EMA/CHMP/532991/2020
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment Report

Upkanz

International non-proprietary name: deferiprone

Procedure No. EMEA/H/C/005004/0000

Note

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

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Table of Contents

List of abbreviations

Abbreviation	Definition
µg	microgram
ADR	Adverse drug reaction
AE	adverse event
Ae	amount excreted in urine
ALT, SGPT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	Analysis of covariance
AST, SGOT	aspartate aminotransferase
AUC	area under the serum concentration versus time curve
AUC0-t	area under the serum concentration versus time curve to the last measurable concentration
AUC0-∞	area under the serum concentration versus time curve to infinity
BAD (scale)	Barry-Albright Dystonia (scale)
b.i.d.	*Bis in die* (twice daily dosing)
CBC	Complete blood count
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CL/F	total body clearance, corrected for bioavailability
CLr	renal clearance
Cmax	maximum measured serum concentration
Cmin	minimum measured serum concentration
CRF	case report form
CV	coefficient of variation
DBS	Deep brain stimulation
DFP	Deferiprone
DSMB	Data safety monitoring board
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European medicines agency
F	Fahrenheit
FDA	Food and Drug Administration
Fe	fraction of dose excreted in urine
FSH	follicle-stimulating hormone
FIM	Functional independence measure
g	gram
GCP	Good Clinical Practice
h	hour
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation
IR	immediate release
IRB	Institutional Review Board
ITT	Intention to treat
kg	kilogram
LS	Least square
LSM	Least square mean
MAA	Marketing authorization application

ME	medical events
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mITT	Modified intention to treat
mL	milliliter
MMRM	Mixed effects model for repeated measures
MRI	Magnetic resonance imaging
NBIA	Neurodegeneration with brain iron accumulation
PedsQL	Paediatric quality of life scale
PGI-I	Patient global impression of improvement
PKAN	Pantothenate kinase-associated neurodegeneration
PP	Per protocol
PR	interval between the P and R waves on the electrocardiogram Tracing
PRN	*Pro re nata* (as needed)
PSQI	Pittsburgh sleep quality index
PT	prothrombin time
PTT	partial thromboplastin time
QRS	QRS waves complex on the electrocardiogram tracing
QT	interval from the beginning of the Q and end of the T waves on the electrocardiogram tracing
QTcB QT	interval corrected using Bazett's formula
QTcF QT	interval corrected using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGOT	serum aspartate transaminase
SGPT	serum alanine transaminase
SmPC	Summary of product characteristics
SOC	System organ class
SOP	standard operating procedures
t½	apparent terminal elimination half-life
Tmax	time of the maximum measured serum concentration
UPDRS	Unified Parkinson's disease rating scale
Vd/F	apparent volume of distribution
WBC	white blood cell
WeeFIM	Paediatric functional independence measure

1. Rapporteur CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Upkanz, an orphan medicinal product in the treatment of pantothenate kinase-associated neurodegeneration (PKAN) in patients aged 4 years and older is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at present. The details of these major objections are provided in the list of outstanding issues (See section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objection precluding a recommendation of marketing authorisation, pertain to the negative results of the pivotal study.

Deficiencies arising from concerns over the confidential (ASM - Active Substance Manufacturer restricted) part of the DMF are mentioned in the appendix (this appendix is not supplied to the MAA). These concerns will be conveyed in confidence to the holder of the DMF.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

N/A

GCP inspection(s)

All clinical trials were declared to have been conducted in compliance with the Good Laboratory Practices (GLP), and the ICH harmonized tripartite guideline E6 regarding Good Clinical Practices (GCP).

The Committee for Medicinal Products for Human Use has asked for an inspection to be carried out of the conduct of the clinical study TIRCON2012V1, in accordance with Article 57 of Regulation (EC) No. 726/2004 and Article 15 of Directive 2001/20/EC.

New active substance status

n/a – hybrid application

Additional data exclusivity /Marketing protection

The applicant requested consideration of one-year data exclusivity in regards to its application for a new indication in accordance with Article 10(5) of Directive 2001/83/EC.

Similarity with authorised orphan medicinal products

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Derogation(s) from market exclusivity

n/a

2. Executive summary

The MAA is submitted under the Centralised Procedure as a hybrid application on the legal basis of Article 10 of Directive 2001/83/EC: Article 10(3) hybrid application - changes in therapeutic indications. The reference medicinal product is Ferriprox (deferiprone) 500 mg immediate-release film-coated tablets. Marketing authorisation is requested for Upkanz 80 mg/ml oral solution. The drug was first approved in the European Union in 1999 by the European Medicines Agency (EMA) (EU/1/99/108/001) as Ferriprox® 500 mg immediate-release tablets. In 2007, the EMA approved a 100 mg/mL oral solution (EU/1/99/108/002-003), an alternative dosage form intended for patients who have difficulty in swallowing tablets, and in 2010, a 1000 mg immediate-release tablet formulation (EU/1/99/108/004), both bioequivalent to Ferriprox 500 mg tablets.The applicant seeks approval for: the treatment of neurodegeneration with brain iron accumulation.

2.1. Problem statement

2.1.1. Disease or condition

Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of genetic disorders characterized by the focal accumulation of iron in the brain, usually in the basal ganglia. While iron is essential for normal physiological function, an excessive amount of it in tissues is toxic, irrespective of the reason that led to its accumulation; and the available data strongly suggest that the clinical manifestations of NBIA are due, at least in part, to the neuronal damage secondary to prolonged iron-mediated oxidative insult.

2.1.2. Epidemiology

PKAN is a rare condition in the EU and worldwide. The estimated prevalence of PKAN is 0.025 in 10,000 persons in the European Community.

Biologic features

At present, there are 10 identified genetic disorders that are recognized as NBIA, as well as several other conditions with clinical characteristics of NBIA in which the gene defect responsible has not been identified. Despite the different underlying genetic causes, many of the clinical manifestations of these disorders are similar, and in all cases, there is iron overload in a brain region, although the precise location and the pathologic process leading to its accumulation may vary.

Although iron is essential for normal physiological function, an excessive amount of it in tissues is toxic, irrespective of the reason that led to its accumulation. Once the system for storage of cellular iron is overwhelmed, free iron can react with reactive oxygen intermediaries (ROI), producing noxious reactive oxygen species (ROS) such as OH·radicals. ROS can chemically damage membrane components such as lipids by peroxidation; they can damage proteins by oxidation of amino acids such as tyrosine, methionine, lysine, and cysteine or via carbon monoxide formation; and they can damage nucleic acids by base modification and DNA breaks, which can lead to impaired cellular function and cell death. In patients with NBIA, while the link to iron accumulation remains unknown, the available data strongly suggest that disturbance of mitochondria is linked to neurodegeneration, and its clinical

manifestations are considered to be due, at least in part, to the neuronal damage secondary to prolonged iron-mediated oxidative insult.

2.1.3. Clinical presentation, diagnosis,and stage/prognosis

PKAN has been described as either classical or atypical. Most PKAN cases are classical, with symptom development before 6 years of age (average, 3.5 years), and loss of ability to walk independently 10-15 years thereafter. Individuals with classical PKAN are also more likely to have specific eye problems. The pattern of progression is saltatory, with step-wise decline occurring over a few days or weeks, followed by plateauing that may be sustained for weeks or months. In general, motor skills that have been lost are not regained. The overall trajectory of change is that of relentless progression, and no clear exacerbating factors have been identified to account for the periods of more precipitous decline. Atypical PKAN usually becomes evident after the age of ten years (average~13 years) and progresses more slowly. Some individuals experience plateauing of symptoms for many months, years or even decades. Static disease or minimal progression over 5-10 years is not uncommon for people with atypical PKAN. Loss of independent ambulation often occurs 15-40 years after the initial development of symptoms. Some patients may develop the disease in adulthood (Aggarwal et al., 2010; Antonini et al., 2006). Clinically, the disease manifests as rigidity, dystonia,and chorea. Although dystonia is also prominent in atypical PKAN, Parkinsonism usually contributes more significantly to the disability as disease advances, and dysarthria has a significant impact on quality of life (Hogarth et al, 2017).

The hallmark clinical manifestations of these disorders are dystonia, choreoathetosis, spasticity, and parkinsonian symptoms such as tremor, slowness, muscular rigidity, and poor balance, with many patients developing the need for wheelchairs and/or devices to help with vocalization. Life expectancy is variable, with premature deaths resulting from dystonia and impaired swallowing, both of which can lead to poor nutrition or aspiration pneumonia.

2.1.4. Management

In the last decade, progress has been made in stratifying NBIA and PKAN according to gene mutations and phenotype. However, no genetic or other specific therapies are available for this condition. There is, therefore, an urgent need for a therapy that could interrupt the pathologic process and/or slow the progression of the disorder.

Optimum symptomatic management of PKAN requires a multidisciplinary approach. Implementing a comprehensive management plan can improve quality of life and function.

Pharmacological and surgical interventions are aimed at palliation of symptoms. For many of the interventions that offer improvement of clinical symptoms, the period of benefit is however limited.

Pharmacological symptomatic treatments include anticholinergics, benzodiazepines and other anti-spasticity agents, alone or in combination to relieve spasticity and dystonia, as well as botulinum toxin. First line drugs that are most commonly effective in PKAN are trihexyphenidyl, clonazepam and baclofen (oral or intrathecal). Second line drugs include clonidine, gabapentin, tetrabenazine, pregabalin.

PKAN-associated dystonia and even the Parkinsonism observed in older individuals with PKAN are rarely responsive to dopaminergic medications. Most people with PKAN have had a trial of levodopa at some point in their disease and very few report any benefit. Similarly, dopamine agonists seem to be of limited utility in the disease.

Tics, chorea and myoclonus are usually treated with noradrenergic agents, such as clonidine, guanfacine or atomoxetine.

Deep brain stimulation (DBS) can be used to relieve dystonia. Numerous case reports and series that include mixed NBIA etiologies report benefit for many people in the first year or years with placement in the globus pallidus interna. However, benefit usually is not sustained as disease advances. Adolescents and adults with atypical PKAN are more likely to benefit from DBS. While DBS is considered to be part of the current management arsenal for PKAN, there is no consensus about the efficacy of DBS in relieving dystonia in PKAN nor of the optimal candidate, timing in disease progression or stimulator settings.

Thalamotomy and pallidotomy have been performed in PKAN, sometimes with good symptomatic relief, for patients with severe disabling dystonia that is refractory to medical management. Concerns have been raised about the irreversible nature of these procedures, especially in children and adolescents, and these ablative procedures have been largely replaced by DBS.

2.2. About the product

Deferiprone (1,2-dimethyl-3-hydroxypyrid-4-one) is a bidentate chelating agent that complexes selectively with trivalent iron cations (Fe3+) in a 3:1 (deferiprone:iron) ratio. It possesses the ability to enter cells and bind iron intracellularly. The drug readily crosses the blood-brain barrier in animals (Waldmeier et al. 1993), and there is indirect evidence to suggest that it does so in humans (Boddaert et al. 2007). This ability to access brain cells, and to facilitate removal of iron and its acceptance by transferrin for subsequent endogenous use, suggests that deferiprone could be exploited clinically for treating diseases involving regional iron accumulation.

2.3. The development programme/compliance with CHMP guidance/scientific advice

NBIA comprises a group of rare (prevalence estimated to be 1 to 3 per million persons in the EU) progressive extrapyramidal disorders in which there is radiographic evidence of regional iron accumulation in the brain. Ten conditions are currently classed as NBIA, with the most common, pantothenate kinase-associated neurodegeneration (PKAN), accounting for approximately 50% of cases. In accordance with Article 3(1)(a) of (EC) No 141/2000, NBIA thus complies with the definition of an orphan disease, and deferiprone is the subject of an approved application for orphan drug designation in NBIA (EU orphan designation number: EU/3/18/2034, granted on 27 June 2018).

ApoPharma has sponsored two completed efficacy and safety clinical trials, TIRCON2012V1 and TIRCON2012V1-EXT, in patients with PKAN, the most prevalent NBIA disorder. TIRCON2012V1 was a randomized, double-blind, placebo-controlled trial, conducted in 89 patients, who were randomly assigned in a 2:1 ratio to receive either deferiprone oral solution (N=59) or placebo (N=30) for up to 18 months. Appropriate stratification ensured that each treatment group contained the same ratio of individuals in whom motor symptoms had begun before or after 6 years of age, in order to balance the numbers of those with the classic versus the atypical form of the disease. The dosage of deferiprone was titrated over the first 12 weeks from 5 mg/kg of body weight twice daily to 15 mg/kg twice daily, with equivalent increases in the volume of placebo solution for patients in the control group.

All patients who completed Study TIRCON2012V1 were offered the opportunity to enroll in TIRCON2012V1-EXT, a single-arm study in which all participants received deferiprone for 18 months, titrated over 2 weeks up to a maximum dosage of 15 mg/kg twice daily. The primary objectives were to evaluate the long-term safety and tolerability of deferiprone in patients with PKAN, and the secondary objectives were to evaluate changes over time in the severity of dystonia and in global improvement.

Scientific Advice was obtained from the European Medicines Agency (EMA) on the development of deferiprone in pantothenate kinase-associated neurodegeneration (PKAN), the most common form of NBIA, procedure no: EMEA/H/SA/2280/1/2012/III.

The requested scientific advice from the SAWP/CHMP pertains to the following areas:

• The design of the TIRCON study to assess the safety and efficacy of deferiprone in the treatment of PKAN for a well-established substance in accordance with Article 10(5) of Directive 2001/83/EC.

• Development of deferiprone in PKAN, which predominantly affects children; the TIRCON study will enroll mostly paediatric patients.

• Application for a marketing authorisation under exceptional circumstances, under article 14(8) of Regulation (EC) No 726/2004; EMEA/357981/2005}, based on the TIRCON study and because PKAN is a rare condition.

Questions on Chemical, Pharmaceutical and Biological development was on acceptability of cyanocobalamine employed as colorant, selected in order to avoid azo and other artificial dyes not suitable for use in paediatrics. CHMP accepted proposed colouring agent and need for a colouring agent. Cyanocobalamin, and 80 mg/mL oral solution has been accepted by the Paediatric Committee to be used in another deferiprone trial in pediatric population. There was a question to be addressed, as the need for a preservative, the quantity proposed would have to be justified as per NfG CPMP/QWP/115/95. Moreover , the shelf life after first opening study would have to mimic in-use testing as planned by future SmPC and would have to include determination of the microbial contamination. Also the measuring device would have to be described, would have to be CE certified and the proof of its suitability for intended use would have to be provided. A container/content study would have to be filed to assess possible leaching of extractable from the container into the solution.

All suggestions in Scientific Advice were followed however two aspects need further clarification:

- preservative and the quantity proposed. The amount of Potassium sorbate is justified by the applicant based on WHO acceptable daily intake (ADI) nevertheless preservative effectiveness results showed that that the product is effectively preserved at lower amount of Potassium sorbate. The antimicrobial activity of pharmaceutical preparation itself need to be discussed.
- in use stability study and proposed shelf life after first opening. The results for one more batch towards end of shelf life were not submitted.

ApoPharma sought Scientific Advice from EMA and the CHMP adopted the advice on March 15, 2012. (EMA/CHMP/SAWP/155383/2012). The requested scientific advice from the SAWP/CHMP pertains to the following non-clinical area:

- the non-clinical developmental program for deferiprone. The position by the applicant that the human safety information available from deferiprone and the long-term animal studies already available are appropriate to support the development of the new indication was endorsed by CHMP.

The CHMP supported the applicants' position: "The position by the applicant that the human safety information available from deferiprone and the long term animal studies already available are appropriate to support the development of the new indication is endorsed. The reasoning for not performing juvenile animal studies based on existing experience in children and on the difficulties emerging from the use of developing animals (rodents) where the potential effects of iron depletion on development could mask other safety aspects is also endorsed. A review analysis of safety data from post-marketing experience of Ferriprox® regarding paediatric population AEs and especially carcinogenic risk is endorsed and is considered the most relevant. These clinical safety data could be considered as sufficient to assess the safety in paediatric population, provided that specific measures to assess and ensure safety in human studies isconsidered".

The issues included in SA were sufficiently addressed by the applicant.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

A QP declaration confirming GMP compliant manufacturing of the drug substance at the proposed drug substance manufacturing sites Srini Pharmaceuticals Pvt. Ltd. and Apotex Pharmachem Inc. has been provided.

The Rapporteur has been assured that acceptable standards of GMP are in place for this product at all sites responsible for the manufacture and assembly.

For manufacturing sites within the Community, the Rapporteur has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GLP

None of primary pharmacodynamics studies were GLP-compliant, although according to the applicant ApoPharma-sponsored studies adhered to high scientific standards of conduct and reporting.

The safety pharmacology studies were GLP-compliant. The pharmacokinetics studies were either to GLP or to high scientific standards under non-GLP conditions. Single-dose toxicity studies, study of effects on fertility and early embryonic development and genotoxicity assay were GLP-compilant.

GCP

The applicant declared that all clinical trials had been conducted in compliance with the Good Laboratory Practices (GLP) and the ICH harmonized tripartite guideline E6 regarding Good Clinical Practices (GCP). The Committee for Medicinal Products for Human Use has asked for an inspection to be carried out of the conduct of the clinical study TIRCON2012V1, in accordance with Article 57 of Regulation (EC) No. 726/2004 and Article 15 of Directive 2001/20/EC.

A GCP inspection has been performed for the clinical study TIRCON2012V1 (a randomised, double-blind, placebo-controlled trial of deferiprone in patients with pantothenate kinase-associated neurodegeneration).

Two investigator sites (one in Germany and one in the US), as well as the Sponsor in Canada were inspected.

During the inspections, findings were observed and are reported in the attached final integrated inspection report (IIR) as follows:

- At the inspection of the investigator site in Germany, there were no critical, 8 major and 2 minor findings.

- At the inspection of the investigator site in the US, there were no critical, 8 major and 9 minor findings.

- At the inspection of the Sponsor site there were no critical, 11 major and 7 minor findings.

A summary of the inspection outcome can be found below:

<u>Assessment of the relevance of the findings for the full study</u>

Several findings were process related and relevant for the overall trial, among those are observations related to eCRF design, the use of 'remote sites' for trial-specific assessments, the valuation of

exclusion criteria and statistical analysis. Still those findings bare little impact on the overall benefit/risk evaluation.

Quality of the data, ethical conduct and GCP compliance

Whilst there were major and minor GCP findings and non-compliances, overall these are not considered to impact on the quality or integrity of the data or the ethical conduct of the trial. It is the inspectors' impression that the trial has generally been performed at an adequate level of compliance with ICH GCP. Specific areas of non-compliance involved eCRF design, the use of 'remote sites' for trial-specific assessments, waiving of exclusion criterion and self-verified programming of statistical analysis. Details how those areas were noncompliant are outlined in the individual inspection reports.

Recommendation for the acceptability of the clinical trial data for the submitted application assessment

Despite the need for CAPAs (corrective action preventive action) to be implemented for the major findings observed and based on what the inspectors saw during the inspections and on the responses provided, the data are still considered to be of sufficient quality to be used for assessment in connection with the marketing authorization application.

Recommendations for follow up actions (GCP systems)

None.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:Article 10.3 of Directive 2001/83/EC – hybrid application.

PRIME

n/a

Accelerated assessment

n/a

Conditional marketing authorisation

n/a

Marketing authorisation under exceptional circumstances

n/a

Biosimilarity

n/a

Additional data exclusivity/ marketing protection

The applicant requested consideration of one-year data exclusivity in regards to its application for a new indication in accordance with Article 10(5) of Directive 2001/83/EC.

New active substance status

n/a

Orphan designation

Upkanz was designated as an orphan medicinal product EMA/OD/006/18 on 2018-06-27 in the following condition: Treatment of neurodegeneration with brain iron accumulation.

Similarity with orphan medicinal products

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Derogation(s) from orphan market exclusivity

n/a

Information on paediatric requirements

applicant informed that this section is not applicable because the paediatric requirements set out in Articles 7 and 8 ofthe Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12December 2006 on medicinal products for paediatric use do not apply to hybrid applicationsunder Article 10(3) of Directive 2001/83/EC.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as an oral solution containing 80 mg/mL of Deferiprone as active substance.

Other ingredients are: Hydroxyethylcellulose, Glycerol, Hydrochloric acid, concentrated, Sucralose, Potassium sorbate, Bubble gum flavor, Cyanocobalamin, Purified water.

The product is available in 250 mL amber polyethyleneterephthalate (PET) round bottles.

White polypropylene child-resistant pictorial caps with foamliner are used as closures.

The product presentation includes a medical device 30 mL graduated/dosing cup.

Active Substance

An ASMF for Deferiprone has been provided by Apotex Pharmachem India Pvt. Ltd. The ASMF number is: EMEA/ASMF/01145. Provided, current version of ASMF is:

applicant's Part version: AP/APIPL.L1-EU v 3.2 dated: 06.11.2018

Restricted Part version: RP/APIPL.L1-EU v 3.2 dated: 06.11.2018

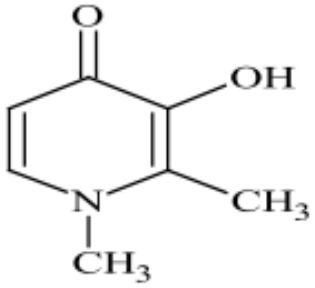
QOS for the applicant's Part and the Restricted Part as well as information about the Expert for ASMF documentation should be presented (formal issue).

Please note that concerns regarding the Restricted Part of the ASMF are addressed in a separate confidential Annex.

General Information

Deferiprone (INN) is a white or pinkish-white powder, sparingly soluble in water, slightly soluble in methanol and ethanol, very slightly soluble in acetone. The drug substance does not show polymorphism and stereoisomerism. Deferiprone is non-hygroscopic by nature. Active substance is described in Ph.Eur.

Its chemical structure is depicted below:



Molecular Formula: $C_7H_9NO_2$, *Molecular Mass*: 139.2 g/mol

Manufacture, process controls and characterisation

Two drug substance manufacturing sites are proposed:

Srini Pharmaceuticals Private Limited
Survey No: 247,
Choutuppal village & Mandal,
Yadadri Bhuvanagiri District,
Bhongiri 508252,
Telangana, India

Apotex Pharmachem Inc.
11, 34, 50 Spalding Drive,
Brantford, Ontario,
N3T 6B8, Canada

The process employed by the two sites is essentially the same with some minor exceptions, clearly described in documentation. The presented batch data demonstrate that drug substance manufactured at both sites is of similar quality.

The manufacturing process for Deferiprone consists of one chemical transformation. One starting material has been defined: maltol. Justification of the selection of proposed starting materials has been presented and is in line with general requirements stated in ICH Q11. Information regarding proposed starting material, generally are acceptable although questions concerning used analytical methods are raised.

In previous version of ASMF documentation two starting materials were proposed: maltol (key starting material) and methylamine (starting material). In current version of ASMF documentation status of methylamine has been changed to reagent. Since no justification for change in classification of raw material has been presented, this issue should be further discussed.

In-process controls have been defined and discussed. Further information is requested regarding the methods used.

Characterisation

The structure of the drug substance has been elucidated applying standard methods. Representative spectra/chromatograms have been given. Drug substance neither show polymorphism nor isomerism. The physicochemical characterization of drug substance is considered sufficient.

Impurities

Discussion consisting of organic, non-organic, residual solvents, elemental impurities and genotoxic impurities has been presented. Impurities listed in Ph.Eur. monograph for Deferiprone are indicated and characterized. Since no stress testing results could be located in dossier, potential degradation products should be commented. Moreover, other concerns are raised regarding missing information in the ASMF on the control strategy of certain potentially genotoxic impurities.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

Active substance is controlled and tested in accordance with Ph.Eur. monograph for Deferiprone. Two drug substance manufacturers have been declared, therefore two separate drug substance specifications have been presented in dossier. Limits for additional tests are acceptable.

Srini Pharmaceuticals Pvt. Ltd.:

Tests	Methods	Specifications
Appearance	Visual	White to Pinkish-white powder
Identification by IR	EP <2.2.24>	The sample IR spectrum conforms to that of standard IR spectrum
Sulfated ash	EP <2.4.14>	NMT 0.1%
Water content	EP <2.5.32>	NMT 0.5%
Related substances by HPLC	EP HPLC Method	EP Impurity A* EP Impurity B (Maltol): NMT 0.10% EP Impurity C* Largest unspecified impurity: NMT 0.05% Total impurities: NMT 0.2% Reporting threshold: 0.03%
Assay by HPLC	EP HPLC Method	98.0% to 102.0% (Anhydrous substance)
Iron Complex content	UV House Method	NMT 0.2%
Residual solvents by GC	GC Head space House Method	Methanol: NMT 0.1%
Additional tests:		
Bulk density	EP <2.9.34> Method-I	Report value
Tapped density	EP <2.9.34> Method-I	Report value
Particle size	Air Jet Sieving In House Method	NLT 90% below 500 µm NLT 60% below 250 µm

** Due to their unlikely presence, EP impurity A and EP impurity C are controlled as unidentified impurities at NMT 0.05%.*

Apotex Pharmachem Inc.:

Test	Method	Acceptance criteria
Appearance	Visual, M-G-001	White to pinkish white powder
Identification	EP 2.2.24-IR M-DEF-011 Rev. 3.0	Sample conforms to Standard IR spectrum
Identification	EP 2.2.25-UV M-DEF-012 Rev.4.0	Sample conforms to Standard UV spectrum
Assay	EP HPLC Method M-DEF-001 Rev.3.0	NLT 98.0% and NMT 102.0% calculated on the anhydrous basis
Water content	EP 2.5.32	NMT 0.5%

	Coulometric Karl Fischer Titration M-DEF-014 Rev.2.0	
Iron Complex Content	UV House Method M-DEF-007 Rev.3.0	NMT 0.2%
Related Compounds	EP HPLC Method M-DEF-002 Rev.3.0	Identified impurities: EP A* EP C* EP B: NMT 0.10% Unidentified impurities: Largest unidentified impurity: NMT 0.05% Total impurities: NMT 0.2% Reporting threshold: 0.03%
Residual Solvents	GC Headspace House Method M-DEF-006 Rev.2.0	Methanol: NMT 1000 ppm
Sulphated Ash	EP 2.4.14 M-G-007	NMT 0.1%
Particle Size	Air Jet Sieving	NLT 90% below 500 µm NLT 60% below 250 µm
Bulk Density	EP 2.9.34 Method I M-G-037	NLT 0.4 g/mL and NMT 0.7 g/mL
Tapped Density	EP 2.9.34 Method I M-G-036	NLT 0.5 g/mL and NMT 1.0 g/mL

** Due to their unlikely presence, impurities EP A and EP C are controlled as unidentified impurities at NMT 0.05%.*

Analytical procedures/Validation of analytical procedures

The analytical methods have been described with sufficient details. It deals with the Ph.Eur. monograph [2236] methods. Satisfactory validation data have also been provided.

Batch analysis

Batch analysis data obtained for lots manufactured at Srini Pharmaceuticals Pvt. Ltd. and Apotex Pharmachem Inc. have been presented and are comparable. All results comply with the proposed specifications and indicate that a consistent quality of the active substance can be obtained based on the proposed manufacturing process at both manufacturing sites.

Reference Standards

In routine control of drug substance, working reference standards are used, qualified against Ph.Eur. CRS. Appropriate certificates of analysis, IR spectra have been enclosed. Information provided on the reference standards is satisfactory.

Container closure

Drug substance is packaged in double antistatic polyethylene bags sealed with cable ties within a HDPE drum (at Srini Pharmaceuticals Pvt. Ltd.) or a fibre drum (at Apotex Pharmachem Inc.).

