data generated with the dispersible tablet formulation and pharmacology data in healthy volunteers.

After adjustment of the strength, the film-coated tablet formulation (360 mg strength) was equivalent to EXJADE dispersible tablets (500 mg strength) with respect to the mean area under the plasma concentration time curve (AUC) under fasting conditions. The C_{max} was increased by 30% (90% CI: 20.3% - 40.0%); however a clinical exposure/response analysis revealed no evidence of clinically relevant effects of such an increase. Bioavailability of deferasirox film-coated tablets was 36% greater than that with dispersible tablets.

An additional PK/PD analysis [Study A2409] included in this submission confirmed the influence of AUC and C_{max} on efficacy. The available data fully support the therapeutic equivalence of the strength-adjusted new FCT formulation. The starting dose calculated on the basis of a higher bioavailability is 14 mg/kg body weight.

Uncertainty in the knowledge about the beneficial effects

There are no data on direct comparison of the efficacy of the FCT vs the DT formulation.

The MAH will submit the results of a Phase II safety study investigating the benefits of the new deferasirox formulation (film-coated tablet) in comparison to the commercially approved dispersible tablet (EXJADE) (see Annex II and RMP).

Risks

Unfavourable effects

There is no apparent new safety signal emerging from the limited data available in healthy volunteers and post-marketing data from the US assessed in the last PSUR.

Uncertainty in the knowledge about the unfavourable effects

Exposure to the new formulation was very low in the clinical trials submitted and in healthy volunteers. As the product has been approved in the US, post-marketing data were made available. No conclusion can be drawn from the interim report from study F2201 due to the low number of patients included and treated so far, except that the number of AE are numerically lower with FCT than with DT formulation and that there is no apparent new safety signal emerging from these limited data. The study F2201 will be completed post approval (see Annex II).

No data exist on the tolerability of the new formulation (FCT) in paediatric population < 10 years. No data are available regarding the GI tolerability of the crushed FCT formulation, particularly used in the youngest population. The MAH shall conduct an observational cohort study in paediatric non-transfusion-dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate, in order to assess the long-term exposure and safety of deferasirox dispersible and film-coated tablets, based on a protocol agreed with the CHMP (see Annex II, RMP).

Effects table

N/A

Balance

Importance of favourable and unfavourable effects

The efficacy and safety of the new formulation should be in line with the data available for the currently approved dispersible tablets.

The film coated tablets provide additional convenience to the patient in terms of mode of administration.

Benefit-risk balance

The benefit-risk balance of the FCT is positive.

Discussion on the benefit-risk assessment

The application cross-refers to the existing efficacy and safety data on the basis of adequate pharmacological data. The dose adjusted formulations are pharmacologically comparable and have the advantage of slightly improved pharmacokinetic properties (a reduced food effect and a more predictable dose-exposure relationship in clinical practice) and a more convenient mode of administration – especially for young children - as FCT would allow patients who have difficulty in swallowing whole tablets, to take crushed tablets with soft food such as apple sauce and yogurt.

Thus, the new FCT formulation could represent an improvement in patient care and support compliance. However, in healthy volunteers, gastrointestinal disorders, such as dyspepsia and diarrhoea were observed, therefore no clinical advantage for the new formulation in terms of better gastrointestinal tolerability can be drawn at this stage. Data related to the tolerance profile of FCT will be documented in post approval studies as agreed in the Annex II.

The MAH has included Post-authorisation measures in the Annex II and the RMP (as amendment version 3.0 of the PASS study CICL670E2422 following approval of deferasirox FCT, to allow enrolment of patients prescribed film-coated tablets and also a new PASS study to conduct an open-label, single-arm, interventional study in 40 paediatric patients (2-<12 years old) with chronic or transfusional iron overload to assess the safety of deferasirox FCT over 6 months of treatment, especially when the tablets are crushed), which is acceptable.

In order to prevent the risk of medication errors by switching formulations, risk minimization measures have also been included (as educational material for patients and prescribers for both formulations for all indications, introductory notification letters for the pharmacists and the prescribers) as requested by the CHMP which is acceptable.

In addition, prescribers' survey required as additional pharmacovigilance activity in order to measure effectiveness of risk minimisation measures has been included. The MAH should submit revised mock-ups for the film-coated tablets, further enhancing the pharmaceutical form and strength in all panels of the unit pack of FCT before the launch of the FCT in order to avoid confusion between the two forms.

Benefit-risk balance

The benefit-risk balance of the FCT is positive as it is in line with the Benefit /Risk of the currently approved dispersible tablet.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of EXJADE 90 mg, 180 mg and 360 mg film-coated tablets in

the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older; the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups: in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years; in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older; in patients with other anaemias aged 2 years and older, the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older

- is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH must inform the European Medicines Agency and the CHMP of the status and results of the surveillance programme in each Member State within 6 months of the Decision and at each update of the EU Risk Management Plan.