Specifications of the primary packaging materials, including specific identification test for the immediate packaging has been provided, along with certificates of analysis. Conformity with current EU legislation on plastic materials intended to come into contact with food has been confirmed.

Suitable specifications together with certificates of analysis have been provided for secondary packaging (HDPE drum / fiber drum).

Drug substance container closure system has been described adequately and no further clarification is required.

Stability

Stability testing has been performed according to ICH guidelines on stability. With regard to manufacturing site Srini Pharmaceuticals Pvt. Ltd., stability data for production batches up to 60

months at long term conditions and up to 6 months at accelerated conditions have been provided in dossier. Moreover, stability studies initiated for the batches manufactured using the alternative source of maltol have been presented in dossier and cover 12 months at long term and 6 months at accelerated conditions. These stability studies are still ongoing and data from further time points could be presented.

For the second manufacturing site, results from 48 months of long-term and 6 months of accelerated conditions testing are available for production scale batches. More recent stability data (batches from 2015 and 2017) are still ongoing and stability data from further time points could be provided.

Performed stability studies proved that drug substance is a stable compound. All impurities remained well inside the limits and no changes or trends are seen for any of the batches, for any of controlled parametres.

Photostability testing has been performed for drug substance and revealed that Deferiprone is not light sensitive. Stability indicating feature of the HPLC methods for assay and related ubstances should be confirmed.

Based on the provided data, a re-test period of 60 months and storage condition "Store in a well-closed, light resistant containers at temperatures up to 25°C" has been claimed and were accepted.

Drug product manufacturer

The applicant presents own module 3.2.S., however a Guideline on ASMF Procedure required also a copy of the AP ASMF in the MA dossier (formal issue).

Sufficient information has been provided with respect to the nomenclature, structure and properties of the active substance.

Manufacturers involved in the production of drug substance have been listed with full addresses in the dossier. A single QP declaration has been provided for both drug substance manufacturing sites indicating that audits have been carried out. A flow chart and a short description of the manufacturing process have been provided as well.

Deferiprone has been characterized using standard analytical method. Representative spectra have been given, however missing X-ray diffraction patterns and thermograms should be provided. Potential process impurities in the drug substance have been listed. Residual solvents, elemental impurities and genotoxic impurities were discussed.

The specification used by Apotex Inc. – Richmond Hill (the finished product manufacturer) is presented below:

Specification parameter	Test method	Test limits
Appearance	GM-87 (House)	White to pinkish white powder
Identification	EP	IR spectrum: Corresponds to standard
Sulphated ash	EP	NMT 0.1%
Water content	EP	NMT 0.5%
Iron complex content	RM3078-07 UV (House)	NMT 0.2%
Residual solvents	RM205048-02 GLC (House)	Methanol: NMT 1000 ppm
Related compounds	AP66-DS-20-SG HPLC (House)	DF RC2 (Maltol): NMT 0.10% Unidentified Impurities: NMT 0.05% each Total Impurities: NMT 0.2%

Assay	AP66-DS-10-SG HPLC (House)	98.0% to 102.0% (on anhydrous basis)

The methods have been adequately described in the dossier. Validation data have been provided for in-house method, however further clarification are required. Batch analysis data has been provided for recent and older batches of drug substance. All batches fulfill the proposed specification.

Drug substance primary reference standards are used by the applicant. Reference standards are well characterized, however should be qualified against Ph.Eur. Deferiprone CRS. Relevant spectra confirming structure have been enclosed, along with certificates of analysis for RS. Maltol USP reference standard is used during control of impurities.

Brief information about primary packaging system has been provided in section S.6. No difference in container and closure system has been introduced by the applicant.

For both drug substance manufacturing sites the same retest period is claimed (60 months) with essential similar storage conditions as stated in AP ASMF. Additional data concerning stress testing studies have been provided by the applicant.

Finished Medicinal Product

Description of the product and Pharmaceutical Development

Upkanz (deferiprone) 80 mg/mL oral solution is a clear, reddish pink solution with a bubble gum-flavoured aroma. The product is presented in a fill size of 250 mL per bottle.

The formulation is packed as a multidose product and is preserved with Potassium sorbate in amount 0,2%. The formulation is packed in 250 mL amber polyethyleneterephthalate (PET) round bottles. White polypropylene child-resistant pictorial caps with foamliner are used as closures.

The product presentation includes a medical device 30 mL graduated/dosing cup.

Table 3.1.3.-1. Complete composition of Upkanz

Ingredient	Reference	Net contents of 250 mL presentation (g)	Amount (grams per litre)	Amount (%, w/v)	Function
Deferiprone	Ph. Eur.	20	80.00	8.0	Active ingredient
Glycerol	Ph. Eur.	125	500.0	50.0	Humectant and sweetening agent
Hydrochloric acid, concentrated	Ph. Eur.	11.8	47.20	4.72	To adjust the pH
Hydroxyethylcellulose	Ph. Eur.	0.25	1.00	0.1	To adjust the viscosity
Sucralose	Ph. Eur./NF	3.75	15.0	1.5	Sweetening agent
Potassium sorbate	NF	0.5	2.0	0.2	Preservative
Bubble gum flavor #33.12676 – refrigerated	Manufacturer's standard	0.188	0.75	0.075	Flavouring agent
Cyanocobalamin	Ph. Eur.	0.015	0.06	0.006	Colouring agent
Purified water	Ph. Eur.	123.75	q.s. to 1.0 L (1141 g)	49.519	To dissolve the ingredients
Total	-	285.25	1L (1141 g)	100.0% (114.1	-

Ingredient	Reference	Net contents of 250 mL presentation (g)	Amount (grams per litre)	Amount (%, w/v) g/100 mL)	Function

Table 3.1.3.-2. Composition of bubble gum flavour used in Upkanz (deferiprone) 80 mg/mL oral solution

Component	Percentage (%)
Propylene glycol	>50
Natural and artificial flavour	15 to 40

All components of the presentation are clearly stated. Function and reference to quality standards are properly defined.

This product contains no overage.

Pharmaceutical development

The drug product contains deferiprone (as the drug substance), which is a highly soluble compound in terms of the BioPharmaceutics Classification System (BCS). It is classified to 1 class of BCS. Deferiprone has an established history in the EU, having been approved in 1999 as Ferriprox® 500 mg immediate release tablets (EU/1/99/108/001) for the treatment of iron overload in patients with thalassemia major for whom deferoxamine therapy is contra-indicated or who present serious toxicity with deferoxamine therapy. Since 19 November 2007 and 28 July 2010, Ferriprox 100 mg/mL oral solution (EU/1/99/108/002 and EU/1/99/108/003) and 1000 mg immediate release tablets (EU/1/99/108/004) have been approved in the EU, respectively. Since 2016, the therapeutic indications approved in the EU are Ferriprox monotherapy is indicated for the treatment of iron overload in patients with thalassemia major when current chelation therapy is contraindicated or inadequate.

For formulation development, the first experimental batch of Upkanz (deferiprone) 80 mg/mL oral solution was prepared based on the marketed Ferriprox® (deferiprone) 100 mg/mL oral solution (EU/1/99/108/002-003). Both formulations are identical except the strength, the flavouring and the colouring agents, and the inclusion of potassium sorbate as a preservative in the 80 mg/mL formulation. Potassium sorbate was added in the formulation (at 0.2%) as an antimicrobial preservative in order to meet Preservative Effectiveness Testing criteria according to EP 5.1.3 and USP however the need, the choice of preservative excipient and its amount should be justified.

Acceptability to the target population, which includes pediatric patients, was considered when choosing the flavouring and colouring agents. Bubble gum flavour has been employed in the 80 mg/mL formulation because it provides a taste recognizable to patients worldwide and is gauged to be among the most acceptable flavours across multiple cultures and regional preferences. The applicant is requested to present evidence of acceptability. An 80 mg/mL formulation containing Allura Red colorant was used in two ApoPharma-sponsored clinical studies (TIRCON2012V1 and TIRCON2012V1-EXT) of deferiprone in patients with pantothenate kinase-associated neurodegeneration (PKAN) (the most common form of NBIA).

Since many patients with PKAN will be paediatric, consideration was given to developing a formulation not containing any form of colorant, and, in particular, to exclude azo and other artificial dyes regarded as better avoided in medicines for children. However, a formulation with a colorant was developed to avoid visible discoloration from trace quantities of chelate.

ApoPharma explored natural colorants that would be both suitable in a product for children and able to mask the chelate. Further studies were carried out and cyanocobalamin (an analogue of vitamin B12), was found a suitable colouring agent in the final formulation however lack of incompatibilities with active substance are requested. Cyanocobalamin is used as a colour in the product. This is not listed in the approved list of colours in medicinal products. Reference is made to Article I of the Directive 2009/35/EC and Directive 94/36/EC Annex I nevertheless, the reliability to use cyanocobalamin in the formulation has been previously discussed and agreed in the scientific advice procedure which was submitted in the dossier.

The choice of pharmaceutical form/strength addresses the clinical needs (i.e. QTPP; bioavailability, patient's compliance, ease of administration, dosing regimen, paediatric population) and was taken under account during formulation development however the formulation choice rationale of strength/concentration and adequacy of dosing device requires further clarification.

The coloring and flavouring agents are unlikely to enhance or impede drug absorption.

Upkanz an 80 mg/mL oral solution of deferiprone:

- has an improved palatability over that of Ferriprox® (deferiprone) 100 mg/mL oral solution.
- is a clear reddish pink solution with a bubble gum-flavored aroma
- has been developed to facilitate a more precise administration of the active ingredient, deferiprone, to patients with NBIA including younger patients with lower body weight.

The chosen formulation adequately accommodates the active substance's physicochemical properties (stability, incompatibilities, solubility, route of administration etc.).

For the clinical studies TIRCON2012V1 and TIRCON2012V1-EXT, an investigational 80 mg/mL oral solution of deferiprone containing Allura Red (FD&C Red No. 40) colorant was used. This formulation and the Upkanz (deferiprone) 80 mg/mL oral solution differ only in the colorant used. This investigational medicinal product is reddish pink in colour with a bubble gum-flavoured aroma. For the clinical trials, the product was presented in a fill size of 500 mL per bottle.

The process was established based on prior knowledge of similar products and the solubility of the ingredients. The process was verified through a series of scale-up studies and modified to some extent based on the availability of the compounding tank and mixers. To achieve a product in which the API remains soluble requires preparation of several sub-phases, which are later combined in a specific order. The process is scalable due to the ingredients being soluble in their respective sub-phases.

QbD elements (risk assessment, prior knowledge) have been used in the pharmaceutical development/ manufacturing development / process design. This approach is acceptable.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product.

The medicinal product includes a medical device 30 mL graduated/dosing cup which comply with the relevant medical devices legislation. Dosing cap is CE-marked. It is the same dosing device as in case of Ferriprox 100 mg/mL oral solution. It complies with the relevant medical devices legislation.

Conformance with the essential requirements of Annex I of Regulation (EU) 2017/745 has been demonstrated.

The suitability of incorporated dosing device in relation to dosing accuracy requires further discussion/clarification.

The packaging components are generally compatible with the product, and the strength, quality and purity of the drug product are not way affected by the use of the chosen packaging components for containment of the product. The container closure system is suitable for use based on development studies, stability studies. Nevertheless, the risk of leaching of potential organic additives of the PET material should be confirmed by results.

Manufacture of the product and process controls

Name and address	Responsibility
Apotex Inc. – Richmond Hill site 380 Elgin Mills Road East Richmond Hill, Ontario Canada L4C 5H2	• Fabrication, primary and secondary packaging and testing of drug product. • Testing of drug substance and excipient batches prior to their use in the fabrication of the drug product. • Stability testing and microbiological testing of drug product.
Apotex Inc. – Etobicoke site 50 Steinway Boulevard Etobicoke, Ontario Canada M9W 6Y3	Alternative testing site for drug substance and excipients prior to their use in the fabrication of the drug product.
Apotex Inc. – Signet site 150 Signet Drive Toronto, Ontario Canada M9L 1T9	Alternative testing site for excipients prior to their use in the fabrication of the drug product.
Apotex Inc. 4100 Weston Road Toronto, Ontario Canada M9L 2Y6	Storage and distribution
Apotex Inc. 200 Barmac Drive Toronto, Ontario Canada M9L 2Z7	Alternative site for storage and distribution
Alpha Laboratories 1262 Don Mills Road Toronto, Ontario Canada M3B 2W7	Alternative testing site for excipients prior to their use in the fabrication of the drug product.

Description of manufacturing process and process controls are at relevant level of details. Flow diagram with indication of the critical steps is presented.

Relevant process parameters are laid down in the process description with set points or ranges. They are justified by pharmaceutical development. The applicant adequately justified the proposed ranges.

The manufacturing process is classified as standard.

No holding times are proposed. The applicant is asked to confirm this.

Adequate control strategy is proposed: temperature control, mixing steps (time and mixing speed), ingredients dispensing sequence, filling process which should lead to consistent quality.

The acceptable process ranges were established and data provided in support of the ranges is acceptable.

Product specification, analytical procedures, batch analysis

Release and shelf-life specifications

Specification parameter	Test limits		Test method
	Release	Stability	
Appearance	A clear, reddish pink solution with a bubble gum- flavoured aroma		GM-87 (Visual/House)
Identification	HPLC Retention Time:	N/A	AP66-OLSO-10-RH (HPLC/House/Issue 2)
Identification	UV spectrum	N/A	AP66-OLSO-61-RH (HPLC/House/Issue 1)
pH	2.5 to 3.5		GM-9 (Potentiometric/USP/BP/EP)
Net content	NLT 250 mL	N/A	GM-25 (Gravimetric/Physical/House)
Deferiprone Assay	95.0% to 105.0% label claim	90.0% to 110.0% label claim	AP66-OLSO-10-RH (HPLC/House/Issue 2)
Potassium sorbate Assay	85.% to 110.0% label claim		AP66-OLSO-10-RH (HPLC/House/Issue 2)
Degradation Products	Unidentified impurity: NMT 0.1% each Total impurities: NMT 0.5%		AP66-OLSO-20-RH (HPLC/House/Issue 2)
Uniformity of Mass of Delivered Dose from Multidose Containers	Perform on 20 doses of 20 mL. NMT 2 of the individual masses deviate from the average by MT 10% and none deviate by MT 20%	N/A	EP <2.9.27>
Microbial Limits	TAMC: NMT 1000 cfu/mL TYMC: NMT 100 cfu/mL		M-3 (Microbiological/USP/EP)
Microbial Limits			M-6 (Microbiological/USP/EP)
E. Coli	Absent in 1 mL		
Enterobacteria	Absent in 1 mL		
P. aeruginosa	Absent in 1 mL		
Salmonella	Absent in 1 mL GM-87		

The proposed release and shelf life specifications, and related analytical tests are acceptable.

Specification consist of:

a. universal test like solution appearance, active substance identification, net content

b. important test relating to safety: assay, uniformity of mass, impurities, microbial purity,

c. specific for dosage form: pH,

d. additional test: potassium sorbate assay.

Risk Assessment report provided in section 3.2.P.5.5 justifies exclusion of sorbate-glycerol interaction products from routine control. This is acceptable however additional data are needed.

Proposed limits/requirement are generally:

- in agreement with Ph. Eur. if test is according to chapter from pharmacopoeia
- in agreement with guideline ICH Q6A and 3AQ11A, ICH Q3B (common unidentified impurities 0.10%).

(Based on Maximum dose 6,750 g and rules in ICH Q3B: Reporting threshold 0.05%, Identification threshold 0.10%, Qualification threshold 0,15%).

The shelf life limits for Deferiprone assay are not supported by results of stability study. Therefore, the applicant is requested to adjust them to results.

Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf-life.

Suitability of the Ph. Eur. method of the microbial enumeration test and test for specified microorganisms in the finished product should be shown.

Analytical procedures and reference standards

The proposed analytical procedures are suitable for their purpose.

The proposed in-house procedures have been satisfactorily validated and they are adequate to control the finished product on a routine basis, i.e. as a release test.

However, control strategy for impurities coming from incompatibility between two excipients: glycerol and sorbic acid should be clarified.

The adequate information regarding the reference standards are submitted but the comparison of IR spectrum of primary standard and secondary standard is requested.

Batch analysis

Batch analysis results (3 batches of production size) confirm consistency & uniformity of the product indicating that the process is under control. The results of clinical, stability batches show the comparable quality of product.

The choice of the container/closure is justified, bearing in mind the physical/chemical properties of the product. The similar/the same as for Ferriprox 100 mg/mL oral solution.

Adequate protection from microbial contamination is confirmed by own stability study of Upkanz 80 mg/mL oral solution and by Ferriprox 100 mg/mL oral solution (approved commercial product).

The containers proposed for routine storage are those which have been used in the stability studies supporting the shelf life.

Stability of the product

The claimed shelf-life: 3 years/ in-use period: 8 weeks and storage conditions: Do not store above 30^0C as per the SmPC.

Stability studies / conditions were performed according to ICH guidelines.

There are no trends in any parameters tested during stability studies of three production batches except monoglycerides consistent with reaction of two excipients present in the oral formulation, glycerol and sorbic acid referred to as DEF-RC3/RC4. The amounts of degradants present are highly unlikely to impact preservative efficacy and there is no measurable effect on the assayed deferiprone content.

As required for semi permeable containers weight loss study were performed.

At the 36-month time point weight loss values (0,2 – 0,5% much below 5%) remained within specifications (under low humidity conditions of 25±2°C / 40±5% RH).

The stability study batches were also subjected to cycling stability study testing. All results confirmed to specifications initially and at the end of the study.

Results of Light stability study in accordance with ICH Q1B obtained when the product was covered by the secondary packaging and results obtained with the product in its primary container are almost the same without any evident trend.

Acceptance of proposed 8 weeks in use period requires further clarifications.

3.1.2. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Apotex B.V. is applying for marketing authorization for Upkanz, 80 mg/mL oral solution for the treatment of neurodegeneration with brain iron accumulation. Active ingredient Deferiprone is a known substance described in European Pharmacopoeia. Deferiprone is a very well characterized compound, non-hydroscopic by nature, which does not show polymorphism and stereoisomerism. For the drug substance, supplied by Apotex Pharmachem India Pvt. Ltd. the ASMF procedure is followed and specification of active substance is in agreement with Ph. Eur. All information provided by ASMF Holder according to the manufacture, development, active substance control and stability study have been assessed as acceptable. In relation to drug substance part of dossier all issues have been resolved satisfactory.

Upkanz (deferiprone) 80 mg/mL oral solution is presented in a fill size of 250 mL per bottle (amber, PET) with a medical device 30 mL dosing cup (compliant with relevant medical devices legislation) however the applicant proposed in Resonse Document to leave the choice of appropriate dosing device at discretion of the Pharmacy (see final conclusion on MO).

The choice of strength/concentration of solution 80 mg/mL needs further clarification.

The development of formulation and its manufacturing process was based on Ferriprox (deferiprone) 100 mg/mL oral solution)

The target population includes pediatric patients which were considered when choosing the flavoring (Bubble gum flavor) and coloring agents (Cyanocobalamin, B12) which replaces previous excipients of the same function however less acceptable for pediatric formulation due to palatability and safety reason ie. azo colorants. Potassium sorbate as preservative is added to formulation unlike Ferriprox. From quality point of view and in case of paediatric formulation the need of preservative requires clarification. The concentration used should be at the lowest feasible level.

The proposed medicinal product specifications are acceptable and generally in agreement with Ph. Eur. and adequate ICH guideline. The discreapancy within Documentation in terms of preservative limits requires clarification.

The discrepancy with regard to recommended/maximum dose with regard is clarified however the applicant is requested to present results of three commercial/industrial batches for elemental impurities because tested batches are not representative for industrial scale and composition of tested batches is slightly different in comparison to proposed formulation ie. Allura red was used in Clinical batches. (see ICH Q3)

There were no trends in any parameters tested except monoglycerides consistent with reaction of two excipients (glycerol and sorbic acid) present in the formulation during stability study. The last one identified incompatibilities has no measurable effect on deferiprone assay.

In view of recent discussions on potential presence of nitrosamine impurities the following comment is raised the applicant is requested to provide a risk evaluation concerning the presence of nitrosamine impurities in the drug product in question.

Upkanz (deferiprone) 80 mg/mL oral solution is presented in a fill size of 250 mL per bottle (amber, PET) with a medical device 30 mL dosing cup (compliant with relevant medical devices legislation) however as the applicant proposed in Resonse Document to leave the choice of appropriate dosing device at discretion of the Pharmacy the issue of dosing device is upgraded to Major Objection.

3.2. Non clinical aspects

3.2.1. Pharmacology

The pharmacology of deferiprone is well characterized by the number of study reports that had been submitted with the original application for Ferriprox and were extensively updated through postmarketing development program as well as long-term clinical experience. Deferiprone is currently therapeutically registered in the EU for similar indication to the one applied for.

The presented pharmacological profile of deferiprone is based on bibliographical data and the results of the applicant's studies. Those data are focused on the mode of action of deferiprone in the treatment of localized iron overload conditions in the absence of systemic iron overload, including neurodegenerative conditions with features relevant to NBIA, such as PD.

Deferiprone is a bidentate chelator containing a ketohydroxy-binding site; the compound intended for oral use became first clinically available in the 1990s. Three molecules are required to bind one molecule of Fe at physiological pH; these complexes are stable over a wide range of pH values. The particular physicochemical properties of deferiprone facilitate not only removal of the excess iron, but its transfer to apo-transferrin for physiological reuse.

At least the following genes are known to be associated with types of NBIA: *PANK2, PLA2G6, C19orf12, FA2H, ATP13A2, WDR45, COASY, FTL, CP*, and *DCAF17*. These relate to beta-propeller protein-associated neurodegeneration, COASY protein-associated neurodegeneration, fatty acid hydroxylase-associated neurodegeneration, Kufor-Rakeb syndrome, aceruloplasminemia, mitochondrial membrane protein-associated neurodegeneration, neuroferritinopathy, PLA2G6-associated neurodegeneration, pantothenate kinase-associated neurodegeneration, or Woodhouse-Sakati syndrome. In this submission, several proof-of-concept for in *vivo* neuroprotection and reversal of motor deficit associated with iron accumulation were presented from both sponsored studies and literature based on several rodent models of Parkinson disease and a genetic mouse model of aceruloplasminemia, one rare form among NBIA. On the one hand, a non-clinical genetic model of iron accumulation, the ceruloplasmin knockout ($Cp^{-/-}$) model of one of the rarest forms of NBIA, and the ceruloplasmin/ Hephaestin double-KO mouse model resulted in proven iron brain accumulation. These models were used to validate the link between iron chelation, brain cell protection and motor behaviour improvement by deferiprone. Such aceruloplasminemia models were not used to investigate

deferiprone activity on cognition. Since cerebellar atrophy occurred in human with aceruloplasminemia, that may be associated to cognition deficit (in humans cerebellum has an important role in motor control, but was also involved, to a lesser extent, in certain cognitive functions, such as attention, language and regulation of reactions of fear and pleasure), the applicant had to discuss whether $Cp^{-/-}$ or ceruloplasmin/ Hephaestin double-KO mice may exhibit similar atrophy and altered cognition. The applicant was requested to the lack of experimental data on cognition that would comply with request during the Scientific Advice.

PKAN pathogenic variants are the most current among NBIA and PKAN model would be a larger model of NBIA population than $Cp^{-/-}$. It is admitted that most of transgenic animal models of PKAN exhibited poor or no motor deficits, or lack of brain iron accumulation, thus these models may be not the most relevant. It was also reported in 2015 that some new models of neuroferritinopathy or PLA2G6-associated neurodegeneration exhibited severe motor deficits with regional iron accumulation (using iPLA2β-KO mice, or FTL-498InsTC transgenic mice with mutations of the ferritin light chain gene*)*, but the applicant did not use such models due to lack of accessibility and validation with a reference drug.

The *in vitro* studies demonstrated that deferiprone penetrates into cells and bounds to low molecular weight molecules in the cytosol: mitochondria, nuclei, and endosomes. Deferiprone facilitated iron transport has been shown between the extracellular solution and the cytosol, mitochondria, and nuclei. In the cell-free system, deferiprone showed the ability to inhibit the Fenton reaction by complexing iron and rendering it redox inert and the ability to preventing free radical-mediated reactions. In cell-based models deferiprone demonstrated the ability to protected a human neuronal cell line against hydrogen peroxide-induced oxidative stress.

In the *in vivo* MPTP mouse model, deferiprone (100 and 150 mg/kg, p.o., bid) dose-dependently and significantly improved motor function, increased striatal dopamine, and protected dopaminergic neurons in SN against toxin-induced death. The elevated total iron in SN was lowered to a level not significantly different from that in control animals. In another study using a similar MPTP model in mice, deferiprone (25 mg/kg, ip, bid) attenuated MPTP-induced deficits in rearing, rearing time, and mobile time to levels not statistically different from those in control. In a follow-up study deferiprone (25 and 75 mg/kg, i.p, q.d) dose-dependently reduced the magnitude of MPTP-induced loss of striatal dopamine transporters (DAT). Only the higher dose gave a statistically significant improvement over the MPTP-treated animals. The response to deferiprone, 75 mg/kg, ip, was similar whether the dose was given once or twice daily but 150 mg/kg ip, q.d. dosing was ineffective. Deferiprone did not affect striatal dopamine transporter levels in animals not exposed to MPTP.

In a 6-hydroxydopamine (6-OHDA) rat model of PD, deferiprone (10 mg/kg, ip, bid) significantly attenuated the 6-OHDA-induced decrease in striatal dopamine, normalized elevated dopamine turnover ratio, and prevented the loss of dopaminergic neurons in SN.

In the rotenone model of PD in male Lewis rats, deferiprone (30 mg/kg, p.o., bid) significantly improved animals' motor functions, normalized elevated dopamine turnover ratio, and attenuated oxidative damage to lipids in ventral midbrain. In Lewis rats given a single 30 mg/kg oral dose, plasma AUC was 29.5 µg·h/mL and striatal AUC was 27.6 µg·h/mL.

The presented overview of bibliographical data and results of applicant's non-clinical studies demonstrated that deferiprone inhibits tyrosine hydroxylase, catechol O-methyltransferase, non-haem iron-dependent enzymes soybean lipoxygenase, ribonucleotide reductase and deoxyhypusine hydroxylase. Deferiprone inhibits cell proliferation in CCL-119 and human PBMCs. Deferiprone treatment resulted in a significant and transient increase in plasma prolactin levels in SD, Fischer, Wistar and Evans rats.

The applicant referred to the known results of *in vitro* assay in which no significant inhibition of hERG K^+ channels were observe with deferiprone at concentration up to 3000 μM. The outcomes of *in vivo* studies presented by the applicant do not reveal relevant concerns on safety pharmacology endpoints. Pharmacovigilance date on Ferriprox would be more evident for the clinical safety.

Since cognitive decline occurred in some subtypes of NBIA, the applicant should discuss the absence of investigation of deferiprone effect on cognition and behaviour to consider applicability to whole NBIA subtypes. The request for investigation of a putative cognitive improvement by deferiprone in animal models is supported by the fact that (i) the Parkinson-like rodent models used by the applicant clearly allow to investigate drugs activity on cognition, since cognitive deficits are known to occur in rodents or non-human primate after MPTP, 6-OHDA or rotenone challenge (evidenced from cognitive performance in passive avoidance task, Morris water maze test, novel object recognition task may be found in literature); (ii) for the Question 4 of the Scientific Advice (EMA/CHMP/SAWP/155383/2012), CHMP answered *"Specific scales to assess other disease/treatment symptomatology may also be considered, such as the UPDRS motor score for parkinsonism and ICARS for ataxia. Cognitive and behavioral assessment is also needed"*. To support the putative enhancement effect of deferiprone on behaviour and cognition, the MAH referred to published studies: deferiprone rescued behavioural deficits induced by mild iron exposure in a mouse model of alpha-synuclein aggregation; deferiprone ameliorated memory impairment in scopolamine treated rats. Whether such findings may be supportive for cognition improvement in the NBIA context is unknown, however it may not be ethical (3R rules) at this stage of development to request additional studies in more representative NBIA-like models. It is therefore considered that there is nothing more to expect from non-clinical investigations at this stage of development, because the MAH reported improved cognition in deferiprone-treated group of patients during the TIRCON study through FIM/WeeFIM scale.

The Apotex has collected safety pharmacology endpoints of *in vitro* and *in vivo* cardiovascular, respiratory and central & peripheral nervous systems safety pharmacology studies as well as toxicology studies. Assessment of cardiovascular function was based on hemodynamic (heart rate, systolic, diastolic and mean arterial pressures and arterial pulse pressure) and electrocardiographic (QRS, PR, QT, QTc and RR intervals). There were no effects of deferiprone on qualitative or quantitative ECG parameters, or on heart rate, blood pressure or body temperature, at the doses evaluated. No abnormal clinical observations were attributed to administration of deferiprone. Administration of deferiprone to animals had no significant effects on arterial blood pressure, heart rate. No abnormal ECG waveforms or arrhythmias were attributed to administration of deferiprone. Neurological signs (excessive salivation and excessive lacrimation in rats) were completely resolved and appeared to have no negative impact on the wellbeing of the animals. Analyzed parameters (tidal volume, respiration rate and minute volume) of respiratory function resolved quickly and no differences from control values. Respiratory and neurological evaluation incorporated into toxicology studies conducted in rats and monkeys did not give any evidences of specific respiratory and nervous system symptoms in animals that were moribund.Drug interactions are addressed in the relevant sections of the Ferriprox SmPC. The absence of a non-clinical pharmacodynamic interaction data is acceptable.

Secondary Pharmacology

None of the *in vitro* or *in vivo* secondary pharmacology studies were GLP-compliant, this is accepted. It should be noted that no large selectivity profile had been provided (deferiprone tested against the classical and large panel of enzymes, ion channels and receptors involved in main physiological function) for previous marketing authorisation. As a consequence, it would not be acceptable to ask for such screening tests in the present submission. In vivo and in vitro data suggest possible inhibition of tryptophan hydroxylase and tyrosine hydroxylase at effective doses in non-clinical models. Increases in plasma prolactin shown in rats at 300 mg/kg have been confirmed in humans. Only deoxyhypusine hydroxylase was inhibited close to therapeutic concentrations only after prolonged (8-10h) exposure

times, which may be unlikely to be achieved in patients. Based on doses and clinical exposure proposed in NBIA (15 mg/kg twice daily), this should produce exposure in patients below the concentration of deferiprone associated with non-clinical findings: anti-proliferative effects, pro-apoptotic effect, DNA synthesis inhibition, inhibition of ribonucleotide reductase and associated inflammatory and vascular effects, interference on the metabolism of endogenous catecholamines, or 5-lipoxygenase (that catalyses biosynthesis of leukotrienes, lipid mediators of inflammation derived from arachidonic acid). Deferiprone is selective for Fe(III), but in displacement studies Cu(II) was the most efficient at displacing Fe(III). Displacement of Al^{3+} and Pb^{2+}, as well as aluminium depletion may be unlikely at the clinical dose.

Safety Pharmacology

Safety pharmacology studies evaluating the impact on the central nervous, cardiovascular, respiratory, renal, endocrine and immune systems were reported performed under GLP compliance according to ICHM3/S7 guidelines. Using a core GLP-battery usual approach, the applicant investigated the effect of deferiprone on the cardiovascular system, central nervous system in vivo, and respiratory system.

No significant treatment-related effects reported on hERG (human ether-à-go-go-related gene) current, arterial blood pressure, heart rate, cardiac conduction, and ECG waveforms. There was no CNS safety concern. Lip smacking, oral discharge, excessive salivation and increases in minute volume in rats during infusion were generally mild and transient and either resolved at the end of infusion or shortly after with no negative impact on the overall well-being of the animals. The only clinical observations made were limited to orange discoloured urine. Regarding the effects of deferiprone on renal function, endocrine and immune systems, the applicant selected results from an overview report of studies performed by independent investigators. Deferiprone caused dose-related increases in urine volume, and increases in Na^+, K^+, and Cl^- excretion over the first and second 3h-monitoring period in rats, which were considered mild and non-adverse effects. Non-adverse effects occurred on rat adrenocortical function. Weak humoral suppression was also detected in rats but at excessively high doses generally associated with debilitation and mortality. Since there was no negative impact on the overall well-being of the animals excepted at excessively high doses generally associated with debilitation and mortality, or only mild/transient non-adverse effects (oral discharge and lip smacking, associated to increases in tidal volume, respiration rate, and minute volume at ≥10 mg/kg) occurred, discoloured urine and increased urination are considered of no safety concern. According to ICH S7 Guidelines, "safety pharmacology studies are defined as those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above". Exposure data were not found within study reports. Then the MAH was requested to demonstrate that animals were appropriately exposed during intravenous infusion (single dose) to correlate with effect in the cardiovascular, central nervous and respiratory systems, and to discuss margins regarding human exposure at clinical dose. Exposures were estimated from other studies performed with a same infusion process and dose range in the same species at the same facility site. These data may be considered a few supportive because not performed during the given safety pharmacology studies. It appeared that Cmax and AUC for the 25-50 mg/kg in monkeys cover human exposure. Cmax and AUC for the 50 mg/kg in rats covered human exposure. Exposure for the highest dose ranged up to ≥ 2-fold the corresponding clinical exposure. Additional investigation to confirm exposure in safety pharmacology studies would not be ethical (3R rule) and would not add further insight in the context of NBIA while no adverse events on these organ systems were identified in the TIRCON or TIRCON-EXT studies in patients with PKAN.

General remark

Delays of one to eight years between studies completion and validation of reports should be clarified for the following studies : NCD-11-06, NCD-10-08, NCD-10-09, NCD-11-22, NCD-14-11, NCD-06-02,

NCD-07-01, NCD-08-01, NCD-09-06, NCD-11-20, NCD-11-21, NCD-12-13, NCD-13-16, NCD-13-17, NCD-14-12 . These reports were finalized only at time of preparation for marketing applications or for requests for clinical trial authorizations. If such delay may be unusual, further investigation would not be useful on a non-clinical perspective view as no GLP-status is required for these pharmacology studies.

3.2.2. Pharmacokinetics

The evaluation of the non-clinical pharmacokinetics of deferiprone includes:

• *in vitro* studies of metabolism of deferiprone in human and animal hepatic microsomes, studies of the impact of UDP-glucuronosyltransferase (UGT) inducers and inhibitors on the glucuronidation of deferiprone, plasma protein binding, blood to plasma distribution, and interactions with cytochrome P450 isoforms

• *in vivo* studies in CD-1 mice, Sprague-Dawley rats and cynomolgus monkeys dosed orally and iv with 14C-deferiprone (N-methyl carbon labelled).

One of the analytical methods, used in studies no.: Covance 1737/4; MDS Pharma 97/006; 97/007 to determine serum levels of deferiprone, did not differentiate between free or iron complexed deferiprone and therefore any difference in the pharmacokinetic profile (or relative amounts) of these two forms of the drug would not have been detectable.

The applicant is asked to explain the lack of incurred sample reanalysis (ISR) which is a necessary component of bioanalytical method validation and is intended to verify the reliability of the reported sample analyte concentrations.(OC) Key toxicology studies submitted in the Upkanz MAA that included serum toxicokinetics, and that were conducted from approximately 2009-2010 onwards, contained incurred sample reanalysis (reproducibility) data. The applicant provided adequate information on incurred samples reanalysis (ISR) and acceptable explanation on the IRS lack in the studies directly performed for the past MAA. With regard to pharmacology studies, please note that these were conducted in a non-GLP environment. In addition, those studies involving analysis by HPLC (NCD-11-20, NCD-11- 21, NCD-11-22) were performed during or before 2011, at which time no formal guidance relating to ISR for non-GLP bioanalysis work was in existence. Furthermore, pharmacokinetic parameters determined in these studies are consistent with corresponding values obtained in other non-clinical (development) studies in rodents at comparable doses, supporting the reliability of the methods used. Extension of the ISR recommendation to ligand-binding assays was proposed in 2010, and confirmed as a requirement for these assays (immunoassays for ligands, peptides, biomarkers) in 2015. However, reanalysis criteria for ISR for ligand-binding assays are still being clarified and refined. Submitted studies that used ELISA, immunoassay or radioactive assays (NCD-10-08, NCD-10-09, NCD-14-11, NCD-06-02, NCD-07-01, NCD-08-01, NCD-09-06, NCD-12-13, NCD-13-16) were performed during the period 2006-2013, and in a non-GLP laboratory. Bioanalytical data reproducibility by IRS tool were adequately verified.

The Rapp agrees with the company that "deferiprone is orally bioavailable and demonstrates significant first-pass metabolic clearance, predominantly to an inactive glucuronide that is rapidly cleared through urinary excretion. It is widely distributed systemically and clears from most tissues at a rate similar to its clearance from plasma. Its absorption, biotransformation and excretion in the laboratory species used closely resembles that seen in humans dosed orally, indicating that the rat and cynomolgus monkey are metabolically and pharmacokinetically appropriate models to describe the fate of deferiprone inhumans".

The discussion of limited significance of non-clinical data extrapolation to the clinical situation regarding the assumption of deferiprone dosage in adults and children over the age 4 in clinical

settings was provided and the non-clinical data may be considered as secondary. A large clinical experience of both adult and paediatric patients exposed to deferiprone during the past 30 years, including 20 years of post-approval experience of Ferriprox® is given. The applicant acknowledged the recognize deferiprone pharmacokinetic profile in children and adults. The company's positions that "administration of 14C-deferiprone to rats or cynomolgus monkeys indicated limited penetration into brain. However this may reflect the limited penetration of the radiolabelled glucuronide metabolite since iv microdialysis studies in rats demonstrate that the appearance of unlabeled deferiprone in the brain is rapid and substantial (distribution t1/2 0.18 ± 0.02 h)" is considered acceptable.

The metabolism of deferiprone was previously examined and it is already considered established in animals and in humans. With regard to the in vitro metabolic studies provided by the applicant, pharmacologically inactive 3-O-glucuronide was detectable in in mouse, rat, monkey and human hepatic microsomes. Nocytochrome P450 (CYP) mediated metabolism was detected in liver microsomes from rats, monkeys or humans. The in vivo studies indicated that deferiprone is glucoronidated in rat and monkey.

Urinary excretion accounted for > 60% in both rats and cynomolgus monkeys. Fecal excretion accounted for ≤ 11% and for ca. 3-4% of total radioactivity in rats and cynomolgus monkeys, respectively. In both species deferiprone was extensively 3-O glucuronidated (40-50% of dose for rats and 35-50% of dose for cynomolgus monkeys; excreted in urine). About10-15% and 1% of the radioactive dose was excreted unchanged inurine of rats and cynomolgus monkeys, respectively.

No significant inhibition of human CYP isozymes (CYP1A1, 1A2, 2C9, 2D6, 2E1 and 3A4) was seen with deferiprone up to 400 µM. The SmPC contains warnings over drug-drug interactions and this is considered acceptable for this type of application.

3.2.3. Toxicology

The single dose toxicity studies were performed in naïve and iron-loaded rodents (mouse ICR, rats SD) and in cynomolgus monkey. The median lethal dose was in the range of 500-800 mg/kg.

In mice and rats the primary effects were lethargy, abnormal gait, labored breathing, low body temperature, ptosis, prostration and lethality. Monkeys were hunched and hypoactive with decreased reactivity to stimulus, squinting eyes, emesis, excessive salivation andptosis, and were cold to the touch.

Repeat-dose oral toxicology studies were conducted in rats and monkeys. Adverse findings related to the pharmacologic effects of the drug were evident in animals.

Findings included anemia, reduced red cell parameters, and bone marrow hypocellularity. Other drug-related toxicities included: mammary gland hyperplasia and tumors, and findings in the liver (e.g. increases in liver weight and liver enzymes, formation of fat vacuoles and/or hepatic centrilobular necrosis/degeneration), in rats. The magnitude of effects in the liver varied depending on whether rats were loaded with iron prior to treatment or were naïve (non-iron-loaded). Other effects attributed to the drug were increased weight of pituitary, adrenal, and heart with no clear microscopic correlates.The TK data do not reveal any significant safety concerns. In both rats and monkeys, Cmax and AUC0-7h generally increased with increasing doses and was noticeably higher in non-iron-loaded animals. Tmax and t1/2 were essentially the same for all groups and were not dose, sex, iron-loading or duration of treatment dependent.Significant interspecies differences were found in: (1) iron homeostasis, (2) response to deferiprone. Any of interspecies differences in local biochemistry, cell environment, enzyme, receptor or transporter control mechanisms, accessibility of deferiprone to local iron pools, rate of mobilization of iron in response to deficiencies at critical molecular sites, and other factors, may influence gross outcomes.

The genotoxic potential of deferiprone was thoroughly assessed as part of Ferriprox registration dossier and deferiprone development program. Previously collected data indicated deferiprone was genotoxic: mutagenic in mammalian cells but not in bacterial cells and clastogenic in in vitro Chinese hamster ovary cells and in vivo mouse micronucleus test. It was suggested that the genotoxic effect is attributed to the chelation of iron. The results of clinical clastogenicity study demonstrated that, in the clinical setting, deferiprone has no greater clastogenic potential than deferoxamine The SmPC states the following in section 5.3: The genotoxic potential of deferiprone was evaluated in a battery of in vitro and in vivo tests. Deferiprone did not show direct mutagenic properties but was clastogenic in in vitro assays and in animals.

The clastogenic potential of deferiprone, and acknowledgement that risk of carcinogenicity cannot be excluded, are adressed in the SmPC.

In the response letter of Scientific Advice in 2012 (EMEA/CHMP/SAWP/155383/2012), CHMP considered that: "The reasoning for not performing juvenile animal studies based on existing experience in children and on the difficulties emerging from the use of developing animals (rodents) where the potential effects of iron depletion on development could mask other safety aspects is also endorsed. A review analysis of safety data from post-marketing experience of Ferriprox® regarding paediatric population AEs and especially carcinogenic risk is endorsed and is considered the most relevant. These clinical safety data could be considered as sufficient to assess the safety in paediatric population, provided that specific measures to assess and ensure safety in human studies is considered".

A post-approval review of Ferriprox® was requested by the Scientific Advice (EMA/CHMP/SAWP/155383/2012) to evaluate the carcinogenicity in humans. This review should be discussed with the findings of tumors in the 52 week-chronic toxicity study in rats in all DEFERIPRONE-treated groups to consider the carcinogenicity risk. The MAH was addressed whether a revised wording in SmPC 5.3 should be required accordingly. Review of the raw histological data from the 52 week-chronic toxicity study in rats showed an incidence of tumors (liver, lung, mammary gland, skin and thyroid) in all deferiprone-treated groups (independent of whether they were naïve or iron-loaded), but with none in male or female control animals. Mammary gland hyperplasia in females (after 3 and 12 months; ≥37.5 mg/kg bid), mammary atrophy in males (3 months; ≥37.5 mg/kg bid), and thyroid changes (12 months; ≥37.5 mg/kg bid) were evident in rats. The mammary gland effects were not dose related in incidence or severity and not remarkably worse after 12 than after 3 months of treatment. Most changes fully or partly resolved during off-dose periods following treatment with deferiprone, although thyroid hypertrophy and colloid basophilia persisted in naïve and iron-loaded rats given 75 mg/kg bid or 100 mg/kg bid, respectively, for 12 months. In addition, secondary pharmacology studies reported an increase of plasma prolactin that was not translated by a tumour at the hypophysis level. However there are no sufficient arguments to exclude that these effect would also reverse in a usual 2-year carcinogenicity study. The MAH argued that the total incidence of malignant tumors in deferiprone-treated animals (63–64 weeks or 67–68 weeks old after recovery), expressed as number of malignant tumors/number of animals, was lower than that reported from about twenty carcinogenicity studies in Charles River SD rats aged up to 57–58 weeks. This would suggest that the tumours occurred spontaneously in SD rats, and there was no dose-related increase in total incidence of malignant (and benign) neoplasms in deferiprone-treated groups. As of 31 August 2018, only 13 cancer events had been reported from clinical trials and 18 years post-marketing experience with Ferriprox), and no tumors were reported during the TIRCON and TIRCON-EXT studies in PKAN patients. Then applicant'suggestion that the current carcinogenicity labelling in the existing Ferriprox SmPC is sufficient is endorsed. Additionally the applicant was asked to present a summary of the available non-clinical data, based on which the safety of deferiprone in children over the age of 4 was estimated. In these considerations the following adverse reactions of deferiprone should be taken

into account: atrophy of thymus, lymphoid tissues and testis, hypertrophy of adrenals, genotoxic potential in eukaryotic cells, and also described previously in Ferriprox® dossier induction of numerous malignant tumors (hepatocellular carcinoma, lung metastasis malignant histiocytoma, lung metastasis hepatocellular carcinoma, mammary adenocarcinoma, mammary carcinoma, mammary fibroadenoma, skin keratoacanthoma, skin malignant fibrous histiocytoma, skin fibrocyte fibroma and thyroid follicular cell adenoma). The major non-clinical findings noted in lymphoid tissues, bone marrow, testis and on the adrenal gland have not been confirmed into clinical practice with deferiprone, and conditions of both systemic (transfusion-dependent anemias) and local (PKAN, Friedreich's ataxia, Parkinson's disease) iron overload, in adults and children from 2 years old and upwards.

The deferiprone effects on the lymphoid system were seen. The most common findings at doses of 100 mg/kg/day and above were hematologic effects such as bone marrow hypocellularity, and decreased WBC, RBC and/or platelet counts in peripheral blood. Atrophy of the thymus, lymphoid tissues, and testis, and hypertrophy of the adrenals have also been reported at doses of 100 mg/kg/day or greater in naïve and iron-supplemented animals The applicant was requested to evaluate potential immunotoxicity of deferiprone in the clinical situation since its marketing in 1999. The MAH indicated immunotoxicity was assessed during the pivotal study for the approval of Ferriprox by the EMA in 1999 conducted in patients with thalassemia (deferiprone at 75 mg/kg/day for up to 12 months). Mean values of total lymphocytes, B cells, and OKT3, OKT4, and OKT8 cells exhibited minor changes compared to controls. Humoral immunology was assessed, and the number of patients with autoantibodies as hallmarks for impact on the immune system was considered low. There have been few reports of immune system disorders from post-marketing data. Deferiprone-induced immunotoxicity potential may be considered low based on clinical experience in patients with thalassemia. Clinical data supersede preclinical data and additional immunotoxicity animal studies would not add further insight in the context of NBIA.

No risk has been identified by the analysis of quality aspects that might have a potential impact on the product toxicological profile. There are no safety concerns related to the impurities, excipients and/or any related substances.

Phototoxicity

The applicant did not provide any experimental or literature about the spectral properties of deferiprone, its MEC (molar extinction coefficient), and photoactivity/sensitising potential of deferiprone. From the published UV-visible spectrum of deferiprone, it can be admitted that deferiprone did not absorb visible light and had no photoxicity potential per se, however the absorption spectra of Fe(III) complexes with deferiprone exhibited intensive absorption bands between 300 and 600 nm (Timoshnikov et al, 2014) with a maximum absorption at 460 nm (Pragourpun et al, 2015). Timoshnikovet al, 2014 also demonstrated that thedeferiprone–Fe(III) complex was stable under irradiation with visible light but undergoes fast photolysis under UV irradiation. Using chemically induced dynamic nuclear polarization (CIDNP) deferiprone was show to exhibit both electron accepting and electron donating abilities, free radical intermediates of deferiprone had been detected under direct and photosensitized UV irradiation (Timoshnikov et al, 2014). Then the applicant must take into account these articles and discuss the risks of skin and ocular photosensitisation/toxicity from deferiprone-iron complexes and free radical species generated from deferiprone, with regard to clinical observations. The MAH described limitation and caveats of CIDNP technique to detect free radicals generation for high-spin ferric complexes such as the deferiprone-Fe(III) over electron paramagnetic resonance (EPR) that would be a more direct and robust technique for the study of free radicals of transition metal complexes and the photochemically induced generation of reactive oxygen species. Timoshnikov et al. published another study in 2015 using EPR, which did not show Fe3+-induced radical oxygen species production in presence of deferiprone. Finally, the clinical background, i.e, 20

years of post-marketing experience in the EU for thalassemia, leads to conclude on a low risk of photosensitization or phototoxicity, since only five reports of skin related adverse events were recorded.

3.2.4. Ecotoxicity/environmental risk assessment

The applicants' position that the introduction of Upkanz 80 mg/mL oral solution on the EU market, in addition to current use of Ferriprox®, is highly unlikely to result in any significant adverse ecotoxicological impact is endorsed. The refined Fpen value, in line with orphan drug designation, for the revised PECSURFACEWATER calculation was used. The applicant correctly assumed that the provided calculation emphasise no environmental hazard arising from defireprone use. The Apotex calculation is supportedIt is unclear whether Dow and Kow were compliant to the EMEA/CHMP/SWP/4447/00 Rev. 1 Guideline to allow supporting the environmental risk assessment. Then the applicant should provide own experimental values for Dow and Kow using a GLP-shakeflask/slow-agitation or HPLC methods that comply with OECD guidelines, or must demonstrate that provided values from literature complied with OECD and GLP requirements. In his response, the MAH reported Kow was found very close to 0.17 in two independent scientific publications, and claimed to have also repeated the measurement using the same method, while not fully conducted according to OECD guideline 107. A better argue comes from the published study conducted in 1996 by Xie et al., who used a shake-flask method (partialy compliant with the OECD method), which gave the value of LogP at -0.77, equivalent to a Kow of 0.17. The applicant suggestion that Kow and Log KoW values can be considered realistic due to convergence of several independent approaches while not fully compliant with ad hoc guidance, is endorsed.

3.2.5. Discussion on non-clinical aspects

Deferiprone is a blood-brain barrier-penetrant iron chelator with properties that fulfil requirements for conservative chelation, i.e., it supports transfer of iron from sites of excess tonormal biologic receptors where it can be used in endogenous metabolism.

A number of non-clinical aspects were raised previously in the original submission for deferiprone and through the post-marketing activities with the drug substance. Some of the deficiencies had been partly addressed by the newly submitted non-clinical data and by adequate clinical data that are likely available to address the non-clinical gaps.

Overall, there are considerable non-clinical concerns over the proposed dose and the extension of indication for this product.

3.2.6. Conclusion on non-clinical aspects

From a non-clinical perspective, Upkanz, 80 mg/mL oral solution, could be recommended for approval providing the points raised are adequately addressed by the applicant.

However SmpC remains to be implemented in the 5.3 Preclinical safety data section accordingly:

1) The MAH did not provided Human Equivalence Doses (HED) as requested. HED should be added (as well as margins) for convenient understanding.

2) It should be added "No studies of deferiprone's secretion into maternal milk have been carried out."

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

LA20-BA	This was an Open-Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution Under Fasting and Fed Conditions.	The study population consisted of 15 healthy adult subjects (12 males and 3 females) with a mean age of 40 years (range of 22 – 52 years). The mean height and weight of all subjects was 169 cm (range of 146 – 186 cm) and 69.6 kg (range of 52.6 – 87.7 kg), respectively.
LA21-BE	Randomized, open-label, comparative, two-way crossover bioavailability study of deferiprone oral solution and Ferriprox® (deferiprone) tablets under fasting conditions	A total of 42 subjects (29 male and 13 female) were dosed, and 41 subjects (28 males and 13 females) completed the study. Pharmacokinetic and statistical analyses were performed on 41 subjects who completed both periods of the study. The safety evaluation was performed on all 42 dosed subjects.
TIRCON2012V1	It was a Multi-center, double-blind, randomized, placebo-controlled, 18-month study in patients with PKAN aged 4 years and older.	Of 100 patients who underwent screening, 89 were enrolled and randomized to receive either placebo (N=30) or deferiprone (N=59).
TIRCON2012V1-EXT	Long-term safety and efficacy study of deferiprone in patients with pantothenate kinase-associated neurodegeneration (PKAN)	Patients who had been randomized to receive deferiprone in the initial study continued to receive it in the extension study (the DFP-DFP group; n= 44), while those who had received placebo were switched to deferiprone (the placebo-DFP group; n=24). Since the initial study was still in progress at the time that the first patients entered the extension study, both patients and study staff remained blinded as to which product had been taken previously.
LA39-0412	The study was a multi-center, open-label, non-randomized, parallel group study in subjects with mild renal impairment (eGFR 60-89 mL/min/1.73m2), moderate renal impairment (eGFR 30-59 mL/min/1.73m2), severe renal impairment (eGFR 15-29 mL/min/1.73m2) and healthy volunteers (eGFR $\geq$ 90 mL/min/1.73m2), as determined by the estimated glomerular filtration rate (eGFR) from the Modification of Diet in Renal Disease Study.	A total of 32 subjects were enrolled, 8 in each of the renal function categories. All 32 subjects completed the study.
LA40-0412	This was a Phase IV, multi-center, non-randomized, open-label, single-dose, parallel group study to determine the effect of	A total of 21 subjects were enrolled in and completed the study. All 21 subjects were included in both the PK and safety analyses.

	impaired hepatic function on the pharmacokinetics (PK) of deferiprone and its 3-O-glucuronide metabolite following a single oral dose of 33 mg/kg deferiprone in subjects with mild or moderate hepatic impairment as compared to healthy volunteers.	
LA54-0116	This was a single-center, randomized, placebo-controlled, blinded, 2-period crossover study whose purpose was to determine the effect of deferiprone on prolactin levels in healthy volunteers.	Subjects were randomized to receive the following 2 treatments in different sequences, with a 7-day washout between doses: • Treatment A: A single 2500 mg dose of deferiprone, administered as five Ferriprox (deferiprone) 500 mg immediate-release tablets, under fasting conditions • Treatment B: A single dose of five matching placebo tablets under fasting conditions
LA56-0117	Single-center, randomized, single-dose, dose-ranging, open-label, 4-period, 4-sequence, crossover study in healthy volunteers. All subjects will receive 4 single doses of deferiprone DR tablets, separated by 7 days, at dosages of 5, 10, 15, and 30 mg/kg.	Sixteen healthy volunteers (7 males and 9 females) were randomized to receive 4 single doses of deferiprone DR 600 mg tablets on separate occasions, with a 7-day washout between doses. The doses were as follows: • Treatment A: 5 mg/kg • Treatment B: 10 mg/kg • Treatment C: 15 mg/kg • Treatment D: 30 mg/kg All doses were rounded to the nearest half-tablet. Subjects were randomized to receive the 4 doses in one of the 4 dosing sequences as per the randomization code list based on Williams design
LA37-1111	This was a Phase IV, single-center, randomized, single-dose, double-blind, double-dummy, placebo and active-controlled, 4-period crossover study to evaluate the effect of deferiprone on QTc prolongation in healthy male and female subjects.	A total of 50 subjects were enrolled in the study, and 40 subjects completed the study. There were 50 subjects included in the safety and cardiodynamic analyses and 49 subjects in the PK analyses.