As well as the requirements in the legislation, the following serious ADRs should be forwarded on an expedited basis to the appropriate competent authority as well as summarised in the above reports:

- Increase in hepatic enzymes >10x ULN
- Serious rise in creatinine
- Results of renal biopsies, if available
- Cataracts
- Hearing loss
- Gallstones

Prior to launch of EXJADE in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to inform healthcare professionals and patients to minimize the risks of:

- Non-compliance of the posology and biological monitoring
- Medication errors due to switching between formulations (dispersible and film-coated tablets).

The MAH shall ensure that, at launch, in each Member State where EXJADE is marketed, all healthcare professionals and patients who are expected to prescribe, dispense and use EXJADE are provided with the following educational package for both formulations and on all indications:

- Physician educational material
- Patient information pack

Additional periodic distributions after launch should be performed, notably after safety substantial product information modifications justifying educational material updates.

The MAH shall use distinct outer cartons, blisters and tablets for both formulations (dispersible and film-coated tablet).

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals shall contain the following key elements:

- Description of available deferasirox formulations
  - Different posology regimen
  - Different conditions of administration
  - Dose conversion table when switching from one formulation to another
- The recommended doses and the rules for starting treatment
- The need to monitor serum ferritin monthly

- That deferasirox causes rises in serum creatinine in some patients
    - The need to monitor serum creatinine
        - On two occasions prior to initiation of treatment
        - Every week during the first month of initiation of treatment or after therapy modification
        - Monthly thereafter
    - The need to reduce by 10 mg/kg the dose if serum creatinine rises:
        - Adults: >33% above baseline and creatinine clearance <LLN (90 ml/min)
        - Paediatrics: either >ULN or creatinine clearance falls to <LLN at two consecutive visits.
    - The need to interrupt treatment after a dose reduction if serum creatinine rises:
        - Adults and Paediatrics: remain >33% above baseline or creatinine clearance <LLN (90 ml/min)
    - The need to consider renal biopsy:
        - When serum creatinine is elevated and if another abnormality has been detected (eg. proteinuria, signs of Fanconi's Syndrome).
- The importance of measuring creatinine clearance
- Brief overview of methods of measuring creatinine clearance
- That rises in serum transaminases may occur in patients treated with EXJADE
    - The need for liver function tests prior to prescription, then at monthly intervals or more often if clinically indicated
    - Not to prescribe to patients with pre-existing severe hepatic disease
    - The need to interrupt treatment if persistent and progressive increase in liver enzyme were noted.
- The need for annual auditory and ophthalmic testing
- The need for a guidance table highlighting pre-treatment measurements of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin, such as:

Before initiating treatment	
Serum creatinine at Day - X	Value 1
Serum creatinine at Day - Y	Value 2

X and Y are the days (to be determined) when pre-treatment measurements should be performed.

- Recommendations for treatment of non-transfusion-dependent thalassaemia (NTDT) syndromes:
    - Information that only one course of treatment is proposed for NTDT patients
    - The recommended doses and the rules for starting treatment

- The rules for stopping when target liver iron concentration and serum ferritin are reached
- A warning to minimise the risk of over-chelation
- A warning on the necessity of closer monitoring of liver iron concentration and serum ferritin in the paediatric population
- A warning on the currently unknown safety consequences of long-term treatment in the paediatric population and the need to detect side effects

Prior to launch of deferasirox film-coated tablets, healthcare professionals will receive introductory notification letters as follows:

- Pharmacists - a detailed letter explaining the switch between the two formulations
- Prescribers - a letter including the following dossiers:
  - A prescribers' guide informing about the switch between the two formulations in order to address the important potential risk of medication error for deferasirox
  - A patient's guide informing about the possibility of two co-existing formulations in the EU market, and the differences concerning their administration, in order to address the important potential risk of medication error for deferasirox

Additionally, prescribers and pharmacists will be informed via a specific letter regarding the timelines for removing EXJADE dispersible tablets from the EU market.

The patient information pack should contain:

- Patient information leaflet
- Patient guide

The Patient guide shall contain the following key elements:

- Information on the need for regular monitoring, and when it should be carried out, of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin
- Information that renal biopsy may be considered if significant renal abnormalities occur
- Availability of several oral formulations and the main differences associated with these formulations (i.e., different posology regimen, different conditions of administration notably with food)

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
The MAH shall submit the results of a Phase II safety study investigating the benefits of the new deferasirox formulation (film-coated tablet) in comparison to the commercially approved dispersible tablet.	September 2016 (final study report)
Non-interventional post-authorisation safety study (PASS): In order to assess the long-term exposure and safety of deferasirox dispersible and film-coated tablets, the MAH should conduct an observational cohort study in paediatric non-transfusion-	June 2021

Description	Due date
dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate conducted according to a CHMP-agreed protocol. The clinical study report should be submitted by	
Interventional post-authorisation safety study (PASS): In order to assess the safety of deferasirox film-coated tablets in the paediatric population (especially when the tablets are crushed), the MAH shall conduct and submit the results of a safety study conducted according to an agreed protocol. The clinical study report should be submitted by	June 2021

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

Paediatric data

Furthermore, the CHMP reviewed the available data of studies subject to the agreed Paediatric Investigation Plan P/0199/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.