3.3.1. Pharmacokinetics

Methods

Validation of a high performance liquid chromatographic mass spectrometric method for the determination of APO-066 and L1-glucuronide in human serum (Study: AA20080-VTL)

The analytical method was developed at MDS PS St-Laurent and validated according to the current validation SOP GL-BIO-10601. The analytical method is documented in SOP LMS-S-8152-01. An aliquot of human serum containing each analyte and internal standard was extracted using a protein

precipitation extraction procedure. The extracted samples were analysed by an HPLC equipped with an AB/MDS Sciex API 4000 mass spectrometer. Positive ions were monitored in the selected reaction-monitoring (SRM) mode. Quantitation was determined using weighted linear regression analysis (1/x) of peak area ratios of each analyte and internal standard.

The minimum requirements for validation included an assessment of selectivity, sensitivity, accuracy, precision, matrix effect, stability (freeze-thaw, short-term, stock, and post-preparative), and response function. Supporting assessments included the evaluation of recovery, dilution integrity, and processed sample integrity evaluations.

The high performance liquid chromatographic mass spectrometric method for the determination of APO-066 and L1-glucuronide in human serum met the validation requirements. Stability was demonstrated for APO-066 and L1-glucuronide in human serum samples and solutions under varying conditions of storage.

Validation of a high performance liquid chromatographic mass spectrometric method for the determination of APO-066 and L1-glucuronide in human urine (Study: AA20743-WCM).

The analytical method was developed at MDS PS St-Laurent and validated according to the current validation SOP GL-BIO-10601. The analytical method is documented in VWP-S-8155-02. An aliquot of human urine containing each analyte and internal standard was processed using a dilution procedure. The processed samples were analysed by an HPLC equipped with an AB/MDS Sciex API 4000 mass spectrometer. Positive ions were monitored in the selected reaction-monitoring (SRM) mode. Quantitation was determined using weighted quadratic regression analysis (1/x) of peak area ratios for APO-066 and internal standard, and a weighted linear regression analysis (1/x2) of peak area ratios for L1-glucuronide and internal standard.

The minimum requirements for validation included an assessment of selectivity, sensitivity, accuracy, precision, matrix effect, stability (freeze-thaw, short-term, stock, and post-preparative), and response function. Supporting assessments included the evaluation of recovery, dilution integrity, and processed sample integrity evaluations.

The high performance liquid chromatographic mass spectrometric method for the determination of APO-066 and L1-glucuronide in human urine met the validation requirements. Stability was demonstrated for APO-066 and L1-glucuronide in human urine samples and solutions under varying conditions of storage.

The applicant presented the validation report of a high performance liquid chromatographic mass Spectrometric method for the determination of apo-066 and L1-glucuronide in human serum (Study: AA20080-VTL) and human urine (Study: AA20743-WCM).

In serum validation method, the following parameters were addressed: assessment of selectivity, sensitivity, accuracy, precision, matrix effect, stability (long-term (-80oC 91 days; 4 freeze-thaw cycles, short-term (ambient temperature for 19,6 hours, stock and post-preparative), and response function. Supporting assessments included the evaluation of recovery, dilution integrity, and processed sample integrity evaluations.

In urine validation method, the following parameters were addressed: assessment of selectivity, sensitivity, accuracy, precision, matrix effect, stability (long-term (-80oC 91 days; 4 freeze-thaw cycles, short-term (ambient temperature for 21,5 hours, stock and post-preparative), and response function. Supporting assessments included the evaluation of recovery, dilution integrity, and processed sample integrity evaluations.

Calibration curve allowsperforming quantification in the concentration range from 0,2 – 50 ug/mL. A proper number of calibration concentration levels was used. Further, this range allowed for an adequate description of the pharmacokinetics of the analyte of interest in performed study.

The Inter-batch and Intra-batch accuracy, precision, dilution integrity, matrix effect, stability (long term-frozen, short-term, freeze-thaw cycles sample integrity, met the acceptance criteria for APO-066 and L1-glucoronide in serum and urine.

However, in the validation reports carry-over parameters was not identified. Furthermore, on-instrument/ autosampler stability of the processed sample at injector or autosampler temperature is also missing. The applicant informed that the validation of this method was based on the FDA Guidance on Bioanalytical Method Validation, 2001. In that guidance, there was no requirement for checking carry-over of the drug from high concentration samples to low concentration samples. Hence, this parameter was not investigated during the validation exercise. It is important to note that according to EMA guidelines (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) carry-over effect testing is necessary. According to the guideline, if it appears that carry-over is unavoidable, study samples should not be randomised, and specific measures should be considered and tested during the validation so that it does not affect accuracy and precision. In the absence of such testing, there is a risk that the results obtained are not entirely reliable. Therefore, the applicant is asked to explain what measures have been taken to ensure proper precision and accuracy (LoOI).

The applicant provided certificates of analysis for the analyte standard used in the analytical method.

An analytical run was properly designed - consisted of the blank sample, zero sample, calibration standards (minimum of 6 concentration levels), QC samples (low, medium and high) in duplicate (or at least 5 % of the number of study samples, whichever is higher), and study samples. As for advice, all samples of one subject were analysed together. Acceptance criteria were met for quality control sample analyses, dilution quality control sample analyses, calibration standard concentrations. Reassays of the sample was performed only from analytical reasons.

However, according to guide, it is recommended to evaluate the accuracy of incurred samples by reanalysis of study samples in separate runs at different days. As a guide, 5% of the number of samples exceeding 1000 samples should be reanalysed. Results of the mentioned analysis are missing and should be provided. The applicant informed that, the FDA Guidance 2001 does not include a requirement for performing incurred sample analysis (ISR) during analysis of the study subject samples. Hence, the ISR data were not provided in the study report. In addition, the bioanalytical validation method report had been submitted to the EMA before for the application of the 100 mg/mL OS, and the reported data were found to be acceptable to support the registration.

As outlined by the EMA guideline on bioanalytical method (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) which came in force since 01 Feb 2012, the ISR data are a key element necessary for the validation of bioanalytical methods. In the absence of such data, the provided serum concentration of deferiprone and its metabolite 3-O-glucuronide in human during the pivotal phase III study TIRCON2012V1 (study of interest in this dossier) could not be considered as reliable.

The argument that the bioanalytical methods AA20080-VTL and AA20743-WCM have already been considered acceptable by EMA for the application of the 100 mg/mL product is not acceptable.

Indeed, the assessment of this dossier dates back to 2007, so before entry into force of the new guideline. However, the studies were submitted as additional material for the current hybrid application and therefore the applicant is asked to discuss whether the absence of these procedures did not make the data then obtained unreliable. Thus, the requirement for ISR data provided by the bioanalytical guideline 2012 cannot be waived for the current application.

The applicant is still asked to provide ISR data. Indeed, in absence of such data, serum concentration of deferiprone and its metabolite 3-O-glucuronide collected during the pivotal phase III study TIRCON2012V1 could not be considered as valid. Thus, the PK parameters calculated based on these measurements are not considered reliable yet. In absence of these data, the issue should be upgraded to PK major objection. (OC, please refer to LoOI).

Validation of an LC-MS/MS method for the determination of deferiprone and deferiprone-glucuronide in human serum (Study: AA99306-01).

The analytical method was developed at Celerion, Lincoln, Nebraska, and validated according to the standard operating procedures (SOPs) in effect during the conduct of the validation. The analytical method is documented in BAM SOP AA99306-01. An aliquot of human serum containing the analyte and internal standard was extracted using a protein precipitation procedure. The processed samples were analyzed by an HPLC equipped with an AB SCIEX API 4000Ô triple quadrupole mass spectrometer using an ESI source. Positive ions were monitored in the multiple reaction monitoring (MRM) mode. Quantitation was determined using weighted linear regression analysis (1/concentration2) of peak area ratios of the analyte and internal standard. The reference standard materials deferiprone and d3-deferiprone (IS) are light sensitive. All storage and handling of reference standard material for deferiprone and d3-deferiprone (IS) should be conducted under UV-shielded light conditions (i.e., protected from white light).

The minimum requirements for validation included an assessment of accuracy, precision, response function, sensitivity, selectivity, matrix effect, matrix factor, multiple analytes measured by assay, over-the-counter cocktail testing, hemolyzed sample integrity, lipemic sample evaluation, recovery, stability (long-term, freeze-thaw, short-term, post-preparative, long-term stability for stock solutions, short-term stability for stock solutions, stability of analyte during sample collection and handling), and integrity (dilution integrity and processed sample integrity), and stress test.

The LC-MS/MS method for the determination of deferiprone and deferiprone-glucuronide in human serum met the requirements as specified in the validation protocol. Stability was demonstrated for deferiprone and deferiprone-glucuronide in human serum samples and solutions under varying conditions of storage.

Validation of an LC-MS/MS method for the determination of deferiprone and deferiprone-glucuronide in human urine (Study: AA99574-01).

The analytical method was developed at Celerion, Lincoln, Nebraska, and validated according to the standard operating procedures (SOPs) in effect during the conduct of the validation. The analytical method is documented in BAM SOP AA99574-01.

An aliquot of human urine containing the analyte and internal standard was processed using a dilution procedure. The processed samples were analyzed by an HPLC equipped with an AB SCIEX API 4000Ô triple quadrupole mass spectrometer using an ESI source. Positive ions were monitored in the multiple reaction monitoring (MRM) mode. Quantitation was determined using weighted linear regression analysis (1/concentration2) of peak area ratios of the analyte and internal standard.The reference standard materials for deferiprone and d3-deferiprone (IS) are light sensitive. All storage and handling of reference standard material for these analytes should be conducted under UV-shielded light conditions (i.e., protected from white light).

The minimum requirements for validation included an assessment of accuracy, precision, response function, carryover, sensitivity, selectivity, matrix effect, matrix factor, multiple analytes measured by assay, recovery, stability (long-term, freeze-thaw, short-term, post-preparative, long-term stability for

stock solutions, short-term stability for stock solutions), integrity (dilution integrity and processed sample integrity), and stress test.

The LC-MS/MS method for the determination of deferiprone and deferiprone-glucuronide in human urine met the requirements as specified in the validation protocol. Stability was demonstrated for deferiprone and deferiprone-glucuronide in human urine samples and solutions under varying conditions of storage.

The applicant presented the validation report of an LC-MS/MS method for the determination of deferiprone and deferiprone-glucuronide in human serum (study: AA99306-01) and in human urine (Study: AA99574-01).

In validation method, the following parameters were addressed: accuracy, precision, response function, carryover, sensitivity, selectivity, matrix effect, matrix factor, multiple analytes measured by assay, recovery, stability (long-term, freeze-thaw, short-term, post-preparative, long-term stability for stock solutions, short-term stability for stock solutions), integrity (dilution integrity and processed sample integrity), and stress test. Most of the parameters met the acceptance criteria.

However, according to guideline, mean concentration, at each level of stability evaluation, should be within ±15% of the nominal concentration. The freeze-thaw stability of LLOQ (100 µg/mL) in the study: aa99306-01, has not met the acceptance criteria and was assessed as 16,3%. Also,the autosampler stability of the processed sample at injector or autosampler temperature is missing.

During calibration curve preparation,a proper number of standards were used in the concentration range between 0,1 – 20 ug/mL. Back-calculated calibration curve standard concentrations of precision and accuracy batches for deferiprone met acceptance criteria (±15% of the nominal value, and for LLOQ within ±20%). However, analysis of bioanalytical report (LA39-0412), revealed that chosen range of the curve does not allow for an adequate determination of deferiprone concentration in human serum as it has been showed that part of the probes wasthe upper limit of quantification. The response of the instrument with regard to the concentration of analyte should be known and should be evaluated over a specified concentration range. According to the guideline, if a large number of the analyte concentrations of the study samples appear to be above the ULOQ, the calibration curve range should be extended, if possible, and QC samples added or their concentrations modified.

Incurred samples reanalysis was performed on 22 randomly chosen samples. As guidelines recommend to reanalyze, depending on a number of samples in the study, from 5 to 10% of samples.

VALIDATION OF AN HPLC METHOD USING MS/MS DETECTION FOR THE DETERMINATION OF DEFERIPRONE AND DEFERIPRONE 3-O-β-D GLUCURONIDE IN HUMAN SERUM (DFN-V3-523 (R6))

The sample pre-treatment procedures, chromatographic conditions, stock solution preparation procedures, and calibrants and QC samples preparation procedures are described in bioanalytical method LAS-1583, which contains representative chromatograms.

Sample pre-treatment involved the protein precipitation extraction of Deferiprone and Deferiprone 3-O-β-D Glucuronide from 0.100 mL of human serum; Deferiprone-D3 and Deferiprone-D3 3-O-β-D Glucuronide were used as the internal standards (IS1 and IS2).The compounds were identified and quantified using reversed-phase HPLC with MS/MS detection over a theoretical concentration range of 0.100 µg/mL to 50.000 µg/mL for Deferiprone and 0.100 µg/mL to 60.000 µg/mL for Deferiprone 3-O-β-D Glucuronide. The concentrations were calculated using peak area ratios, and the linearity of the calibration curve was determined using a weighted ($1/x^2$) linear ($y=mx+b$) least squares regression analysis for Deferiprone and Deferiprone 3-O-β-D Glucuronide.

The method for the determination of Deferiprone and Deferiprone 3-O-β-D Glucuronide in human serum using HPLC with MS/MS detection has met acceptance criteria with respect to specificity, sensitivity, precision, accuracy, matrix effect, linearity, percent extraction yields and dilution integrity, spanning a theoretical concentration range of 0.100 µg/mL to 50.000 µg/mL and 0.100 µg/mL to 25.000 µg/mL for Deferiprone and 0.100 µg/mL to 60.000 µg/mL and 0.100 µg/mL to 30.000 µg/mL for Deferiprone 3-O-β-D Glucuronide. Stability evaluations in matrix and solutions have also met acceptance criteria, demonstrating insignificant degradation over the specified storage durations and conditions.

The applicant presented the Validation of an HPLC method using MS/MS detection for the Determination of deferiprone and deferiprone 3-o-β-d Glucuronide in human serum (Validation Report N° DFN-V3-523 (R6)).

The method for the determination of deferiprone and deferiprone 3-O-β-D glucuronide in human serum using HPLC with MS/MS detection has met acceptance criteria with respect to specificity, sensitivity, stability (short-term – 22,9 h, long-term – 252 days in 4° C, in whole blood, freeze and thaw cycles- 3 cycles at – 20oC), precision, accuracy, matrix effect, linearity, percent extraction fields, carry over and dilution integrity. Further, autosampler storage stability was confirmed up to 142.7 hours at 4°C. Partial validation of a new injection procedure was performed, the range of the curve was truncated to 30 ug/mL. The range of curves allowed an adequate description of the pharmacokinetics of the deferiprone and its metabolites. Incurred sample reproducibility was performed according to guideline recommendation, and the percent difference between the initial concentration and the concentration measured during the repeat analysis was not greater than 20% of their mean for at least 67 % of the repeats.

LA20-BA - Comparative phase I PK study

Design: LA20-BA was an open-label, single-dose, three-way crossover bioavailability study of Deferiprone tablets (Ferriprox®) and Deferiprone solution under fasting and fed conditions.

Objectives:
The primary objective of this study was to determine the relative bioavailability of deferiprone tablets to deferiprone solution in healthy subjects under fasting conditions. The secondary objective was to examine the effect of food on the bioavailability of deferiprone tablets in healthy subjects.

Test product
A single oral dose of 1500 mg of Ferriprox® (deferiprone) 500 mg film-coated tablets, administered under fasting conditions was considered the test product. For the assessment of food effect, a single oral dose of 1500 mg of Ferriprox® (deferiprone) 500 mg film-coated tablets, administered under fed conditions was considered the test product.

Reference product
A single oral dose of 1500 mg of deferiprone solution 100 mg/mL, administered under fasting conditions, was considered the reference product. For the assessment of food effect, a single oral dose of 1500 mg of Ferriprox® (deferiprone) 500 mg film-coated tablets, administered under fasting conditions was considered the reference product.

Treatments Administered
Subjects were assigned randomly to the treatment groups A, B, C
A = 3 x 500 mg deferiprone tablets administered under fasting conditions.

B = 3 x 500 mg deferiprone tablets administered under fed conditions.
C = 1 x 15 mL of 100 mg/mL deferiprone solution administered under fasting conditions.

Blinding
Although this was an open-label study, the laboratory analysts did not have access to the randomization scheme.

Population: A total of 15 healthy subjects (12 male and 3 female) were dosed, and 13 subjects (10 male and 3 female) completed the study.

Diagnosis
All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers whosatisfied the screening evaluation and completed the baseline assessment. The main inclusion criteriawere:

Main criteria for inclusion:
1. 18 to 55 years of age, healthy male or female non-smoking volunteers.
2. Had a body weight of at least 50 kg.
3. Had a Body Mass Index (BMI) between 21.0 and 28.0.

Main criteria for exclusion:
1. Had a history or presence of significant asthma, chronic bronchitis, seizure, diabetes, migraine, hypertension, cardiovascular, pulmonary, neurological, hepatic, renal, hematopoietic or gastrointestinal disorders or ongoing infectious diseases, or any other significant abnormality as evidenced by a medical history and physical examination.
2. Had a positive screen for Hepatitis B surface antigens, Hepatitis C or HIV antibodies.
3. Had a significant abnormality in the ECG as judged by the study physician.

Selection of doses:
In the treatment of iron overload in patients with thalassemia major, deferiprone is most commonly given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight. In this single-dose bioavailability study, 1500 mg deferiprone was given to each participant. This dose, which does not exceed the usual recommended dose for any subjects that weigh at least 50 kg, was expected to yield a quantifiable concentration of deferiprone in serum throughout the sampling time in order to allow for a reliable estimation of the pharmacokinetic parameters for all treatments.

Exclusions
A total of 13 subjects completed all three periods of the study and 2 subjects completed at least two periods of the study associated with a comparison of interest. Subject Nos. 2 and 6 withdrew from the study for personal reasons following Period 2.

Protocol Deviations
The protocol deviations occurred during the conduct of this study included error in meal consumption (subjects 1,3-5, 7,8,10,11 in Periods 1 and 2), out of range storage condition for serum and urine (1.5 hours reaching a maximum temperature of -55 ^{o}C; 1.75 hours reaching a maximum temperature of -35 ^{o}C; subjects 1-15, periods 1 and 2), voided urine collection (the 12-24 hours urine collection interval in Period 3) and spilled urine (subject 10; 4-8 urine collection interval; Period 2).

Criteria for evaluation:

Pharmacokinetics:
a) Cmax (maximum concentration).
b) Tmax (time of maximum concentration).
c) λ or Kel (1st Order terminal elimination rate constant).

d) t ½ (terminal elimination half-life).
e) AUC0-t (Area under the concentration-time curve from time zero up to the time of the last measurable analyte level, calculated by the linear trapezoidal rule.)
f) AUC0-∞ or AUCinf (Area under the concentration-time curve from zero to infinity)
g) AUMC (Area under the first moment curve, the curve of the product of sampling time and concentration versus sampling time)
h) MRTpo (The sum of mean absorption time and mean residence time).
i) CL/F (apparent total body clearance of the parent after oral administration of deferiprone)
j) CL/fm (apparent total body clearance of the metabolite after oral administration of the parent drug (deferiprone))

1) The 90% confidence intervals of the ratio of least-squares means of the deferiprone and deferiprone glucuronide pharmacokinetic parameters AUC0-t, AUC0-∞ and Cmax of the test formulation (deferiprone tablet form **under fasting conditions**) to reference formulation (deferiprone in a solution form under fasting conditions) should be within 80% to 125% range.

2) The 90% confidence intervals of the ratio of least-squares means of the deferiprone and deferiprone glucuronide pharmacokinetic parameters AUC0-t, AUC0-∞ and Cmax of the test formulation (deferiprone tablet formulation **under fed conditions**) to reference formulation (deferiprone tablet form under fasting conditions) should be within 80% to 125% range.

Pharmacokinetic results

Table 7.4.7-1 Summary of pharmacokinetic results - Mean (CV%) serum deferiprone pharmacokinetic parameters when administered as a tablet under fasting and fed conditions and as a solution under fasting conditions

	Tablet Fasting (A)	Tablet Fed (B)	Solution Fasting (C)
AUC_{0-t} * (µg·h/mL)	49.2 (34.2) n = 15	43.9 (36.3) n = 14	49.5 (33.0) n = 14
AUC_{inf} * (µg·h/mL)	50.4 (33.9) n = 15	44.6 (36.7) n = 13	50.4 (32.6) n = 14
C_{max} (µg/mL)*	18.8 (37.8) n = 15	11.7 (35.2) n = 14	18.8 (29.7) n = 14
t_{max}(h)	1.06 (64.0)	1.99 (97.1)	0.525 (31.8)
MRTpo (h)	3.21 (15.0)	3.76 (17.4)	2.84 (12.0)
CL/F (L/h)	31.3 (34.6)	35.7 (38.2)	31.2 (32.5)
kel (1/h)	0.370 (11.8)	0.363 (14.7)	0.378 (13.9)
Half-life (h)	1.90 (12.5)	1.95 (15.8)	1.87 (13.8)

n: number of observations
* Geometric means are presented for these parameters.

Table 7.4.7-3 Pharmacokinetic statistical results for deferiprone in serum - Results before correction for measured drug content

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Tablet Fast (A) vs Solution Fast (C)	Deferiprone Tablet Fed (B) vs Tablet Fast (A)
AUC_{0-t}	100.4% (94.6% – 106.5%)	88.6% (83.5% – 94.0%)
AUC_{inf}	100.8% (95.2% – 106.7%)	90.2% (85.1% – 95.7%)
C_{max}	100.7% (83.0% – 122.3%)	62.0% (51.1% – 75.3%)

Table 7.4.7-2 Summary of pharmacokinetic results - Mean (CV%) serum deferiprone glucuronide pharmacokinetic parameters when administered as a tablet under fasting and fed conditions and as a solution under fasting conditions

	Tablet Fasting (A)	Tablet Fed (B)	Solution Fasting (C)
AUC_{0-t} * (µg.h/mL)	139 (17.1) n = 15	133 (17.2) n = 14	141 (15.7) n = 14
AUC_{inf} * (µg.h/mL)	142 (17.5) n = 15	135 (17.6) n = 13	144 (15.9) n = 14
C_{max} (µg/mL)*	26.2 (15.4) n = 15	22.2 (14.7) n = 14	26.5 (13.2) n = 14
t_{max} (h)	2.50 (22.7)	3.51 (41.7)	2.25 (25.8)
CL/fm (L/h)	4.74 (17.6)	4.96 (17.7)	4.65 (15.8)
kel (1/h)	0.320 (10.8)	0.311 (12.8)	0.316 (8.7)
Half-life (h)	2.19 (12.7)	2.27 (17.1)	2.21 (10.5)

n: number of observations
* Geometric means are presented for these parameters.

Table 7.4.7-5 Pharmacokinetic statistical results for deferiprone glucuronide in serum - Results before correction for measured drug content

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Glucuronide Tablet Fast (A) vs Solution Fast (C)	Deferiprone Glucuronide Tablet Fed (B) vs Tablet Fast (A)
AUC_{0-t}	99.5% (96.9% – 102.1%)	95.1% (92.6% – 97.6%)
AUC_{inf}	99.8% (97.3% – 102.3%)	96.7% (94.2% – 99.2%)
C_{max}	99.4% (93.5% – 105.6%)	83.9% (79.0% – 89.2%)

Comparison of the Tablet vs. the Solution (Under Fasting Conditions):

The pharmacokinetic results of deferiprone and deferiprone glucuronide demonstrated that the half-life and clearance results were comparable under fasting conditions between the deferiprone tablets and solution formulations. However, the tmax values for deferiprone was faster (by approximately 30

minutes) when the deferiprone solution formulation was administered to healthy volunteers as compared to the tablet formulation.

Statistical comparison (ANOVA): The ratio of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC0-t, AUCinf and Cmax for deferiprone and deferiprone glucuronide inserum, before and after correction for measured drug content, were within the 80-125% range for assessing relative bioavailability.

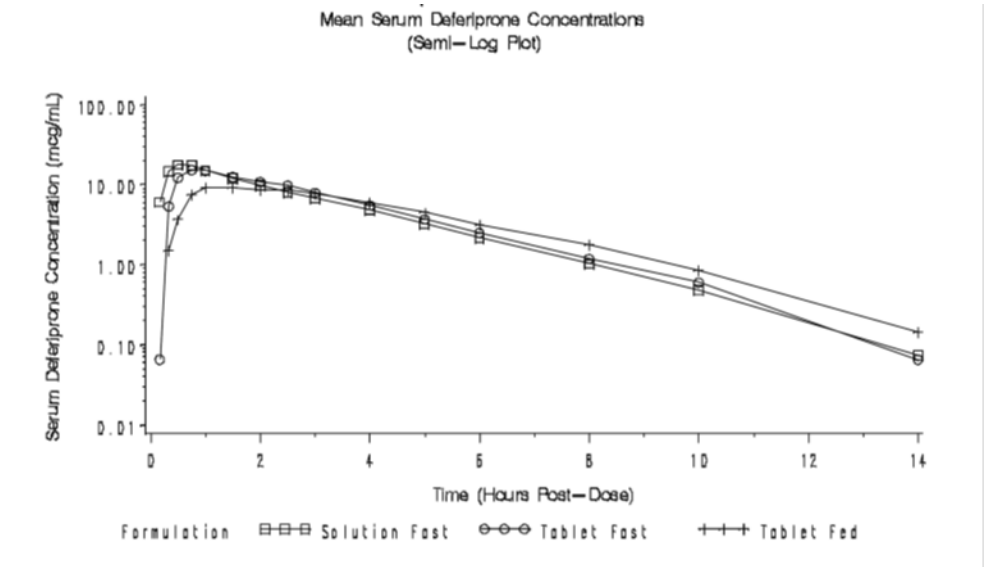
Based on these results, the rate and the extent (Cmax and AUC) of absorption for deferiprone tablet are equivalent to those for deferiprone solution under fasting conditions.

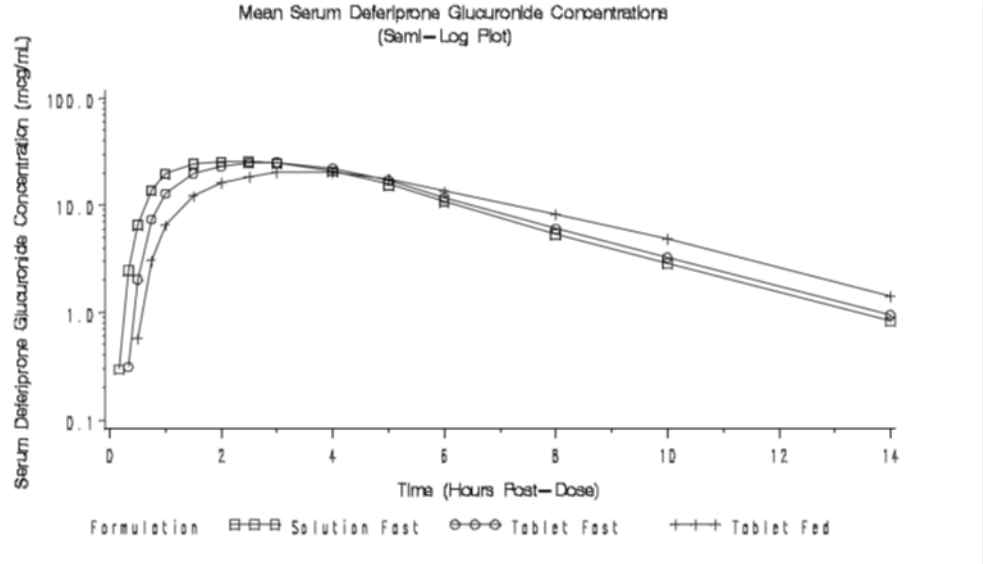
Comparison of the Tablet Under Fed Conditions vs. the Tablet Under Fasting Conditions:

The pharmacokinetic results for deferiprone and deferiprone glucuronide demonstrated that the half-life results were comparable when the drug was administered under fasting or fed conditions. CL/F and MRT slightly increased for deferiprone by approximately 14 and 17%, respectively, when the drug was administered with food.

Statistical comparison (ANOVA): The ratio of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC0-t and AUCinf for deferiprone and deferiprone glucuronide in serum were within the 80-125% acceptance range. However, the ratio of least-squares means derived from the analysis of the ln-transformed pharmacokinetic parameter Cmax was within the 80 125% acceptance range for deferiprone glucuronide but not for deferiprone in serum. In addition, the 90% confidence intervals derived from the analyses of the lntransformed pharmacokinetic parameters Cmax for deferiprone and deferiprone glucuronide in serum was not within the 80-125% acceptance range, indicating that the rate of absorption of the drug (Cmax) was significantly decreased when the drug was administered with food as compared to the fasting state by approximately 38 and 16%, respectively. This indicates that food decreased the rate of absorption of deferiprone and the subsequent formation of deferiprone glucuronide in healthy subjects while the overall extent of absorption (AUC) remained unchanged.

Also, the tmax values of deferiprone and deferiprone glucuronide were delayed by approximately 1 hour, when deferiprone was taken under fed conditions as opposed to the fasting state. This also suggests that more time was required to reach peak serum concentrations when the drug was administered with food.





Exclusions

A total of 13 subjects completed all three periods of the study and 2 subjects completed at least two periods of the study associated with a comparison of interest. Subject Nos. 2 and 6 withdrew from the study for personal reasons following Period 2.

Protocol Deviations

The protocol deviations occurred during the conduct of this study included error in meal consumption (subjects 1,3-5, 7,8,10,11 in Periods 1 and 2), out of range storage condition for serum and urine (1.5 hours reaching a maximum temperature of -55 oC; 1.75 hours reaching a maximum temperature of -35 oC; subjects 1-15, periods 1 and 2), voided urine collection (the 12-24 hours urine collection interval in Period 3) and spilled urine (subject 10; 4-8 urine collection interval; Period 2).

Brief Summary of Adverse Events

Eight subjects (53%) presented with 32 treatment-emergent AEs, 6 subjects (40%) in Treatment A, 5 (33%) in Treatment B, and 4 (27%) in Treatment C.

Feels tired was the most frequently reported AE, occurring only slightly more frequently in Treatments B and C than in Treatment A. Headaches were more frequent in Treatment A than in the other treatments, whereas feels sleepy was reported with equal frequency across treatments. Nausea occurred in Treatments A an C, whereas loose stools occurred in Treatments B and C.

No deaths, other serious AEs, or significant AEs occurred during this study. No subject was withdrawn due to an AE.

Pharmacokinetic Conclusions

Based on the results of this study, deferiprone tablet and deferiprone solution provide equivalent bioavailability of the drug and thus, are bioequivalent under fasting conditions. The administration of deferiprone tablets with food leads to a decrease in the rate of drug absorption, while the overall extent of absorption is unaffected.

The study was performed under fasting and fed conditions.The subjects were administered a single oral dose of 1500 mg of deferiprone of either the test or reference product at a particular stage of the study. Certificates of analysis for the test and reference products could not be found in the dossier.

The inclusion and exclusion criteria are acceptable and drawn up according to the protocol. All subjects are observed and treated according to the same rules. The data from all treated subjects were treated in the same way.However, the method of study calculation is not clear.

The sampling periods are acceptable with sample time points around Tmax for deferiprone and with an adequate wash-out period (at least 3 treatment-free days) at greater than five times the t1/2. The sampling frequency allowed for adequate estimation of Cmax. The sampling schedule covered the plasma concentration-time curve that was long enough to provide a reliable estimate of the extent of exposure.

Various pharmacokinetic parameters, i.e. Cmax, AUC0-t, AUC0-∞, Tmax, Kel, CL/F, CL/fm, and t1/2 were calculated. The pharmacokinetic parameters Cmax and, AUC0-tlast of deferiprone were estimated to evaluate bioavailability. The pharmacokinetic variables are adequate. Acceptance range for bioequivalence is 80.00%-125.00% for 90% confidence intervals of the geometric least square means ratio for Cmax and AUC0-tlast for deferiprone. This is a conventional approach.

The ratios of the mean of the ln-transformed data (T/R ratio) for lnCmax and lnAUC0-t were 101.5 and 101.2 respectively for deferiprone. For mean ratio T/R, the 90% confidence intervals for lnCmax ranges from 83.6 – 123.3 and for lnAUC0-t ranges from 95.4 – 107.4 which were within the bioequivalence range of 80.00% - 125.00% for deferiprone. It can be concluded that Test deferiprone solution 100 mg/ml is bioequivalent with reference deferiprone tablets 500 mg, in healthy, adult, subjects under fasting conditions.

LA21-BE - Comparative phase I PK study

Design:
This was an open-label, single-dose, randomized, two-way crossover comparative bioavailability study performed on 42 healthy subjects. An oral dose of 1500 mg ofdeferiprone either in the solution form or in the tablet form was administered under fasting conditions at the time (0) at each of the two periods of the study.

Objectives:
The objective was to determine the relative bioavailability of deferiprone oral solution and deferiprone tablets in healthy subjects under fasting conditions.

Test product, dose, and mode of administration, batch number:
A single oral dose of 1500 mg of deferiprone was administered in the form of 15 mL of Deferiprone Oral Solution 100 mg/mL, Lot No.: GT9851, under fasting conditions.

Reference therapy, dose, and mode of administration, batch number:
A single oral dose of 1500 mg of deferiprone was administered in the form of 3 x Ferriprox® Deferiprone 500 mg film-coated tablets, Lot No.: GW4454, under fasting conditions.

Selection of Doses in the Study
In the treatment of iron overload in patients with thalassemia major, deferiprone is most commonly given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body

weight. In this single-dose bioavailability study, 1500 mg deferiprone was given to each participant. This dose, which does not exceed the usual recommended dose for any subjects that weigh at least 50 kg, was expected to yield quantifiable concentrations of deferiprone in serum throughout the sampling time in order to allow for a reliable estimation of the pharmacokinetic parameters for all treatments.

Treatment administration:

On the morning of each period, at the time (0), a single-dose of deferiprone, 1500 mg, in the form of either solution or tablet, was administered orally to each subject with a total of 240 mL distilled water at room temperature, according to the randomization scheme presented.

A = 1 x 15 mL of 100 mg/mL deferiprone solution administered under fasting conditions.

B = 3 x 500 mg deferiprone tablets administered under fasting conditions

Blinding

Although this was an open-label study, the laboratory analysts did not have access to therandomization scheme.

Population: A total of 42 subjects (29 male and 13 female) were dosed, and 41 subjects (28 males and 13 females) completed the study. Pharmacokinetic and statistical analyses were performed on 41 subjects who completed both periods of the study. The safety evaluation was performed on all 42 dosed subjects.

Diagnosis and main criteria for inclusion:

All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who satisfied the screening evaluation and completed the baseline assessment.

Main inclusion Criteria

Healthy subjects were included in the study if all of the following criteria were met:
1. Were 18 to 55 years of age.
2. Were a non-smoking male or female for at least six months.
3. Had a body weight of at least 50 kg.
4. Had a BMI between 21.0 and 28.0

Main Exclusion Criteria

Healthy subjects were excluded from the study for any of the following reasons:
1. Had a history or presence of significant asthma, chronic bronchitis, seizure, diabetes, migraine, hypertension, cardiovascular, pulmonary, neurological, hepatic, renal, hematopoietic or gastrointestinal disorders or ongoing infectious diseases, or any other significant abnormality as evidenced by a medical history and physical examination.
2. Had a positive screen for Hepatitis B surface antigens, Hepatitis C, or HIV antibodies.
3. Had a significant abnormality in the ECG as judged by the study physician.
4. Had a history of allergy or sensitivity to the study drug(s) or related compounds.

Criteria for evaluation:

Efficacy:

Based on measured serum concentrations of deferiprone, the following pharmacokinetic parameters were estimated for each subject:

a) AUC0-t (Area under the concentration-time curve from time zero up to the time of the last measurable concentration, calculated by the linear trapezoidal rule.)

b) AUC0-∞ or AUCinf (Area under the concentration-time curve from time zero to infinity)

c) AUC0-t / AUC0-∞ (The ratio of AUC0-t to AUC0-∞).

d) Cmax (maximum concentration).

e) Tmax (time of maximum concentration).

f) Kel (1st order terminal elimination rate constant).

g) t½ (terminal elimination half-life).

The following standards were used to determine if the solution and the tablet formulations have equivalent bioavailability (relative bioavailability) under fasting conditions:

The 90% confidence intervals of the ratio of least-squares means for AUC0-t, AUC0-∞ and Cmax of the test formulation to reference formulation should be within the 80% to 125% range.

Safety:
Safety was assessed by monitoring adverse events throughout the study, as well as laboratory evaluations, vital signs, and ECGs.

Exclusions:
A total of 41 subjects (28 males and 13 females) completed both periods of the study. Subject No. 42 was withdrawn from the study by the Investigator following Period 2 (Formulation A) dosing due to adverse events.

Protocol Deviations:
The protocol deviations occurred during the conduct of this study included: episodes of pulse rate below 50 (subjects 2, 3, 7, 10, 16, 20, 41, different Periods), 55 minutes late in health check questionnaire (all subjects, Period 2), freezer reaching a high temperature reading of –63C for samples from predose to 4-hour time points in Period 2), missing sample (Subject 5, at the 0.17-hour time point; Period 2), beer consumption (subject 10, 28, 32) between Period 1 check-out and 48 hours prior to Period 2 dosing, exact time and date unknown) and withdrawn (subject 41).

Discussion of Pharmacokinetic Results
The pharmacokinetic results of deferiprone demonstrated that the half-life and tmax results are comparable under fasting conditions between the deferiprone tablet and solution formulations. The rate and the extent (Cmax and AUC) of bioavailability for deferiprone tablet are equivalent to those for deferiprone solution under fasting conditions. These results are consistent with previous data.

Table 7.4.7-1 Summary of pharmacokinetic results - Mean (CV%) serum deferiprone pharmacokinetic parameters when administered as a solution and a tablet under fasting conditions

Parameter	Solution (A)	Tablet (B)
AUC_{0-t} * (µg·h/mL)	48.2 (22.6) n = 41	48.0 (23.3) n = 41
AUC_{inf} * (µg·h/mL)	49.3 (22.9) n = 41	49.2 (23.4) n = 41
C_{max} (µg/mL)*	18.9 (30.8) n = 41	19.2 (36.2) n = 41
t_{max} (h)	0.805 (66.6)	0.911 (50.5)
kel (1/h)	0.412 (13.8)	0.410 (14.3)
Half-life (h)	1.71 (13.4)	1.72 (13.3)

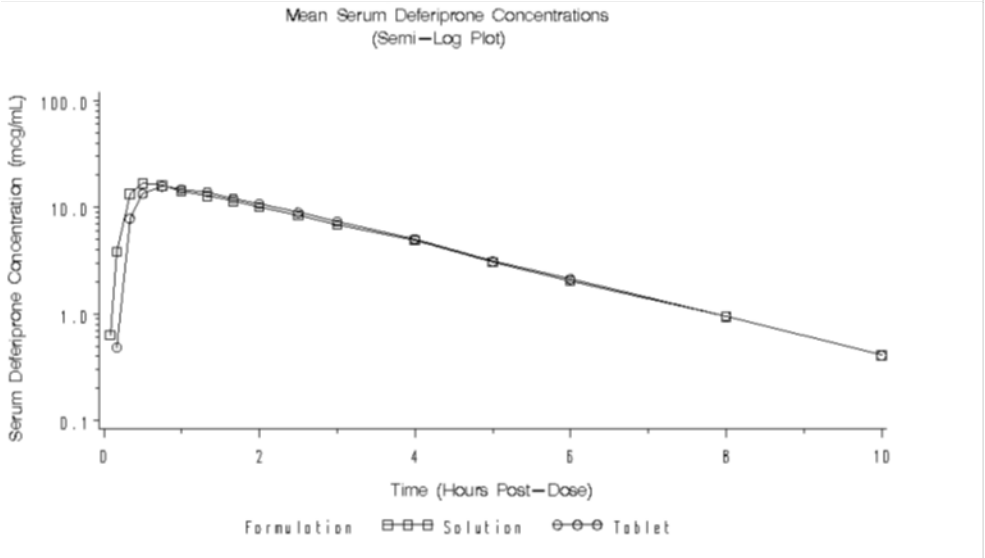
n: number of observations

*Geometric means are presented for these parameters.

Table 7.4.7-2 Pharmacokinetic statistical results for deferiprone in serum

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Solution (A) vs Tablet (B)
AUC_{0-t}	100.6% (98.0% – 103.4%)
AUC_{inf}	100.4% (97.7% – 103.1%)
C_{max}	98.3% (88.9% – 108.7%)



Exclusions:

A total of 41 subjects (28 males and 13 females) completed both periods of the study. Subject No. 42 was withdrawn from the study by the Investigator following Period 2 (Formulation A) dosing due to adverse events.

Protocol Deviations:

The protocol deviations occurred during the conduct of this study included: episodes of pulse rate below 50 (subjects 2, 3, 7, 10, 16, 20, 41, different Periods), 55 minutes late in health check questionnaire (all subjects, Period 2), freezer reaching a high temperature reading of –63C for samples from pre-dose to 4-hour time points in Period 2), missing sample (Subject 5, at the 0.17-hour time point; Period 2), beer consumption (subject 10, 28, 32) between Period 1 check-out and 48 hours prior to Period 2 dosing, exact time and date unknown) and withdrawn (subject 41).

Safety results:

No deaths, or other serious or severe adverse events occurred in this study. One subject was withdrawn from the study due to vomiting shortly after dosing in Period 2. Fifteen subjects (36%) presented with 41 treatment-emergent AEs. Ten subjects (24%) had 26 AEs after dosing with the 1500 mg deferiprone solution, and 6 subjects (14%) had 15 AEs after receiving the 1500 mg deferiprone tablet. Of the 26 AEs in subjects dosed with deferiprone solution, 22 (85%) were mild, and 4 (15%) were moderate. All AEs in subjects who received the deferiprone tablet were mild. In subjects dosed with deferiprone solution, 20 AEs (77%) were considered related to the study treatment. In subjects dosed with the deferiprone tablets, 12 AEs (80%) were judged related to the study treatment.No clinical laboratory, vital signs, or ECG results indicated a safety concern.

There were no statistically significant differences in the proportion of subjects with AEs between treatments throughout the study. Most AEs were mild, and none were severe. All moderate AEs in Subject 42 occurred after he was dosed with deferiprone solution, and he was withdrawn from the study due to vomiting shortly after dosing in Period 2.

Onset times of AEs judged related to administration of 1500 mg deferiprone solution ranged from 3 minutes (dizziness, Subject 42) to 6 days postdose (somnolence, Subject 14), and lasted between 1 minute (vomiting, Subject 42) and 6 days (fatigue, Subject 42). Onset times of AEs judged related to administration of 1500 mg deferiprone tablets ranged from 37 minutes (nausea, Subject 9) to 6 days postdose (fatigue, Subject 9), and lasted between 15 minutes (headache, Subject 34) and approximately 3 days (headache, Subject 5).

Pharmacokinetic Conclusions

The 90% confidence intervals of the ratios of LSM, derived from the analyses of the ln-transformed PK parameters AUC 0-t, AUCinf, and Cmax for deferiprone in serum, were within the 80-125% acceptance range. Based on these results, deferiprone oral solution and Ferriprox® (deferiprone) tablets are bioequivalent under fasting conditions.

Safety conclusions:

There were no significant differences in the incidence of any adverse events, including those that were gastrointestinal in nature. Single oral doses of 1500 mg deferiprone, administered as a solution or as tablets, appeared to be equally safe in this group of healthy adult subjects.

The study was performed under fasting conditions. The subjects were administered a single oral dose of 1500 mg of deferiprone of either in the solution form or in the tablet form at a particular stage of the study.

The sampling periods are acceptable with sample time points around Tmax for deferiprone and with an adequate, 4 days wash-out period at greater than five times the t1/2. The sampling frequency allowed for adequate estimation of Cmax. The sampling schedule covered the plasma concentration-time curve that was long enough to provide a reliable estimate of the extent of exposure.

Certificates of analysis for both the test and reference products have been provided. Assay values of 98.7% and 100.4% for the test and reference are reported, respectively. The assayed content of the batch used as test product did not differ more than 5% from that of the batch used as reference product which is in accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01 Corr**).

The inclusion and exclusion criteria are acceptable and drawn up according to the protocol. All subjects are observed and treated according to the same rules. The data from all treated subjects were treated in the same way.

The study population is appropriate, and the main inclusion and exclusion criteria are in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01). According to the protocol calculations, 42 subjects were considered to be enough to power the study with 41 subjects completing the study.

Various pharmacokinetic parameters Cmax, AUC0-t, AUC0-∞, Tmax, Kel, and t1/2 were calculated. The pharmacokinetic parameters Cmax and, AUC0-tlast of deferiprone were estimated to evaluate bioavailability. The pharmacokinetic variables are adequate. Acceptance range for bioequivalence is 80.00%-125.00% for 90% confidence intervals of the geometric least square means ratio for Cmax and AUC0-tlast.

The ratios of the mean of the ln-transformed data (T/R ratio) for lnCmax and lnAUC0-t were 98.3 and 100.6 respectively for deferiprone. For mean ratio T/R, the 90% confidence intervals for lnCmax ranges from 88.9-108.7% and for lnAUC0-t ranges from 98.0 - 103.4, which were within the bioequivalence range of 80.00% - 125.00%. It can be concluded deferiprone 1500 mg (solution 100mg/ml) is bioequivalent with deferiprone 1500 mg (3 x 500 mg tablets) under fasting conditions.

Both products were found to be safe and well-tolerated. There were no serious adverse events (AEs) reported in this study. The adverse events were not life-threatening nor did they required the subjects to be hospitalized. Based on the results obtained in the bioequivalence study in healthy adult subjects, both formulations of deferiprone could be judged as bioequivalent under fasting conditions.

Special population studies

Impaired renal function

An Open-Label Study to Compare the Pharmacokinetic Profiles of a Single Dose of Ferriprox® in Subjects with Impaired Renal Function and Healthy Volunteers. Sponsor Project, No LA39-0412.

Objectives:
Primary objective: To determine the effect of impaired renal function on the pharmacokinetics of deferiprone and its 3-O-glucuronide metabolite following a single oral 33 mg/kg dose of Ferriprox in subjects with renal impairment as compared to healthy volunteers.

Secondary objective: To evaluate the safety and tolerability of Ferriprox in subjects with renal impairment.

Investigation product: Product: Ferriprox(Deferiprone) 500 mg Film-Coated Tablet, Dose: Single 33 mg/kg dose of deferiprone rounded to the nearest 250 mg (half-tablet) Mode of administration: Oral; Batch number: KF3446

Methodology: The study was a multi-center, open-label, non-randomized, parallel group study in subjects with mild renal impairment (eGFR 60-89 mL/min/1.73m2), moderate renal impairment (eGFR 30-59 mL/min/1.73m2), severe renal impairment (eGFR 15-29 mL/min/1.73m2) and healthy volunteers (eGFR ≥ 90 mL/min/1.73m2), as determined by the estimated glomerular filtration rate (eGFR) from the Modification of Diet in Renal Disease Study. An effort was made to carefully match the healthy subjects with the renally impaired subjects (including mild, moderate or severe renally impaired patients) by age (+/- 10 years), weight (+/ 15 %), and smoking habit of being representative of the patient's population to the extent possible.

Selection of study population:
Main inclusion criteria
All subjects:
1. Adult males or females, 18 – 75 years of age (inclusive). An attempt was made to have a similar number of males and females in the healthy volunteer's group and the renal impairment groups
2. Body weight ≥ 45 kg
3. Body mass index (BMI) range of approximately 18.5-32 kg/m2 (inclusive); subjects with BMI outside of the specified range may have been enrolled if judged acceptable by the Principal Investigator and Sponsor.
4. Absolute neutrophil count (ANC) of >1.5x109/L;
5. Women of childbearing potential must have agreed to either be sexually inactive (abstinent) for 14 days prior to screening and remained so throughout the study or using an acceptable method of birth control;
6. Women who were of non-childbearing age or postmenopausal
7. A fertile male must have agreed to use an effective method of contraception or confirm that his partner agreed to use effective contraception.

Healthy volunteers:
1. Medically healthy with clinically insignificant screening results (e.g., laboratory profiles, medical history, vital signs, physical examination);
2. eGFR ≥ 90 mL/min/1.73m2;

Renally impaired subjects:
1. Considered clinically stable in the opinion of the Investigator; 145
2. Subjects with mild renal impairment (eGFR 60-89 mL/min/1.73m2) OR moderate renal impairment (eGFR 30-59 mL/min/1.73m2) OR severe renal impairment (eGFR 15-29 mL/min/1.73m2).

Main Exclusion Criteria
Subjects were to be excluded from the study for any of the following reasons:
1. History of a renal transplant;
2. Currently undergoing any method of dialysis;
3. History or presence, in the opinion of the Investigator, of clinically significant unstable respiratory, cardiovascular, pulmonary, hepatic, renal (except for subjects assigned to one of the renally impaired groups), hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease;
4. Disorders or surgery of the gastrointestinal tract which may have interfered with drugabsorption or may have otherwise influenced the pharmacokinetics of the investigational medicinal product (e.g., cholecystectomy, resections of the small or large intestine, febrile conditions, chronic diarrhea, chronic vomiting, endocrine disease, severe infections, acute inflammations, etc.);
5. Clinically significant abnormalities on 12-lead ECG at screening (e.g., QTcF ≥430 ms in healthy males or ≥450 ms in healthy females);

6. Evidence of liver damage: hepatitis B and C; aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels considered clinically significant by the Investigator;

Disposition of Subjects: No randomization was performed. Instead, subjects were categorized into either the control group of healthy volunteers with normal renal function (eGFR ≥ 90 mL/min/1.73m2) or one of the three groups of subjects with various degrees of renal impairment: mild renal impairment (eGFR 60-89 mL/min/1.73m2), moderate renal impairment (eGFR 30-59 mL/min/1.73m2), severe renal impairment (eGFR 15-29 mL/min/1.73m2).

Selection of Dose in the Study
The recommended initial dose of Ferriprox is 25 mg/kg, taken orally three times daily for a total of 75 mg/kg/day, and the maximum approved therapeutic dose is 33 mg/kg, taken orally three times daily for a total of 99 mg/kg/day. Hence, 33 mg/kg was chosen as the dose level in this study as it is well-tolerated when administered as a single dose, and as it is the maximum authorized prescribed dose. No significant drug accumulation in serum is expected after multiple three times daily dose administrations.

Blinding
Not applicable. This study was open-label, and all participants received the same treatment.

Pharmacokinetics:
The following pharmacokinetic parameters were determined for deferiprone: Cmax , Tmax, AUC0-t, AUC0-∞, T½, CL/F, CLr, Vd/F, Ae24, and Fe24.
The following pharmacokinetic parameters were determined for deferiprone 3-*O*-glucuronide metabolite: Cmax, Tmax, AUC0-t, AUC0-∞, T½, CLr, Ae24, and Fe24.

Safety:
Medical history, physical examination, vital signs, 12-lead ECG, clinical laboratory tests (hematology, clinical chemistry, urinalysis, coagulation), and AEs.

Results:
Pharmacokinetic results:
Deferiprone:
Following administration of a single 33 mg/kg dose of deferiprone to subjects with different stages of renal impairment or no impairment, the renal clearance of deferiprone was adversely impacted, with a decrease in the amount excreted in 24 hours as the severity of renal impairment increased. The impact appeared to become statistically significant only when the impairment was at least moderate. The systemic exposure to deferiprone, as indicated by Cmax and AUCs, was not significantly different among subjects with various degrees of renal impairment.

Table 11.1 Summary of Serum Deferiprone Pharmacokinetic Parameters

	Renal function / impairment							
	Normal		Mild		Moderate		Severe	
Variable	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%
C_{max} (µg/mL)	37.075	32.4	33.388	28.3	43.257	52.9	30.608	53.0
T_{max} (h)*	0.500	0.25-1.00	0.750	0.50-1.00	1.000	0.50-2.00	0.750	0.25-4.00
AUC_{0-t} (µg*h/mL)	77.771	35.7	76.453	20.5	73.989	20.1	70.106	12.7
$AUC_{0-\infty}$ (µg*h/mL)	78.142	35.5	76.874	20.4	74.910	20.1	70.896	12.0
$T_{1/2}$ (h)	1.68	16.0	1.77	9.6	2.03	15.9	2.20	41.2
Cl/F (L/h)	33.446	47.0	31.475	23.8	34.837	20.9	33.998	20.9
CLr (L/h)	0.999	20.3	0.905	22.2	0.485	27.7	0.326	44.0
Vd/F (L)	77.654	38.2	79.834	22.8	102.800	26.1	114.121	57.1

*For T_{max}, the values presented are of median and range

3-*O*-glucuronide metabolite:
The renal clearance of the metabolite deferiprone 3-O-glucuronide was more adversely impacted. As this metabolite is mainly eliminated by excretion in the urine, as indicated by Fe24, the significant slowdown in its urinary excretion resulted in higher Cmax, AUC0-t and AUC0-∞, and longer Tmax, and T1/2 in the renally impaired groups compared to the healthy volunteers. The rates of increase in Cmax and AUCs as eGFR decreases are greater in subjects with more severe renal impairment than in subjects with milder renal impairment.

Table 11.2 Summary of Serum Deferiprone-3-*O*-Glucuronide Pharmacokinetic Parameters

	Renal function / impairment							
	Normal		Mild		Moderate		Severe	
Variable	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%
C_{max} (μg/mL)	47.813	13.0	60.825	16.9	118.829	40.6	150.833	21.5
T_{max} (h)*	2.500	1.33-3.00	2.500	2.00-3.00	3.000	2.00-6.00	4.000	2.00-6.00
AUC_{0-t} (μg*h/mL)	251.842	14.1	318.436	17.0	698.329	32.5	1413.131	23.2
$AUC_{0-\infty}$ (μg*h/mL)	252.595	14.0	319.140	16.9	703.223	32.6	1438.457	23.3
$T_{1/2}$ (h)	2.14	14.9	2.58	17.6	2.58	14.9	3.35	14.3
CLr (L/h)	17.756	17.1	15.580	20.4	6.934	33.6	2.874	47.4

*For T_{max}, the values presented are for median and range

Urine Deferiprone
Of the 32 enrolled subjects, 31 were included in the main pharmacokinetic and statistical analysis for urine deferiprone, while 1 (#200002-D) was excluded. A summary of the mean pharmacokinetic parameters for urine deferiprone is shown below:

Table 11.3 Summary of Urinary Deferiprone Pharmacokinetic Parameters

	Renal function/impairment							
	Normal		Mild		Moderate		Severe	
Variable	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
Ae24 (mg)	78	43.0	69	29.0	36	31.9	24	42.2
Fe24 (%)	3.49	47.0	2.94	20.5	1.49	32.3	1.00	36.9

Safety results:

In this study, a single oral 33 mg/kg dose of Ferriprox was well tolerated by both healthy volunteers and renally impaired subjects. Most of the AEs that were reported occurred in the healthy volunteers and the subjects with mild renal impairment, with only 2 events reported by subjects with moderate or severe renal impairment. The significant differences in incidence may possibly be due to the fact that subjects were housed at different clinical sites; the healthy and mildly impaired subjects at a research center site and the others at a hospital and the different clinical conditions may account for subjects reacting differently to the study conditions and to the administration of the drug.

There were no SAEs and no deaths. No clinically significant effects on laboratory values, vital signs, ECGs, or physical examinations were noted during this study. One subject with severe renal impairment experienced an adverse event that required the use of concomitant medication (ibuprofen) following the occurrence of headache after the study drug administration. No subjects were withdrawn from the study for safety reasons. Overall, the increase in the severity of renal impairment did not result in a significant increase in the incidence of AEs.

Safety Conclusions:

Ferriprox was well tolerated by the subjects included in this study.

Pharmacokinetic Conclusions

The study is a multi-center, non-randomized, open-label, single-dose, parallel-group study in renally impaired patients and healthy subjects. The primary goal of these types of studies is to determine if the pharmacokinetics are altered to such an extent that the dosage requires adjustment from that established in the usual patient population. From this point of view, the investigational plan seems to be generally designed correctly.

Primary objective formulated as (to determine the effect of impaired renal function on the pharmacokinetics of deferiprone and its3-O-glucuronide metabolite following a single oral 33 mg/kg dose of Ferriprox in subjects with renal impairment, as compared to healthy volunteers and secondary objective (evaluate the safety and tolerability of Ferriprox in subjects with renal impairment) were formulated correctly.

The study project assumed the evaluation of primary and secondary objectives after a single administration. This is an assumption not fully representative for the clinical conditions and the target population included in the indication.

Also, a small number of participants in the study are noteworthy. It is not clear on what basis this number of participants was considered sufficient. Explanations concerning this issue can be found in Study report la39-0412; 9.7.2. Determination of Sample Size: "No formal sample size calculation was done for this study. Based on a review of the literature and internal pharmacokinetic data on deferiprone, a sufficient number of subjects were recruited in order to ensure that there would be 8 evaluable subjects in each of the 4 categories of renal impairment" seem insufficient.

The categorization of patients according to their degree of renal failure was carried out correctly based on the estimated glomerular filtration rate (eGFR). Subjects with mild renal impairment (eGFR 60-89 mL/min/1.73m2), moderate renal impairment (eGFR 30-59 mL/min/1.73m2), severe renal impairment (eGFR 15-29 mL/min/1.73m2) and healthy volunteers (eGFR ≥ 90 mL/min/1.73m2).End-stage renal disease patients were not included in the study.

Demographic Characteristics of the Safety Population seems to be well balanced. The systemic exposure to deferiprone, as indicated by Cmax and AUCs, was not significantly different among subjects with various degrees of renal impairment.However, the regression analysis showed that following administration of a single 33 mg/kg dose of deferiprone to subjects with different stages of renal impairment a significant trend was observed for Tmax, T1/2, and CLr in the regression analysis using eGFR as the predictor variable. CLr also exhibited a significant trend in the regression analyses using creatinine clearance as the predictor variable. The trend for CLr displayed that the value decreased as the severity of renal impairment increased.

The renal clearance of the metabolite deferiprone 3-O-glucuronide was more adversely impacted. The significant slowdown in its urinary excretion resulted in higher Cmax, AUC0-t, and AUC0-∞, and longer Tmax, and T1/2 in the renally impaired groups compared to the healthy volunteers. The rates of increase in Cmax and AUCs as eGFR decreases were higher in subjects with more severe renal impairment than in subjects with milder renal impairment.

The regression analysis using eGFR as the predictor variable showed a significant trend for Fe24 the metabolite deferiprone 3-O-glucuronide.

Impaired hepatic function

An Open-Label Study to Compare the Pharmacokinetic Profiles of a Single Dose of Ferriprox® in Subjects with Impaired Hepatic Function and Healthy Volunteers. Study LA40-0412.

Objectives:
Primary Objective: To determine the effect of impaired hepatic function on the pharmacokinetics of deferiprone and its 3-*O*-glucuronide metabolite following a single oral 33 mg/kg dose of Ferriprox® in subjects with hepatic impairment as compared to healthy volunteers. Secondary Objective: To evaluate the safety and tolerability of Ferriprox® in subjects with hepatic impairment.

Test Product, Dose, Mode of Administration, and Batch Number: The test product was Ferriprox® 500 mg tablets [Lot No.: DR12125 (KF3446)]. Subjects received a single oral dose of 33 mg/kg Ferriprox® rounded to the nearest 250 mg half-tablet.

Selection of Study Population
A total of 21 subjects were enrolled in the study: 7 with mild hepatic impairment, 7 with moderate hepatic impairment, and 7 healthy volunteers.
This was a non-randomized study. All subjects were given a 6-digit subject identification number at Screening, assigned sequentially. Each subject who completed the screening assessments and met all the eligibility criteria was assigned a group letter representing 1 of the 3 groups based on hepatic function:
A – Normal hepatic function (healthy volunteers)
B – Mild hepatic impairment
C – Moderate hepatic impairment

Inclusion Criteria
Subjects fulfilled all of the following inclusion criteria to be eligible for participation in the study:

All subjects:
1. Informed consent was obtained prior to the first study intervention and subjects were able to adhere to study requirements and restrictions;
2. Adult males or females, 18 – 75 years of age (inclusive). An attempt was made to have a similar number of males and females in the healthy volunteers' group and the hepatic impairment groups (± 2 subjects);
3. Body weight ≥ 50 kg;
4. Body mass index (BMI) between 19 and 32 kg/m2 (inclusive). Subjects with BMI outside of the specified range could have been enrolled if judged acceptable by the PI and the Sponsor;

Healthy volunteers:
1. Medically healthy with no clinically significant screening results (e.g., laboratory profiles, medical history, vital signs, physical examination);
2. Healthy subjects were matched with the hepatically impaired subjects (mild or moderate groups) with respect to age, BMI, and smoking habits when feasible. At a minimum, the following criteria were to be fulfilled:
• The age of healthy subjects was matched according to the mean age (± 10 years) of all subjects with hepatic impairment combined.
• The weight of healthy subjects was matched according to the mean BMI(± 15%) of all subjects with hepatic impairment combined.

Hepatically impaired subjects:
1. Considered clinically stable in the opinion of the PI;
2. Subjects with different degrees of impaired hepatic function as assessed by a Child-Pugh classification score: mild (Class A: 5– 6 points) or moderate (Class B: 7– 9 points) impaired hepatic function.

Exclusion Criteria
Subjects were excluded from the study for any of the following reasons:

All subjects:

1. In the opinion of the PI, history or presence of significant clinically unstable respiratory, cardiovascular, pulmonary, renal, hepatic (except for subjects assigned to one of the hepatically impaired groups), hematologic, gastrointestinal, endocrine (except for subjects with hepatic impairment with clinically stable and treated diabetes, hypertension and thyroid disorders), immunologic, dermatologic, neurologic, or psychiatric disease;
2. Disorders or surgery of the gastrointestinal tract which interfered with drug absorption or otherwise influenced the PK of the investigational medicinal product (e.g. resections of the small or large intestine, febrile conditions, chronic diarrhea, chronic vomiting, clinically unstable endocrine disease, severe infections, acute inflammations, etc.);
3. Clinically significant abnormalities on 12-lead ECG at screening (e.g., QTcF ≥ 450 msec);

Healthy volunteers only:
1. Evidence of liver impairment in healthy volunteers: hepatitis B and C; or aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, clotting factors (e.g., prothrombin time [PT]/international normalized ratio [INR]), or serum protein that was considered clinically significant by the PI;
2. History or presence of alcohol and/or drug abuse within the past 2 years;
3. Positive testing for HIV, hepatitis B surface antigen (HBsAg), or hepatitis C (HCV) antibodies.

Hepatically impaired subjects only:
1. For subjects with hepatic impairment, fluctuating or rapidly deteriorating hepatic function as indicated by clinical and/or laboratory signs of hepatic impairment (e.g., advanced ascites, infection of ascites, fever, or active gastrointestinal bleeding);
2. History or presence of alcohol and/or drug abuse within the past year;
3. Positive testing for HIV.

Disposition of Subjects
A total of 21 subjects, 7 healthy volunteers and 14 subjects with either mild or moderate impaired hepatic function, entered the study and received study treatment. All subjects completed the study.

Protocol Deviations
There were no major deviations and none of the reported deviations were determined to have affected the results or conclusions of the study.

Pharmacokinetic evaluation:

Demographic and Other Baseline Characteristics

Trait		Group A	Group B	Group C	Overall
Gender	Female	2	0	3	5
	Male	5	7	4	16
Race	Black or African American	1	0	1	2
	White	6	7	6	19
Ethnicity	Hispanic or Latino	5	3	2	10
	Not Hispanic or Latino	2	4	5	11
Age (yrs) Mean (min,max)		55.0 (48, 63)	57.4 (53, 65)	55.6 (54, 58)	56.0 (48, 65)
Weight (kg) Mean (min,max)		80.66 (65.0, 92.0)	83.64 (64.9, 96.9)	80.16 (68.1, 90.4)	81.49 (64.9, 96.9)
Height (cm) Mean (min,max)		170.33 (162.0, 178.0)	173.39 (160.0, 185.5)	171.36 (159.0, 186.5)	171.69 (159.0, 186.5)
Body Mass Index (kg/m^2) Mean (min,max)		27.7 (25, 29)	27.9 (22, 32)	27.3 (23, 32)	27.6 (22, 32)
Child-Pugh Class Score Mean (min,max)		NA	5.9 (5, 6)	7.4 (7, 8)	6.6 (5, 8)

Group A – Normal hepatic function (healthy volunteers)
Group B – Mild hepatic impairment (Child-Pugh Class A: 5-6 points)
Group C - Moderate hepatic impairment (Child-Pugh Class A: 7-9 points)
NA = Not applicable
Source: Table 14.1.2

The following serum PK parameters were assessed for both deferiprone and deferiprone 3-*O*-glucuronide: AUC0-t, AUC0-inf, AUCextrap%, Cmax, Tmax, Kel, and t½. In addition, CL/F and Vz/F were calculated for deferiprone only. The following urine PK parameters were assessed for both deferiprone and deferiprone 3-*O*-glucuronide: CumAe, Fe, and CLr.

Deferiprone and deferiprone-3-*O*-glucuronide concentration-time profiles were well characterized over the 24-hour post-dose period following a single oral dose of 33 mg/kg deferiprone. Measurable concentrations were generally quantified within 0.25 hours from dosing. Mean serum concentrations around the peak of the profiles were higher for the normal hepatic function group than for the 2 hepatic impairment groups, but all 3 groups otherwise had relatively similar serum concentration profiles.

Following a single oral 33 mg/kg deferiprone dose, the maximum serum deferiprone concentration was reached at a median time of 0.75 hours (Tmax) for all 3 groups, and the mean T1/2 values were approximately 2 hours for all 3 groups. The mean deferiprone CL/F values were 29.4, 36.6, and 27.7 L/hour for healthy volunteers, mild impairment group, and moderate impairment group, respectively, indicating no correlation between total body clearance and hepatic impairment. Similarly, there was no significant trend of volume of distribution (Vz/F) as the severity of hepatic impairment increased.

Following a single oral 33 mg/kg deferiprone dose, median deferiprone 3-*O*-glucuronide Tmax values were 2 hours for the normal hepatic function group and 3 hours for the 2 impairment groups, and the mean T1/2 values were approximately 2.5 hours for all 3 groups.

For serum deferiprone, based on the ratios of LSM, AUC was 15% lower for subjects with mild hepatic impairment in comparison to the control group, and 9% higher for subjects with moderate hepatic impairment in comparison to the control group. For both impairment groups, Cmax was 20% lower than that of the control group.

Table 7 Summary of Serum Deferiprone Pharmacokinetic Parameters

Parameters	Group A	Group B	Group C
	Mean ± SD	Mean ± SD	Mean ± SD
C_{max} (ug/mL)	49.0 ± 24.1	36.3 ± 8.48	35.9 ± 7.84
T_{max}* (hr)	0.750 (0.500, 2.00)	0.750 (0.500, 1.00)	0.750 (0.500, 1.33)
AUC_{0-t} (ug*hr/mL)	92.1 ± 19.2	81.5 ± 28.1	105 ± 41.5
$AUC_{0-\infty}$ (ug*hr/mL)	92.6 ± 19.2	82.0 ± 28.2	106 ± 41.7
$T_{1/2}$ (hr)	1.99 ± 0.270	1.86 ± 0.454	2.18 ± 0.832
K_{el} (1/hr)	0.354 ± 0.0539	0.391 ± 0.0857	0.353 ± 0.109
CL/F (L/hr)	29.4 ± 4.79	36.6 ± 11.3	27.7 ± 8.64
V_Z/F (L)	83.7 ± 12.1	93.7 ± 18.1	79.7 ± 14.2

*T_{max} is presented as Median (Minimum, Maximum)
Group A = Normal hepatic function (healthy volunteers)
Group B = Mild hepatic impairment (Child-Pugh Class A: 5-6 points)
Group C = Moderate hepatic impairment (Child-Pugh Class B: 7-9 points)

Source: Tables 14.2.1.1.4 through 14.2.1.1.6

Table 8 Summary of Serum Deferiprone-3-*O*-glucuronide Pharmacokinetic Parameters

Parameters	Group A	Group B	Group C
	Mean ± SD	Mean ± SD	Mean ± SD
C_{max} (ug/mL)	69.0 ± 9.92	56.9 ± 11.4	55.3 ± 25.3
T_{max}* (hr)	2.00 (1.00, 3.00)	3.00 (1.67, 4.00)	3.00 (3.00, 4.00)
AUC_{0-t} (ug*hr/mL)	337 ± 45.1	304 ± 53.5	304 ± 111
$AUC_{0-\infty}$ (ug*hr/mL)	337 ± 45.3	305 ± 53.7	306 ± 112
$T_{1/2}$ (hr)	2.62 ± 0.357	2.52 ± 0.557	2.48 ± 0.672
K_{el} (1/hr)	0.270 ± 0.0465	0.290 ± 0.0762	0.299 ± 0.0843

*T_{max} is presented as Median (Minimum, Maximum)
Group A = Normal hepatic function (healthy volunteers)
Group B = Mild hepatic impairment (Child-Pugh Class A: 5-6 points)
Group C = Moderate hepatic impairment (Child-Pugh Class B: 7-9 points)

Source: Tables 14.2.1.2.4 through 14.2.1.2.6

It is known that liver impairment may have a significant impact on all PK processes of drugs: absorption, distribution, metabolism, and elimination. Also, hepatic impairment may alter protein binding, tissue binding, and fluid levels, thus affecting drug distribution.

The study project assumes the evaluation of primary and secondary objectives after a single administration of deferiprone. This is an assumption that does not fully apply to a clinical situation in which the Upkanz, for "the treatment of neuro-degeneration with iron accumulation in the brain," which implies chronic treatment.

The presented results indicate that there is no increased exposure to deferiprone or its glucuronide metabolite in patients with impaired hepatic function. Following a single oral, 33 mg/kg dose of deferiprone.

Moreover, it is surprising to note that there are tendencies to reduce deferiprone exposure in patients within-subjects with mild and moderate hepatic impairment, which is manifested by a decrease in Cmax in subjects with mild and moderate hepatic impairment as well as AUC was 15% lower for subjects with mild hepatic impairment in comparison to the control group. The peak exposure of both deferiprone and its glucuronide metabolite were somewhat lower in subjects with mild or moderate hepatic impairment than in healthy subjects as their mean Cmax were close to or slightly lower than 80% of that in healthy subjects. However, the extent of exposure of both compounds was not significantly affected as the AUC ratios were within 80 - 125% in comparison to the healthy subjects. Therefore, theoretically, no dosage adjustment should be needed in patients with chronic liver disease having mild or moderate hepatic impairment following a single dose administration of deferiprone.

Less than 3% of the dose was recovered as unchanged deferiprone in urine over 24 hourspost-dose across the 3 groups studied, with a slightly decreasing trend as the severity of hepaticimpairment increased. CLr of deferiprone was approximately 30% lower for the group withmoderate hepatic impairment versus the control group, but no decrease in CLr was observedwith the mild hepatic impairment group.

Taking into account the observed tendencies and ambiguities in PK parameters, the criteria for sample size calculation are critical for the decision about the need to adjust deferiprone dosing in patients with liver impairment. Poor group size calculation may cause the observed effects to be statistically unknown.

There is no PK data in patients with other forms of NBIA. Since the applicant proposes to restrict the indication to the treatment of patients with PKAN, the issue of extrapolating the PK profile of PKAN patients to other groups of NBIA patients is not further pursued.

- As expected, the systemic exposure as measured by the secondary PK parameters (C_{max}, AUC) is lower than those previously reported in thalassemia patients (receiving higher doses). For instance, the observed mean C_{max} and AUC_{ss} for deferiprone were respectively 9.9 µg/mL and 23 µg*h/mL, about half of those reported with a 33 mg/kg dose. The same findings are valid for the major metabolite DFP-3-O-Glucuronide. The consequence of this lower systemic exposure on the efficacy /safety could not be anticipated. Therefore, there is no rationale to support the claimed (reduced) dose in patients with PKAN. In conclusion, a lower dose (15 mg/kg b.i.d) was tested in the claimed indication. The rationale for this reduction is not discussed / justified by the applicant .

- In study TIRCON2012V1, PK analysis was stratified with regards to age as follows: <6 years (n=4) and ≥6 years (n=5). No significant difference in PK parameters and systemic exposure was observed between the two age groups (<6 years and ≥6 years). However, this statement should be sought cautiously as a very limited number of patients have been tested.Of note, no patients under 4 years have been investigated and administration of deferiprone is not intended for patients <4 years of age (see section 4.1 of SmPC).

3.3.2. Pharmacodynamics

Effect of a single dose of deferiprone on prolactin levels in healthy volunteers. Sponsor Project, No LA54-0116.

Objectives:
Primary: To evaluate the effect of a single dose of deferiprone on serum prolactin levels in healthy volunteers.
Secondary: To evaluate the pharmacokinetics of deferiprone and the relationship between serum concentrations of deferiprone and prolactin levels in healthy volunteers. To collect data on the safety and tolerability of a single dose of deferiprone in healthy volunteers.
Exploratory: To evaluate the effect of a single dose of deferiprone on levels of cortisol in healthy volunteers.

Methodology: This was a single-center, randomized, placebo-controlled, blinded, 2-period crossover study whose purpose was to determine the effect of deferiprone on prolactin levels in healthy volunteers.

Investigational product:
Name: Ferriprox (deferiprone) 500 mg IR film-coated tablets
Dosage Form/Route of administration: immediate-release tablet / oral
Regimen: Single 2500 mg dose (5 x 500 mg) of deferiprone immediate-release tablet formulation
Batch number: MR7340

Reference product:
Name: Matching placebo
Dosage Form/Route of administration: film-coated tablet / oral
Regimen: A single dose of five tablets
Batch number: FD6090-78H

Treatments Administered
Subjects received either Ferriprox IR formulation or the placebo, as follows:
Treatment A: A single 2500 mg dose of deferiprone, administered as five Ferriprox (deferiprone) 500 mg immediate-release tablets, under fasting conditions
Treatment B: A single dose of five matching placebo tablets under fasting conditions

Selection of Study Population

Number of Subjects

A planned total of 16 healthy volunteers were enrolled; 8 males and 8 females.

Main Inclusion Criteria

Individuals meeting all of the following criteria were considered for enrollment in the study:

1. Male or female aged ≥ 18 to <50 years
2. Absolute neutrophil count (ANC) of ≥1.8 x 109/L
3. Non- or ex-smoker; an ex-smoker was defined as someone who had not smoked at all or consumed any nicotine-containing products in at least the past 6 months prior to randomization
4. Body mass index ≥ 18.5 to < 30.0 kg/m2 and body weight ≥ 60 kg
5. In good health, as determined by medical history, complete physical examination (including vital signs), and safety laboratory tests (biochemistry, hematology, urinalysis)

MainExclusion Criteria

Individuals were excluded from enrollment if they met any of the following criteria:

1. History or presence of gastrointestinal, liver or kidney disease, or any other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs or known to potentiate or predispose to undesired effects
2. Presence of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease
3. Any clinically significant illness in the previous 28 days before Day 1 of this study
4. Positive results on HIV Ag/Ab Combo, Hepatitis B surface Antigen (HBsAG (B) (hepatitis B)) or anti Hepatitis C Virus (HCV (C)) tests
5. Clinically significant ECG abnormality, as judged by the investigator

Selection of Doses in the Study

A dosage of 33 mg deferiprone per kilogram of body weight has been established as the maximum therapeutic level for the treatment of systemic iron overload. For an individual who weighs 70 kg (commonly considered an average weight for an adult), the fixed-dose of 2500 mg approximated this dosage. If no effect on prolactin levels was shown at this dose level, it was to be concluded that no effect would have been seen at lower levels; if an effect was seen, it might be necessary to repeat the study using a range of lower doses, in order to determine at what exposure the effect appears.

Blinding

This was a blinded study. Placebo tablets matched the deferiprone tablets in number and appearance. Neither the subjects nor the study personnel responsible for administering the product and collecting blood samples and safety data knew which formulation was being administered in each period. Study personnel who analyzed the blood samples were blinded as to which formulation was received. Unblinding took place only after the bioanalytical tables had been finalized, locked and audited by the Quality Assurance department.

Results

Table 10.2 Demographic Characteristics of Safety Population

Demographic Variables	Overall (N=16)
Age (years)	
Mean (SD)	38 (7)
Min, Max	27, 48
Gender [(n%)]	
Male	8 (50.0)
Female	8 (50.0)
Ethnicity [n(%)]	
Hispanic or Latino	4 (25.0)
Not Hispanic or Latino	12 (75.0)
Race [n (%)]	
White	15 (93.8)
Black	1 (6.3)
Weight (kg)	
Mean (SD)	74.3 (11.1)
Min, Max	60.2, 94.0
Height (cm)	
Mean (SD)	167.2 (7.8)
Min, Max	156.0, 182.5
Body Mass Index (kg/m^2)	
Mean (SD)	26.5 (2.7)
Min, Max	21.0, 29.8

Pharmacokinetic results

Deferiprone

Serum deferiprone levels were below the lower limit of quantification (LOQ, 0.100 µg/mL) in all samples collected prior to dosing. The wash-out period between doses was considered appropriate. Two subjects had a Cmax value at the first point of the concentration-time curve. The PK profiles observed after a single dose of the deferiprone tablets showed that the median time of peak deferiprone concentration was 0.67 hour, and the mean maximal concentration was 39.663 µg/mL. After that, the drug concentration declined rapidly with a mean half-life of 1.74 hours. As expected, all concentrations were below the LLOQ for the matching placebo, and no PK parameters were calculated for this treatment arm.

Table 11.1 Summary of Serum Deferiprone Pharmacokinetic Parameters

PARAMETER	Deferiprone (n=16)	
	MEAN	C.V. (%)
C_{max} (µg/mL)	39.663	(40.5)
T_{max} (hours)[a]	0.67	(0.33-1.50)
AUC_{0-T} (µg·h/mL)	90.979	(34.0)
$AUC_{0-\infty}$ (µg·h/mL)	95.865	(34.1)
λz ($hours^{-1}$)	0.4052	(14.3)
$T_{1/2}$ (h)	1.74	(14.5)

Prolactin:

The PD profiles of prolactin observed after a single dose of the deferiprone tablets showed that the maximal effect (Emax) was much higher compared to that after the administration of matching placebo (109 µg/L *vs.*5 µg/L, respectively). The area under the effect curve was also higher following the administration of a single dose of deferiprone tablets (359 µg·h/L *vs.*-25 µg·h/L, respectively)

Table 11.2 Summary of Serum Prolactin Pharmacodynamic Parameters

PARAMETER	Deferiprone (N=16)		Placebo (N=14)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
E_{max} (µg/L)	109	(56.2)	5	(116.0)
T_{Emax} (h)[a]	1.00	(1.00-1.50)	3.17	(0.00-8.00)
$AUEC_{0-t}$ (µg·h/L)	359	(56.7)	-25	(-107.8)

A negative mean AUEC0-t was observed for placebo, indicating no increase in prolactin level after placebo administration. The negative value could have been due to the random or diurnal fluctuation of prolactin level. In the ANOVA, a statistically significant treatment effect was observed for AUEC0-t ($p<0.001$), Emax ($p<0.0001$), and TEmax ($p=0.0204$) of prolactin. The relative mean (IR/placebo) for Emax and AUEC0-t of prolactin were 2342.00% and -1360.82%. No other significant effects were observed.

When the effect of gender was included in the ANOVA, the gender effect was found to be significant for Emax ($p=0.0017$) and AUEC0-t ($p=0.0197$). A summary of PD parameters by gender is presented below.

Table 11.4 Summary of Serum Prolactin Pharmacodynamic Parameters by Gender

PARAMETER	Deferiprone (N=16)		Placebo (N=14)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
E_{max} (µg/L) Female	157	(28.5)	8	(81.0)
E_{max} (µg/L) Male	60	(42.3)	2	(119.2)
T_{Emax} (h)[a] Female	1.00	(1.00-1.50)	4.17	(0.00-8.00)
T_{Emax} (h)[a] Male	1.00	(1.00-1.50)	3.00	(0.00-8.00)
$AUEC_{0-t}$ (µg·h/L) Female	520	(28.1)	-23	(-157.3)
$AUEC_{0-t}$ (µg·h/L) Male	197	(44.6)	-26	(-75.5)

After accounting for the gender effect, the relative mean (IR/placebo) for Emax and AUEC0-t of prolactin were 2131.74% and -1143.19%, respectively. When the treatment by gender interaction was assessed in a separate ANOVA, it was found to be statistically significant (p-value < 0.05) for AUEC and Emax. A summary of the relative means (IR/placebo) for Emax and AUEC0-t and their 90% confidence interval for each gender are provided below.

Cortisol:

The PD profiles of cortisol observed showed that the cortisol level declined after the administration of either treatment, with the maximal decrease (Emax) being smaller in magnitude after a single dose of the deferiprone tablets compared to that after the administration of matching placebo (-185 nmol/L *vs.*-217 nmol/L, respectively). The area under the effect curve for the decline in cortisol was also smaller in magnitude following the administration of a single dose of deferiprone tablets (-795 nmol·h/L *vs.*-1160 nmol·h/L, respectively)

Table 11.6 Summary of Serum Cortisol Pharmacodynamic Parameters

PARAMETER	Deferiprone (N=16)		Placebo (N=14)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
E_{max} (nmol/L)	-185	(-63.7)	-217	(-47.6)
T_{Emax} (h)[a]	4.00	(0.33-8.00)	3.50	(0.67-8.00)
$AUEC_{0-t}$ (nmol·h/L)	-795	(-114.6)	-1160	(-70.8)

[a] Median (range) is presented.

PK/PD Analysis

Correlation of the PD and PK parameters was evaluated by the determination of the Pearson's correlation coefficient. All r values were under 0.5 (or r2 under 0.25), suggesting a weak correlation between drug exposure and the changes observed in the levels of prolactin and cortisol.

Figure 11.9 Correlation between $AUEC_{0-T}$ of Prolactin vs AUC_{0-T} of Deferiprone

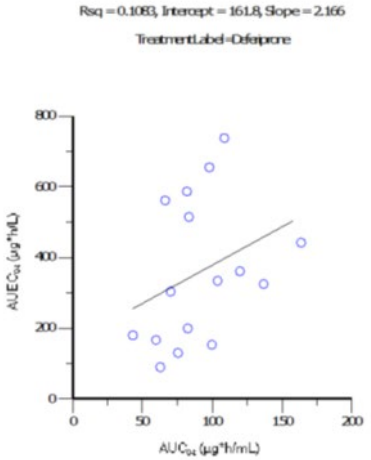
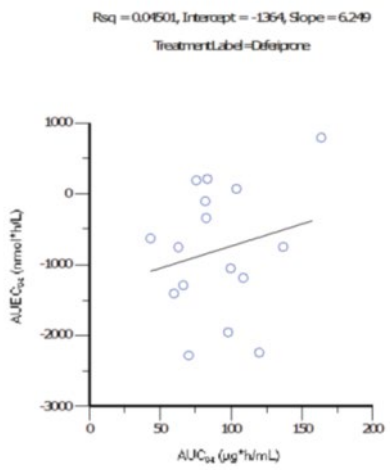


Figure 11.12 Correlation between $AUEC_{0-T}$ of Cortisol vs AUC_{0-T} of Deferiprone



Safety results:

The administration of a single 2500 mg dose of deferiprone was observed to be safe and well-tolerated. There were no deaths or SAEs, and no adverse events of severe intensity. One subject

experienced outof- range (lower) blood calcium values that led to discontinuation from the study. Of the 16 enrolled subjects, 5 (31%) experienced a total of 13 adverse events. Of these events, 8 (62%) were deemed reasonably possibly related to the study drug. The only drug-related AE that was experienced by more than 1 subject was a headache, seen in 2 subjects following Treatment A. A higher incidence of drug-related AEs was reported following the administration of Ferriprox IR tablets (19% of subjects) than following the administration of the placebo (7% of subjects). The assessment of vital signs, ECG parameters, and physical examinations did not reveal any safety concerns.

Pharmacokinetic Conclusions

The PK profiles observed after a single dose of deferiprone tablets showed that the median time to peak deferiprone concentration was 0.67 hour, and the mean maximal concentration was 39.663 µg/mL. After that, the drug concentration declined rapidly with a mean half-life of 1.74 hours.

The pharmaceutical form (a single 2500 mg dose of deferiprone, administered as five Ferriprox (deferiprone) 500 mg immediate-release tablets) are different from those submitted for registration (80 mg/mL oral solution).

Pharmacodynamics Conclusions

There was a statistically significant transient increase in prolactin levels following the administration of deferiprone tablets. The PD profile of prolactin observed after a single dose of deferiprone tablets showed that the maximal effect (Emax) was 109 µg/L, compared with 5 µg/L after the administration of matching placebo tablets. The area under the effect curve was also higher following deferiprone tablets (359 µg·h/L vs. -25 µg·h/L, respectively). These findings indicate that prolactin levels (extent of the effect and maximal effect) increased significantly following the administration of deferiprone tablets compared to the administration of placebo, and then returned to the baseline level within 8 hours post-dosing. The effect of deferiprone tablets was much higher in female subjects.

The PD profile of cortisol observed after the administration of either treatment showed that the cortisol level declined, with the maximal decrease (Emax) being smaller in magnitude after a single dose of deferiprone tablets compared to that after the administration of placebo (-185 nmol/L vs. -217 nmol/L, respectively). The area under the effect curve (AUEC0-t) for the decline in cortisol was also smaller in magnitude following deferiprone tablets (-795 nmol·h/L vs. -1160nmol·h/L, respectively). These findings indicate that the decreases in cortisol level are significantly reduced following the administration of deferiprone tablets compared to the administration of a placebo.

Since patients with treatment of neurodegeneration with brain iron accumulation (NBIA) will be exposed to chronic deferiprone exposure, it must be assumed that they will be exposed to increased levels of prolactin and decreased the level of cortisol with all known consequences at the same time. Therefore, this study is not able to illustrate the situation that will occur in the clinical practice of this group of patients. The applicant presented a discussion on the significance of changes in prolactin levels as a result of chronic deferiprone use. The analysis of data from studies on healthy volunteers and unpublished data from PD patients, as well as data from the pivotal study was presented.

Short-term studies in healthy volunteers revealed no prolactin-related adverse effects. The data from the study in PD patients also do not indicate significant consequences associated with deferiprone use in this population. Similar results were obtained from safety analysis in patients with PKAN. PKAN patients over 18-36 months did not exhibit prolactin-related SAEs.

The graphical displays of the PD and PK parameters reveal a weak correlation between drug exposure and the changes in prolactin and cortisol levels. Despite the more significant effect on prolactin in female subjects, the correlation appeared to be higher in male than in female subjects.

Taking into account the proposed indication: Treatment of neurodegeneration with brain iron accumulation (NBIA), the target population may include patients with Parkinson symptoms who may be treated with drugs that alter dopamine transmission. Therefore, a study that aims, among other things, to collect data on the safety and tolerability of a single administration of deferiprone in healthy volunteers is not relevant to clinical practice. There is a possibility that in healthy volunteers, it would not be able to accurately assess the effect on changes in prolactin levels and the safety of deferiprone.

It is not clear how the determination of sample size was conducted. Taking into account differences in the physiology of prolactin metabolism between females and males, the observed differences for PD and relations between PK/PD parameters seem to be understandable.

A dose-ranging study of the effect of deferiprone on prolactin levels in healthy volunteers. Study code LA56-0117.

Objectives:

Primary: To evaluate the effect of 4 different dosages of deferiprone delayed-release (DR) tablets on serum prolactin levels in healthy volunteers

Secondary: To evaluate the pharmacokinetics of deferiprone and the relationship between systemic exposure of deferiprone and prolactin levels in healthy volunteers. To collect data on the safety and tolerability of 4 different dosages of deferiprone DR in healthy volunteers

Exploratory: To evaluate the effect of 4 different dosages of deferiprone DR on levels of cortisol, dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), norepinephrine, 3-methoxy-4- hydroxyphenylglycol (MHPG), serotonin, 5-hydroxyindoleacetic acid (5- HIAA), and tetrahydrobiopterin (BH4), as well as on the phenylalanine:tyrosine ratio, in healthy volunteers.

Methodology: Single-center, randomized, single-dose, dose-ranging, open-label, 4-period, 4-sequence, crossover study in healthy volunteers. All subjects will receive 4 single doses of deferiprone DR tablets, separated by 7 days, at dosages of 5, 10, 15, and 30 mg/kg.

Treatment administration
Sixteen healthy volunteers (7 males and 9 females) were randomized to receive 4 single doses of deferiprone DR 600 mg tablets on separate occasions, with a 7-day washout between doses. The doses were as follows:
• Treatment A: 5 mg/kg
• Treatment B: 10 mg/kg
• Treatment C: 15 mg/kg
• Treatment D: 30 mg/kg
All doses were rounded to the nearest half-tablet.
Subjects were randomized to receive the 4 doses in one of the 4 dosing sequences shown below, as per the randomization code list based on Williams design

Subject disposition: A total of 16 healthy volunteers were randomized, of whom 14 (87.5%) completed the study, and 2 (12.5%) were discontinued.

The reasons for discontinuation were as follows:
• Subject 008 (47 years old, male) received only Treatment D (30 mg/kg) in Period 1. He was withdrawn from the study due to an event of high blood pressure experienced approximately 12 hours after dosing that was judged clinically significant by the Investigator and reported as a TEAE. The subject was withdrawn from the study 3 days after the onset of the event.

• Subject 009 (33 years old, female) received only Treatment A (5 mg/kg) in Period 1 and Treatment B (10 mg/kg) in Period 2. She did not show up at check-in of Period 3 and withdrew consent from the study prior to Period 4, for personal reasons.

Table 10.1 Subject Disposition

	Sequence 1: ABCD	Sequence 2: BCDA	Sequence 3: CDAB	Sequence 4: DABC	Total
Subjects Randomized [N]	4	4	4	4	16
Subjects Included in Each Analysis Population [n(%)]					
Safety Population	4 (100)	4 (100)	4 (100)	4 (100)	16 (100)
Pharmacokinetic Population	4 (100)	4 (100)	4 (100)	4 (100)	16 (100)
Pharmacodynamic Population	4 (100)	4 (100)	4 (100)	4 (100)	16 (100)
Subject Completed the Study [n(%)]					
Yes	3 (75)	4 (100)	4 (100)	3 (75)	14 (88)
No	1 (25)	0	0	1 (25)	2 (13)
If No, Reason of Study Discontinuation [n(%)]					
Adverse event	0	0	0	1 (25)	1 (6)
Withdrawal by subject	1 (25)	0	0	0	1 (6)
Study terminated by sponsor	0	0	0	0	0
Physician decision	0	0	0	0	0
Protocol deviation	0	0	0	0	0
Death	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Other	0	0	0	0	0

Demographic and Other Baseline Characteristics
Subjects were between the ages of 22 and 49 years (mean 35 ±9 years). Seven were male (43.8%), and 9 were female (56.3%), and the majority were white (87.5%).

Pharmacodynamics measures:
The change from baseline for prolactin will be calculated at each post-dose timepoint. The following PD parameters will be determined for each dosage:Emax, TEmax, AUEC0-T.

Pharmacokinetics measures:
The following PK parameters for deferiprone will be determined for each dose:Cmax, Tmax, AUC0-T, AUC0-∞, λZ, T½. The correlation between the PD and PK parameters for deferiprone will be evaluated.

Exploratory measures:
The change from baseline for cortisol, DOPAC, HVA, norepinephrine, MHPG, serotonin, 5-HIAA, BH4, and the phenylalanine: tyrosine ratio will be calculated at each post-dose time point. The following PD parameters will be determined for each dosage:Emax, TEmax, AUEC0-T.

Safety measures:
- AEs: Frequency, severity, time to onset, duration, and relatedness to study drug
- Serious adverse events (SAEs): Frequency, severity, time to onset, duration, and relatedness to study drug
- Number of discontinuations due to AEs
- Biochemistry assessments
- Hematology assessments
- Coagulation assessments
- ECG assessments
- Vital sign assessments
- Physical examination

Analysis of Deferiprone Pharmacokinetics

All 16 subjects were included in the PK analysis. However, the Treatment C (15 mg/kg dose) data for subject 006 were omitted from the analysis as the administration of this dose had deviated from the procedure established in the study protocol. The data showed that the Cmax value (6.053 µg/mL) for this subject was within the observed range (5.739–9.208 µg/mL) seen in the other subjects following the administration of the same dose, but the AUC values (~21 µg·h/mL) were below the minimum calculated value for the others (~28 µg·h/mL). Thus, a possible impact of the dosing deviation on the estimation of PK parameters cannot be excluded, thereby justifying the exclusion of the above data. The mean measured serum concentration versus time profile is depicted in Figure 11.1, and the log-transformed mean concentration versus time profile is depicted in Figure 11.2.

Figure 11.1 Mean Serum Deferiprone Concentration -Time Profiles (Linear Plot)

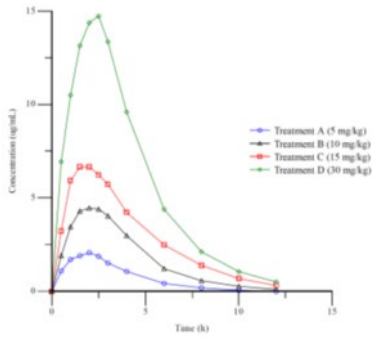
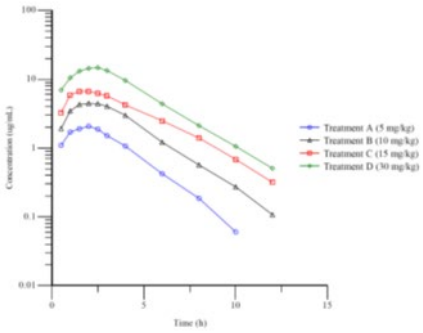


Figure 11.2 Mean Serum Deferiprone Concentration -Time Profiles (Semi-logarithmic Plot)



The wash-out period between doses was considered appropriate as all serum deferiprone levels were below the LOQ (0.100 µg/mL) in all samples collected prior to dosing for all 4 treatment groups.

Table 11.1 Summary of Serum Deferiprone Pharmacokinetic Parameters

Parameter	Treatment A (5 mg/kg) (n=15)		Treatment B (10 mg/kg) (n=15)		Treatment C (15 mg/kg) (n=13)		Treatment D (30 mg/kg) (n=15)	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
C_{max} (µg/mL)	2.188	17.1	4.923	26.1	7.811	13.0	15.592	20.2
T_{max} (h)*	1.50	(0.50-2.50)	2.00	(1.50-4.00)	2.00	(1.00-6.00)	2.00	(0.55-3.00)
AUC_{0-t} (µg·h/mL)	8.247	13.9	20.916	26.1	34.507	12.5	69.898	16.9
$AUC_{0-\infty}$ (µg·h/mL)	8.596	13.5	21.414	25.9	35.383	13.2	71.339	17.0
λ_z (1/h)	0.4217	17.2	0.3872	15.6	0.3637	12.5	0.3693	11.4
$T_{1/2}$ (h)	1.69	17.9	1.83	15.1	1.93	12.6	1.90	11.4

* Median and range are presented

Peak and extent of exposure as indicated by Cmax and AUCs, respectively, were significantly increased with increasing doses. However, the increases were not linearly related to the increasing doses for Cmax, AUC0-t, and AUC0-∞ as their respective 95% confidence intervals of the slope estimate β did not contain 1. Dose-proportionality has also evaluated over 3 consecutive doses, either the 5 to 15 mg/kg or the 10 to 30 mg/kg dose range. Closer to dose proportionality was observed with the 10 to 30 mg/kg dose range, although a dose-proportional increase was demonstrated only for Cmax, for which the 95% confidence interval of the slope estimate β contained 1 (95% CI: 0.9871, 1.1424). In the analysis of the 5 to 15 mg/kg dose range, further deviation from dose proportionality was observed for all three PK parameters.

Analysis of Pharmacodynamics

Prolactin

Following administration of deferiprone at doses of 5, 10, 15, and 30 mg/kg, the maximal effect on prolactin (Emax) was 57 µg/L, 81 µg/L, 83 µg/L, and 98 µg/L, respectively. The median time of maximal effect (TEmax) was approximately 1.0 to 1.5 hours across all dose levels. Prolactin levels returned to the baseline level within 10 hours post-dosing for all treatments. Following administration of deferiprone at doses of 5, 10, 15, and 30 mg/kg, the area under the effect curve (AUEC0-T) was 101 µg·h/L, 212 µg·h/L, 238 µg·h/L, and 370 µg·h/L, respectively.

Table 11.3 Summary of Serum Prolactin Pharmacodynamic Parameters

Parameter	Treatment A (5 mg/kg) (n=15)		Treatment B (10 mg/kg) (n=15)		Treatment C (15 mg/kg) (n=13)		Treatment D (30 mg/kg) (n=15)	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
E_{max} (µg/L)	57	53.6	81	62.4	83	57.0	98	76.5
TE_{max} (h)[a]	1.10	(1.00-2.50)	1.50	(1.00-3.00)	1.00	(1.00-6.00)	1.50	(1.00-3.00)
$AUEC_{0-T}$ (µg·h/L)	101	47.2	212	65.4	238	50.0	370	73.6

[a] Median and range are presented

Relationship Analysis between Deferiprone and Prolactin Levels

Correlation of the PD and PK parameters was evaluated by determination of the Pearson's correlation coefficient, r.

Table 11.5 PK/PD Relationship Between Deferiprone and Prolactin Levels

Parameter	r	p-value[a]	Correlation	Strength of Correlation[b]
C_{max}/E_{max}	0.36958	0.0043	significantly correlated	Weak
$C_{max}/AUEC_{0-T}$	0.61441	< 0.0001	significantly correlated	Moderate
AUC_{0-t}/E_{max}	0.29936	0.0224	significantly correlated	Weak
$AUC_{0-t}/AUEC_{0-T}$	0.55254	< 0.0001	significantly correlated	Moderate
$AUC_{0-\infty}/E_{max}$	0.29503	0.0246	significantly correlated	Weak
$AUC_{0-\infty}/AUEC_{0-T}$	0.54789	< 0.0001	significantly correlated	Moderate

[a] The correlation is statistically significant if $p < 0.05$.

[b] The strength of the correlation is at least moderate if $r > 0.5$

All the PK/PD correlations were statistically significant ($p < 0.05$). All the r values were under 0.5 when assessing the three correlations between deferiprone systemic exposure (Cmax and AUCs) and the maximal effect on prolactin (Emax), thereby suggesting a weak correlation between drug exposure and the maximum change in prolactin level. However, the correlations between deferiprone systemic exposure (Cmax and AUCs) and the area under the effect curve (AUEC0-T) were at least moderate as all r values were above 0.5. Figure 11.12 also shows that the correlation between the time to maximal effect on prolactin (TEmax) and the time to Cmax of deferiprone (Tmax) was at least moderate as r was above 0.5, given the r2 being 0.3134.

Gender Analysis

There was a significant dose-by-gender interaction detected in the ANOVA for Emax (p=0.0386) and AUEC0-T (p=0.0009) when comparing doses across the 5 to 30 mg/kg range. The dose-by-gender interaction was found to be significant ($p < 0.05$) for both Emax and AUEC0-T across the 5–15 mg/kg dose range and only for AUEC0-T across the 10–30 mg/kg dose range.

Cortisol

Cortisol levels declined after deferiprone administration, with the mean maximal decrease (Emax) ranging from -229 to -208 nmol/L across doses. The median time of Emax (TEmax) was 10 hours following Treatment A (5 mg/kg), Treatment C (15 mg/kg), and Treatment D (30 mg/kg), and 12 hours following Treatment B (10 mg/kg). The area under the effect curve, depicted as AUEC0-T, averaged between -1453 and -1165 nmol·h/L following the four different treatments. No notable dose-dependent changes were observed for all three PD parameters.

Pharmacokinetic Conclusions

The PK profiles observed after a single dose of deferiprone DR tablets showed that the median time to peak deferiprone concentration was 1.5 hours following administration of Treatment A (5 mg/kg) and 2 hours after Treatments B, C, and D (10, 15, and 30 mg/kg). Mean maximal concentration was 2.188 µg/mL for Treatment A (5 mg/kg), 4.923 µg/mL for Treatment B (10 mg/kg), 7.811 µg/mL for Treatment C (15 mg/kg), and 15.592 µg/mL for Treatment D (30 mg/kg). The half-life across all doses averaged approximately 1.8 hours.

The deferiprone delayed-release (DR) tablets used in the study do not fully correspond to the product submitted for registration. In previous studies, noticeable pharmacokinetic differences were observed between this form and the immediate release form, e.g., The Cmax was decreased by approximately 50% as compared to an immediate-release formulation. Therefore, the conclusions obtained during this study cannot directly concern deferiprone 80 mg/mL oral solution, and are only supportive.

Pharmacodynamic Conclusions

The Emax of prolactin increased with increasing doses, with values of 57 µg/L, 81 µg/L, 83 µg/L, and 98 µg/L following administration of 5, 10, 15, and 30 mg/kg deferiprone DR tablets, respectively. Emax was reached within approximately 1.0–1.5 hours for all doses. The AUEC0-T of prolactin increased with increasing doses, with values of 101 µg·h/L, 212 µg·h/L, 238 µg·h/L, and 370 µg·h/L following administrations of 5, 10, 15, and 30 mg/kg deferiprone DR tablets, respectively. The ln-transformed PD parameters Emax and AUEC0-T were analyzed to determine dose proportionality using the power model. Emax and AUEC0-T increased significantly ($p < 0.05$) with increasing doses of deferiprone DR.

There were significant correlations between the PD and PK parameters ($p < 0.05$). The extent of the effect on prolactin (AUEC0-T) was considered at least moderately correlated to the peak (Cmax), and extent of exposure (AUCs) of deferiprone as the Pearson's correlation coefficients (r) was above 0.5. On the other hand, the correlation of the maximal effect on prolactin (Emax) and deferiprone systemic exposure (Cmax and AUCs) showed only a weak correlation since r was less than 0.5 for each comparison.

A significant dose-by-gender interaction was observed for the change from baseline of prolactin. Overall, the Emax and AUEC0-T of prolactin in female subjects were at least 2 times higher than those in male subjects for each dose level of the 5 to 30 mg/kg dose range. The dose-effect on change in prolactin level was significant for female subjects but not for male subjects. Unlike prolactin, the cortisol levels declined after all treatments. Emax, TEmax, and AUEC0-T were comparable across all 4 deferiprone doses, indicating an absence of a dose-dependent effect on cortisol by deferiprone.

Proposed indication: Treatment of neurodegeneration with brain iron accumulation (NBIA), i.e., concerns a heterogeneous group of genetic disorders characterized by the focal accumulation of iron in the brain, usually in the basal ganglia. Clinical manifestations of these disorders are dystonia, choreoathetosis, spasticity, and parkinsonian symptoms. The decrease in dopamine transmission is one of the main causes of the extrapyramidal disorder leading to parkinsonian symptoms.

Therefore, evaluating the effect of deferiprone on prolactin levels (where the likely cause of these changes is a modification of dopamine transmission) as well as collect data on the safety and tolerability of different dosages of deferiprone DR in healthy volunteers, does not correspond to clinical conditions.In the same sense, assessing the effect of deferiprone DR on the level of dopamine, DOPAC, HVA, norepinephrine, MHPG, 5-HT and 5- HIAA in healthy volunteers, instead of patients with parkinsonian symptoms who may additionally use the dopamine mimetic drugs in clinical conditions - it causes that the conclusions of this study do not have a direct reference to clinical reality. The question of the absence of a control group remains debatable. It is too optimistic to assume that a study

conducted under different conditions with other subjects using a different pharmaceutical form can be referred directly to observations from other studies.

The assessment of PD parameters as such as dopamine, DOPAC, HVA, norepinephrine, MHPG, serotonin, 5 HIAA, and the phenylalanine: tyrosine in blood and the attempt to correlate them with PK parameters is interesting from the scientific point of view. Whereas concerning the attempt to inhibit central neurodegenerative processes, it is of limited importance because, in practice, there is no strict correlation between peripheral and central changes of some of the PD parameters studied.

The attached documentation does not contain the results of similar analyses of PD parameters performed on the exploratory measures (cortisol, dopamine, DOPAC, HVA, norepinephrine, MHPG), serotonin, 5-HIAAA, and BH4 concentrations and the phenylalanine:tyrosine ratio). The evaluation of these results may be helpful to understand the potential causal relationship between the use of deferiprone and its side effects. Additionally, given that deferiprone has been reported to reversibly inhibit tyrosine hydroxylase and tryptophane hydroxylase, the assessment of the effect of deferiprone (especially if administered over a long period of time) on dopamine and serotonergic transmission is very important for the evaluation of its safety, as well as for potential interactions with antiparkinsonian, antidepressant, antipsychotic and antiplatelet drugs?

The applicant presented data that in treated PD patients, there is a known baseline increase in prolactin compared with controls. PD is characterized by a reduction of central dopamine, which could explain the hyperprolactinemia (HP). The applicant showed, recent, not published yet, results of the study that analyzed the effect of long term deferiprone treatment in patients with Parkinson's disease. The provided data indicate that the pre-dosing prolactin values after 1-month, are slightly lower than the baseline values and that the 1-month, 2 hours post-dose concentrations are higher than baseline and the pre-dosing value. The study indicates that in PD patients, deferiprone induced a slight to a mild increase of prolactin, two hours after administration (median value of 1.5-fold the upper normal value), while the residual value remained normal. None of the 70 PD patients treated in either study reported any PD worsening. It seems that deferiprone reduces dopamine turnover, mainly by inhibiting iron-related oxidative catabolism, which is pivotal in PD. The reduction of the turnover may induce a transient HP. On the other hand, there is a marginal effect on hyperprolactinemia, without any prolactin-related SAEs and a net positive impact on the patient's PD status. Moreover, it has been demonstrated, in rats, that deferiprone also reduces the activity of tyrosine hydroxylase activity, which requires iron as a cofactor, and COMT activity by direct inhibition. It is not known whether the inhibition of tyrosine hydroxylase occurs in patients with the concentrations generated by a dose of 20 to 30 mg/kg/day. However, the overall consequence is favourable with a significant reduction of the dopamine metabolite homovanillic acid (HVA)/dopamine ratio, showing an overall reduction of dopamine turnover, with a favourable impact on dopamine transmission. A slight favourable inhibition on the COMT activity has been suggested but needs further confirmation. Taking all of these factors together, it is evident that deferiprone reduces dopamine turnover, mainly by inhibiting iron-related oxidative catabolism, which is pivotal in PD. The reduction of the turnover may induce a transient HP, for which preclinical data showed a favourable impact on the dopamine transmission at the striatal level.

3.3.3. Discussion on clinical pharmacology

The applicant submitted documentation on deferiprone in the form of 80 mg/ml solution for the treatment of neurodegeneration associated with pathological iron accumulation. The pharmacokinetic/pharmacodynamic study program did not include any studies carried out with the proposed drug form. Individual studies concerned: LA20-BA study (500 mg film-coated tablets and solution 100mg/ml); LA21-BE study (500 mg film-coated tablets and solution 100mg/ml), LA39-0412

study (500 mg film-coated tablets), LA40-0412 study (500 mg film-coated tablets), LA54-0116 study (500 mg film-coated tablets), LA56-0117 study (600 mg delayed-release tablets). Given the absence of a study that would demonstrate bioequivalence between the solution of deferiprone 80 mg/ml and other pharmaceutical forms of deferiprone, the applicant is required to provide a detailed explanation as to why extrapolation of the results of these studies to the submitted product is justified. The applicant stated that the 100 mg/mL oral solution had been demonstrated to be bioequivalent to the 500 mg film-coated tablets. In the context that the 80 mg/mL formulation does not differ significantly from the 100 mg/mL formulation that would affect the bioavailability and the only differences are minor differences in coloring and flavouring agents. Therefore no dedicated relative BA study has been performed. The assumptions regarding the bioequivalence of aqueous drug solutions contained in guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** indicate that bioequivalence studies may be waived if the test product is an aqueous oral solution and contains an active substance in the same concentration. The concentration of deferiprone in both formulation is different (80 mg/ml vs. 100mg/ml); therefore, it could not be anticipated without bioequivalence study that bioavailability of both formulations is essentially similar.(LoOI)

Moreover, there are several additional uncertainties regarding Pharmacokinetic profile of deferiprone 80 mg/mL oral solution.

- The analytical methods used to determine the concentration of deferiprone in human plasma and urine seem to be adequately described; the validations were performed according to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)". The analytical methods used are acceptable. The calibration curves are appropriate, and the stability testing justifies the conditions the samples were exposed to during collection and testing. However, some issues regarding validations or/and bio-analysis need to be clarified.

The validation reports *(AA20080-VTL and AA20743-WCM)* carry-over parameters were not identified. The applicant informed that the validation of this method was based on the FDA Guidance on Bioanalytical Method Validation, 2001. In that guidance, there was no requirement for checking carry-over of the drug from high concentration samples to low concentration samples. Hence, this parameter was not investigated during the validation exercise. It is important to note that according to EMA guidelines (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) carry-over effect testing is necessary. According to the guideline, if it appears that carry-over is unavoidable, study samples should not be randomised, and specific measures should be considered and tested during the validation so that it does not affect accuracy and precision. In the absence of such testing, there is a risk that the results obtained are not entirely reliable. Therefore, the applicant is asked to explain what measures have been taken to ensure proper precision and accuracy (LoOI).

In addition there was no carry-over exercise performed in AA20080VTL and AA20743-WCM and ISR was not included in the PK study. The applicant informed that, the FDA Guidance 2001 does not include a requirement for performing incurred sample analysis (ISR) during analysis of the study subject samples. Hence, the ISR data were not provided in the study report. In addition, the bioanalytical validation method report had been submitted to the EMA before for the application of the 100 mg/mL OS, and the reported data were found to be acceptable to support the registration.

As outlined by the EMA guideline on bioanalytical method (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) which came in force since 01 Feb 2012, the ISR data are a key element necessary for the validation of bioanalytical methods. In the absence of such data, the provided serum concentration of deferiprone and its metabolite 3-O-glucuronide in human during the pivotal phase III study TIRCON2012V1 (study of interest in this dossier) could not be considered as reliable.

The argument that the bioanalytical methods AA20080-VTL and AA20743-WCM have already been considered acceptable by EMA for the application of the 100 mg/mL product is not acceptable.

Indeed, the assessment of this dossier dates back to 2007, so before entry into force of the new guideline. However, the studies were submitted as additional material for the current hybrid application and therefore the applicant is asked to discuss whether the absence of these procedures did not make the data then obtained unreliable. Thus, the requirement for ISR data provided by the bioanalytical guideline 2012 cannot be waived for the current application.

The applicant is still asked to provide ISR data.(LoOI)

-The protocols of the studies-LA39-0412, LA40-0412, LA54-0116, LA56-0117 assumed the evaluation of primary and secondary objectives after a single deferiprone administration. The regression analysis (study LA39-0412) showed no significant differences in Cmax, AUC0-t, AUC0-∞, CL/F and Vd/F among subjects with renal impairment and healthy volunteers, however it was observed that following administration of a single 33 mg/kg dose of deferiprone a significant trend for Tmax, T1/2, and CLr using eGFR as the predictor variable was observed. The trend for CLr displayed that the value decreased as the severity of renal impairment increased. The renal clearance of the metabolite deferiprone 3-O-glucuronide was more adversely impacted. The significant slowdown in its urinary excretion resulted in higher Cmax, AUC0-t, and AUC0-∞, and longer Tmax, and T1/2 in the renally impaired groups compared to the healthy volunteers. The rates of increase in Cmax and AUCs as eGFR decreases were higher in subjects with more severe renal impairment than in subjects with milder renal impairment. Additionally, the regression analysis using eGFR as the predictor variable showed a significant trend for Fe24 the metabolite deferiprone 3-O-glucuronide. All these data suggest an altered renal elimination of deferiprone depending on the degree of renal failure. Individual parameters of PK, when viewed separately and collectively, indicate quite clearly that with the severity of the renal failure, the elimination of deferiprone and its primary metabolite deferiprone 3-O-glucuronide from urine is reduced. The fact that renal elimination impairment is more pronounced for the metabolite deferiprone 3-O-glucuronide becomes particularly relevant in the light of results of study LA37-1111. The data on the concentration-response relationship revealed some weak but statistically significant trends of increase in dQTcF and ddQTcF with increasing exposure to deferiprone and deferiprone 3-O-glucuronide. It indirectly suggests that the metabolite deferiprone 3-O-glucuronide may also show some pharmacological activity.

- The presented results indicate that there is no increased exposure to deferiprone or its glucuronide metabolite in patients with impaired hepatic function (study LA40-0412). Following a single oral, 33 mg/kg dose of deferiprone. Moreover, it is surprising to note that there are tendencies to reduce deferiprone exposure in patients within-subjects with mild and moderate hepatic impairment, which is manifested by a decrease in Cmax in subjects with mild and moderate hepatic impairment as well as AUC was 15% lower for subjects with mild hepatic impairment in comparison to the control group. The peak exposure of both deferiprone and its glucuronide metabolite were somewhat lower in subjects with mild or moderate hepatic impairment than in healthy subjects as their mean Cmax were close to or slightly lower than 80% of that in healthy subjects. However, the extent of exposure of both compounds was not significantly affected as the AUC ratios were within 80 - 125% in comparison to the healthy subjects. Therefore, theoretically, no dosage adjustment should be needed in patients with chronic liver disease having mild or moderate hepatic impairment following a single dose administration of deferiprone.

- Less than 3% of the dose was recovered as unchanged deferiprone in urine over 24 hours post-dose across the 3 groups studied, with a slightly decreasing trend as the severity of hepatic impairment increased. CLr of deferiprone was approximately 30% lower for the group with moderate

hepatic impairment versus the control group, but no decrease in CLr was observed with the mild hepatic impairment group.

- In study TIRCON2012V1, no significant difference in PK parameters and systemic exposure was observed between the two age groups (<6 years and ≥6 years). However, this statement should be sought cautiously as a very limited number of patients have been tested (n= 4 for <6 years; and n= 5 for ≥6 years).

- Since patients (study LA54-0116) with the treatment of neurodegeneration with brain iron accumulation (NBIA) will be exposed to chronic deferiprone exposure, it must be assumed that they will be exposed to the steadily increased level of prolactin and decreased the level of cortisol with all the known consequences of this state of affairs. The data from the study in PD patients also do not indicate significant consequences associated with deferiprone use in this population. Similar results were obtained from safety analysis in patients with PKAN. PKAN patients over 18-36 months did not exhibit prolactin-related SAEs.

- Taking into account the proposed indication: Treatment of neurodegeneration with brain iron accumulation (NBIA), the target population may include patients with parkinson symptoms who may be treated with drugs that alter dopamine transmission. There is a possibility that in healthy volunteers, we will not be able to accurately assess the effect on changes in prolactin levels and the safety of deferiprone. On the other hand, short-term studies in healthy volunteers revealed no prolactin-related adverse effects. Treatment of neurodegeneration with brain iron accumulation (NBIA), i.e., concerns a heterogeneous group of genetic disorders characterized by the focal accumulation of iron in the brain, usually in the basal ganglia. Clinical manifestations of these disorders are dystonia, choreoathetosis, spasticity, and parkinsonian symptoms. The applicant presented data that in treated PD patients, there is a known baseline increase in prolactin compared with controls. PD is characterized by a reduction of central dopamine, which could explain the hyperprolactinemia (HP). The applicant showed, recent, not published yet, results of the study that analyzed the effect of long term deferiprone treatment in patients with Parkinson's disease. The provided data indicate that the pre-dosing prolactin values after 1-month, are slightly lower than the baseline values and that the 1-month, 2 hours post-dose concentrations are higher than baseline and the pre-dosing value. The study indicates that in PD patients, deferiprone induced a slight to a mild increase of prolactin, two hours after administration (median value of 1.5-fold the upper normal value [1.2-1.9]), while the residual value remained normal. None of the 70 PD patients treated in either study reported any PD worsening. It seems that deferiprone reduces dopamine turnover, mainly by inhibiting iron-related oxidative catabolism, which is pivotal in PD. The reduction of the turnover may induce a transient HP. On the other hand, there is a marginal effect on hyperprolactinemia, without any prolactin-related SAEs and a net positive impact on the patient's PD status. Regarding concomitant medicines, L-DOPA, DOPA decarboxylase inhibitors (e.g., carbidopa), MAO inhibitors (e.g., safinamide), COMT inhibitors e.g. entacapone) are the most commonly prescribed medicine for Parkinson symptoms. All these drugs are employed to increase dopamine level in brain. Deferiprone also inhibits COMT and may have a protective effect by minimizing metabolism of L-DOPA by COMT (Devos et al). The elevated dopamine level in brain, in general, inhibits prolactin synthesis and secretion by the pituitary gland. Thus, the subset of NBIA patients taking the above most common Parkinson drugs would have relatively less disturbance in prolactin levels if the deferiprone treatment is co-administered. Deferiprone does not interact with dopamine receptor (D2R) and thus is less likely to interact with dopamine agonists (e.g., pramipexole, rotigotine, and ropinirole), commonly used to treat Parkinson symptoms. The PD properties are considered adequately decribed.

3.3.4. Conclusions on clinical pharmacology

There are still several uncertainties which make it difficult to draw definitive conclusions regarding Pharmacokinetic profile as well as pharmacodynamic properties of deferiprone 80 mg/mL oral solution conclusions.

3.3.5. Clinical efficacy

	Age	Gender	Number	Severity of the disease
TRICON 2012V1	Mean age was 19.2 for placebo and 20.8 for DFP treated patients	47 males and 42 females were enrolled	DFP = 58 Placebo = 30	Baseline BAD score: (mean ± *SD) according to age of motor symptoms onset* *Age<6 20.3 ± 8.9 Age ≤ 17.0 ± 7.6*
TRICON 2012V1 EXT	Placebo-DFP 19.9 DFP-DFP 22.4	38 males and 30 females were enrolled	DFP = 68	Baseline BAD score: (mean ± *SD)* *Placebo-DFP 16.0 (8.0)* *DFP-DFP 19.4 (8.1)*

Main study(ies)

TRICON2012V1. A randomized, double-blind, placebo-controlled trial of deferiprone in patients with pantothenate kinase-associated neurodegeneration (PKAN)

Methods

TIRCON2012V1 was a multi-center, double-blind, randomized, placebo-controlled, 18-month study in patients with PKAN aged 4 years and older. At baseline, eligible participants were randomized in a 2:1 ratio to receive either deferiprone oral solution or placebo, using stratification to ensure that each treatment group contained the same ratio of individuals in whom motor symptoms had appeared before 6 years of age versus at or after 6 years. For the first 6 weeks, patients in the deferiprone group received a dose of 5 mg/kg twice daily (b.i.d.). If this was tolerated and there were no signs of toxicity, the dose was increased to 10 mg/kg b.i.d. over the next 6 weeks and then to 15 mg/kg b.i.d. for the remainder of the study. Patients in the control group received a matching volume of placebo during each of these periods.

Study Participants

Main Inclusion Criteria
Patients were eligible to enroll in the study if they met all of the following criteria:
1. Male or female 4 years of age or older at the screening visit
2. Diagnosis of PKAN, confirmed by genetic testing (supporting evidence required)
3. BAD total score ≥ 3 at the screening visit

Main Exclusion Criteria
Patients were excluded from enrollment if they met any of the following criteria:
1. Evidence of iron deficiency defined by Fe:TIBC ratio <15%, or serum ferritin <12 ng/mL
2. Treatment with deferiprone in the past 12 months
3. Previous failure of treatment with deferiprone, or previous discontinuation of treatment with deferiprone due to adverse events

4. Conditions are known to contraindicate the use of deferiprone (history of agranulocytosis or recurrent episodes of neutropenia)

Treatments

Patients received either deferiprone oral solution or placebo. The assigned study product was taken twice-daily, a minimum of 8 hours apart. Study product could be taken with or without food, but the food was recommended if a patient was experiencing nausea or vomiting.

As some patients who are naïve to deferiprone may experience gastrointestinal adverse events at the start of therapy, titration was employed in an attempt to reduce this. The dose was started at 5 mg/kg b.i.d., which was lower than the dosages described in the literature that was found to be well tolerated. After 6 weeks, if no toxicities were observed, the dose was to be increased to 10 mg/kg b.i.d. over the next 6 weeks, and after another 6 weeks was to be increased to 15 mg/kg b.i.d. (i.e., 30 mg/kg/day) for the remainder of the study. Patients in the reference group received a matching volume of placebo during each of these periods. The dose could be adjusted during the study based on tolerability and on the assessment of safety markers for adverse reactions that were possibly dose-dependent, such as gastrointestinal upset, increases in serum liver enzyme levels, and arthropathies. The duration of participation in the study for each patient was up to 20 months, including the screening period and the follow-up visit.

Efficacy Measurements: Baseline and Months 6, 12, and 18 or early termination visit:
Pharmacokinetics Measurements: Month 6
Safety Measurements
• Screening, weekly after baseline, and follow-up: Hematology
• Screening and Months 1.5, 3, 6, 12, and 18: Biochemistry, urinalysis
• Screening, Months 1.5, 3, 6, 12, and 18, and follow-up: Physical examination
• Screening, baseline, Months 1.5, 3, 6, 12, and 18, and follow-up: Adverse events(AEs), serious adverse events (SAEs), concomitant medications, vital signs
• Screening and Month 18: 12-lead ECG

Objectives

Primary objectives: To evaluate the change in severity of dystonia in patients with PKAN treated withdeferiprone vs. placebo for 18 months. To evaluate the patient's global impression of improvement in patients with PKAN treated with deferiprone vs. placebo for 18 months

Secondary objectives:
To evaluate the effect of deferiprone compared to placebo on motor symptoms
To evaluate the effect of deferiprone compared to placebo on functional independence
To evaluate the effect of deferiprone compared to placebo on quality of life
To evaluate the effect of deferiprone compared to placebo on quality of sleep
To evaluate the effect of deferiprone compared to placebo on the change in iron levels in the globus pallidus (subset of patients).
To evaluate the pharmacokinetics of deferiprone and its 3-O-glucuronide metabolite at steady-state (subset of patients)
To evaluate the safety and tolerability of deferiprone in patients with PKAN

Outcomes/endpoints

Primary endpoints
• Change from baseline to Month 18 in BAD total score
• PGI-I score at Month 18

To claim superiority of deferiprone over placebo, the null hypothesis of no difference was to be rejected at a two-sided 0.05 level of significance for both co-primary endpoints.

Secondary endpoints, efficacy
• Proportion of patients with improved or unchanged BAD total score between baseline and Month 18
• Change from baseline to Month 18 in BAD score per body region
• Proportion of patients showing no change or an improvement on PGI-I at Month 18
• Change from baseline to Month 18 in each of the UPDRS scores
• Change from baseline to Month 18 in global WeeFIM and FIM score, PedsQL, PSQI WeeFIM or FIM score per item
• Change from baseline to Month 18 in iron levels in the globus pallidus as measured by MRI R2*

Secondary endpoints, pharmacokinetics
The following PK parameters were determined at steady-state for deferiprone and its main metabolite: Cmax, Tmax, Cmin, AUCSS, CL/F, T½, Vd/F.

Secondary endpoints, safety
• Frequency of AEs
• Frequency of SAEs
• Number of discontinuations due to AEs

Randomisation and blinding (masking)

Patients were assigned in a 2:1 ratio to receive either deferiprone or placebo, according to a randomization list issued by the sponsor using a computer random number generator. A centralized randomization was used for all study sites. Randomization was stratified based on the patient's age at diagnosis, with one list generated for individuals who had been younger than 6 years at the onset of motor symptoms and one for those who had been 6 years or older.

The placebo product matched the active product with respect to appearance, odor, and taste, and was provided in identical bottles. The patients, the staff at the study sites, employees of ApoPharma who were involved in the trial, and the neurologists who analyzed the videotapes for determination of BAD scores were all blinded as to which product was assigned. The only unblinded individuals during the trial were the statistician who generated the randomization codes, and certain designated ApoPharma employees who were responsible for the treatment assignments. Members of this team had no involvement in the study, and signed an agreement that they would not disclose any unblinding information to others.

To maintain blinding, the placebo product was matched to deferiprone oral solution for color and flavor, was provided in the same type of bottle, and was provided with the same label. Batch numbers were JX4927, KK5444, KP3514, and MC2074. After blinded labeling, the final batches shown on the label were DR12132, DR13019, DR13067, P001022, and P001784.

The applicant should provide a way of allocating individual batches (DFP and placebo) in the TIRCON2012V1 study to the final (blinded) batches. The description is not fully clear at the moment.
OC

Statistical methods

Primary Efficacy Endpoints
A Mixed-Effect Model Repeated Measures (MMRM) model was used as the primary analysis method to assess the changes in BAD total score from baseline to Month 18, with baseline value and age at onset of motor symptoms as covariates and treatment group as the main factor in the model. The least squares estimate of the mean (LSmean) change at Month 18 was used for determining the treatment effect in the primary analysis. Age at onset of motor symptoms (before 6 years versus at or after 6 years) was used as a stratification factor at randomization, and thus was included as a binary variable

in all the models where it was treated as a covariate. Since changes in DBS settings, the use of medications that have the potential to affect dystonia symptoms, and the use of PRN drugs or rescue medications might have confounded the treatment effect assessment, these variables were also included in the MMRM model as visit-dependent covariates. A similar MMRM model was used for the analysis of the co-primary endpoint, PGI-I. As the PGI-I score is by definition a measurement of change from baseline, the score obtained at each scheduled measurement was treated directly as the outcome variable, and baseline BAD score was used as the baseline value in the model. A sensitivity analysis was conducted on the Per Protocol (PP) population for the co-primary endpoints, using the same MMRM model as with the mITT population.

Secondary Efficacy Endpoints
The MMRM model that was used for the co-primary efficacy endpoints was also used for the analysis of the secondary endpoints except for the proportion of responders, which was analyzed by a logistic regression model.

Subgroup Efficacy Analyses
In order to explore potential differences in treatment effect on efficacy endpoints across population subgroups, subgroup analyses, using a similar MMRM model, were performed on the co-primary efficacy endpoints on the following factors: age at onset of motor symptoms (≥6 years vs. <6 years), use of DBS device (yes vs. no), use of baclofen pump (yes vs. no), and geographical region (US vs. Europe).

Safety Analysis
The safety data for continuous variables were summarized using descriptive statistics, and the safety data for discrete variables were tabulated with frequency tables.

Pharmacokinetic Analysis
The pharmacokinetics parameters were summarized using descriptive statistics. A two-sided p-value of 0.05 was used as the significance level for the determination of statistical significance in all statistical tests.

Results

Of 100 patients who underwent screening, 89 wereenrolled and randomized to receive either placebo (N=30) or deferiprone (N=59). One patientin the deferiprone (DFP) group was withdrawn before dosing began, due to a medical event, so88 patients received study product. A total of 76 patients (85.4%) completed the study, and12 (in addition to the one patient who was never dosed) withdrew: 3 (10.0%) in the placebo groupand 9 (15.3%) in the DFP group. Reasons for withdrawal in the placebo group were 1 case eachof worsening of the disease, protocol violation (adjustment of DBS voltage, which at the time wasnot permitted), and voluntary withdrawal; while those in the DFP group were adverse event (n=4),worsening of the disease (n=3), sponsor decision (n=1), and voluntary withdrawal (n=1). Ofthe withdrawals due to AEs, 3 were for neutropenia, and 1 was for fever and pneumonia.

Due to a high number of major protocol violations, just 37 patients fulfilled the criteria for being included in the per protocol (PP) population (N=13 for placebo, N=24 for DFP). Finally, a subset of 13 patients were included in the pharmacokinetics (PK) population (N=4 for placebo, N=9 for DFP).

Table 10.1 Patient disposition – ITT population

	Placebo n (%)	DFP n (%)	Overall n (%)
Randomized	30	59	89
Exposed	30	58	88
Completed	27 (90)	49 (83.1)	76 (85.4)
Withdrawn	3 (10)	9 (15.3)	12 (13.5)
Reason for withdrawal:			
Adverse event	0 (0.0)	4 (6.8)	4 (4.5)
Worsening of the disease	1 (3.3)	3 (5.1)	4 (4.5)
Protocol violation	1 (3.3)	0 (0.0)	1 (1.1)
Voluntary withdrawal	1 (3.3)	1 (1.7)	2 (2.2)
Sponsor decision	0 (0.0)	1 (1.7)	1 (1.1)

Baseline data

Table 10.2 Summary of demographics data at baseline – ITT population

	Placebo (N=30)	DFP (N=59)	Overall (N=89)	Placebo vs. DFP p-value
Age (years) (Mean ± SD)	19.2 ± 12.5	20.8 ± 10.7	20.2 ± 11.3	0.54
Min, Max	5, 55	4, 52	4, 55	
Sex: n(%)				
F	17 (56.7)	25 (42.4)	42 (47.2)	0.26
M	13 (43.3)	34 (57.6)	47 (52.8)	
Ethnic Origin: n (%)				
Hispanic/Latino	5 (16.7)	4 (6.8)	9 (10.1)	0.16
Other	25 (83.3)	55 (93.2)	80 (89.9)	
Racial Origin: n(%)				
Asian	1 (3.3)	6 (10.2)	7 (7.9)	
Black	0 (0.0)	2 (3.4)	2 (2.2)	0.26
Multi-Racial; Unknown	1 (3.3)	0 (0.0)	1 (1.1)	
White	28 (93.3)	51 (86.4)	79 (88.8)	

Age at Onset of Disease

There are two forms of PKAN: classic, in which symptoms usually develop before 6 years of age, and atypical, which becomes evident at a later age. The distinction is important, as disease progression is more rapid in patients with earlier onset. By chance, almost equal numbers of patients with each form of PKAN were enrolled in the trial. To ensure that each treatment group ended up with approximately equal numbers of patients in each of these disease categories, stratification based on age at onset (< 6 years vs. ≥ 6 years) was used when assigning patients to either placebo or active treatment. The desired balance was achieved, with the placebo group ending up with 12 patients with earlier onset and 16 with later onset, and the DFP group with 29 of each.

As expected, baseline BAD scores were worse in patients with the earlier onset, but the difference did not reach statistical significance. In both groups, patients had had symptoms of the disease for approximately 12 years at the time of randomization.

Baseline Efficacy Measures

For the primary measure of total score on the BAD scale, there was no statistically significant difference between the mean baseline scores of the two study arms, and the range of values was almost identical in both groups. There were also no differences in mean baseline scores for the

secondary efficacy measures, with the exception of the UPDRS Part II, which was higher (worse) in the DFP group (p=0.0274).

Numbers analysed

A total of 89 patients were randomized and were included in the Intent to Treat (ITT) population (N=30 for placebo, N=59 for DFP). One of the patients assigned to the DFP arm was withdrawn before dosing began, so was excluded from the Safety population (N=30 for placebo, N=58 for DFP) and the modified ITT (mITT) population. Two patients in the placebo arm withdrew before providing at least one post-baseline efficacy assessment, so were excluded from the mITT population (N=28 for placebo, N=58 for DFP). Due to a high number of major protocol violations, just 37 patients fulfilled the criteria for being included in the per protocol (PP) population (N=13 for placebo, N=24 for DFP). Finally, a subset of 13 patients were included in the pharmacokinetics (PK) population (N=4 for placebo, N=9 for DFP).

Outcomes and estimation

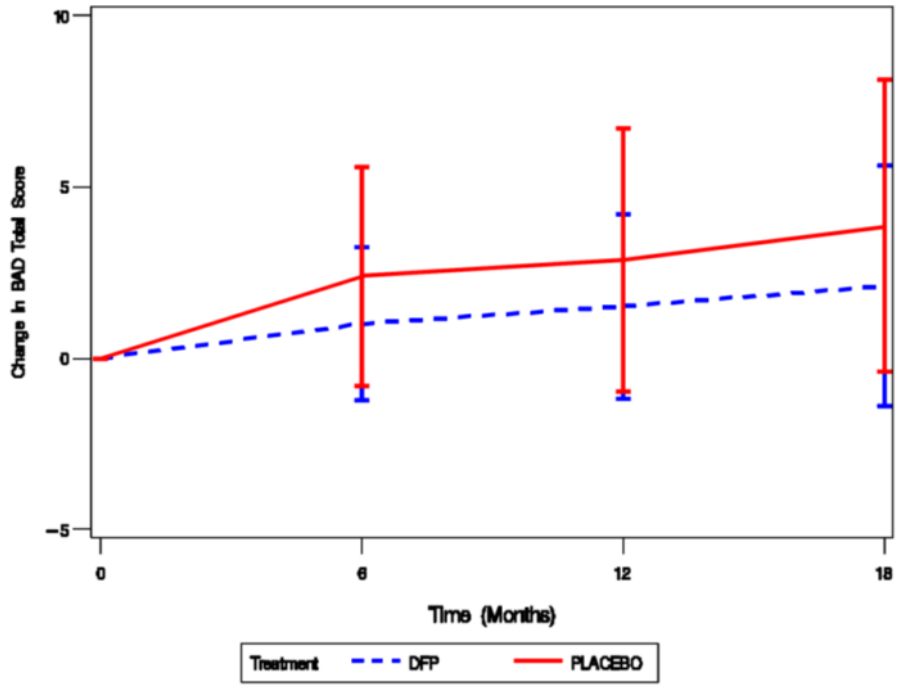
Primary Efficacy Endpoints

The co-primary efficacy endpoints were the change from baseline to Month 18 on the BAD scale, which assessed the severity of dystonia, and the score at Month 18 on the PGI-I, which obtained patients' subjective impressions of the change in their condition since baseline.

Change in Barry-Albright Dystonia Total Score

The difference between the groups approached but did not reach significance (p=0.0761).However, the progression seen in the DFP group at Month 18 was slower (mean worsening in BAD score of 2.48) than that seen in the placebo group (mean worsening in BAD score of 3.99). That is, while both groups worsened, the DFP group did so by 1.51 points less than the placebo group. The observed treatment effect (-1.51 points reduction score compared to placebo) was almost 70% lower than the expected planned treatment effect (≥5-point reduction).

Figure 11.1 Mean change in BAD total score over time – mITT population



Change in Patient's Global Impression of Improvement
At Month 18, the LSmean scores were 4.66 for placebo and 4.55 for DFP, with no significant group difference (p=0.7279), indicating that, overall, patients did not detect either an improvement or a worsening in their condition from baseline.

Table 14.2.1.3 Co-primary efficacy endpoints analysis with MMRM model - Least square mean (LSM) change in score from baseline to month 18 - mITT population

Test	Visit	Placebo Mean (SE)	DFP Mean (SE)	DFP-Placebo LSM Difference (95% CI)	P-value
BAD Total Score	Change at Month 18	3.99 (0.82)	2.48 (0.63)	-1.51 (-3.19, 0.16)	0.0761
PGI-I	Change at Month 18	4.66 (0.38)	4.55 (0.30)	-0.12 (-0.80, 0.56)	0.7279

Correlation Between BAD and PGI-I (Post Hoc Analysis)
Despite the statistical significance, only a weak correlation (r = 0.29; r2 < 0.1) was observed between the two co-primary endpoints (change from baseline in total BAD score and the PGI-I). This indicates that the two endpoints are not good predictors of each other.

Secondary Efficacy Endpoints
The secondary efficacy endpoints were concerned with differences between the treatment groups on the following measures:
• Responder analyses for the co-primary endpoints
• BAD scores for each body region
• UPDRS Parts I, II, III, and VI, for assessment of parkinsonian-like symptoms and activities of daily living
• WeeFIM or FIM, for assessment of functional independence
• PedsQL scale, for assessment of quality of life
• Pittsburgh Sleep Quality Index, for assessment of quality of sleep
• MRI R2*, for the measurement of iron levels in the globus pallidus (subset of patients)

In addition to the above assessments, patients were asked to complete a Likert scale at each efficacy visit to indicate the state of their PKAN symptoms on that particular day. The results of that assessment are presented following the results of the secondary endpoints.

Responder Analyses for the Co-Primary Endpoints

BAD responders:
The percentage of responders in the DFP group (36%) was more than twice that in the placebo group (14%), but the difference did not reach significance (p=0.0893).
PGI-I responders:
There was a higher percentage of responders in the DFP group at Month 18, but the difference was not significant

BAD Scores by Body Region
After 18 months, for both treatment groups, the scores for all body regions worsened over time, but in most cases the progression was less in the DFP group than in the placebo group. Exceptions were mouth and left upper extremity, where the changes were similar between the two treatment groups. The difference between deferiprone and placebo reached significance in favour of DFP for the body regions of neck (-0.43; p=0.0465) and both lower extremities (left, -0.28; p=0.0391; right, -0.25; p=0.0435).

Table 11.2 Change from baseline at Month 18 in BAD score per body region – mITT population

Test	Placebo Mean (SE)	DFP Mean (SE)	DFP-Placebo LSM Difference (95% CI)	P-value
Eyes	0.60 (0.19)	0.40 (0.15)	-0.20 (-0.56, 0.15)	0.2520
Mouth	0.39 (0.18)	0.43 (0.14)	0.05 (-0.28, 0.38)	0.7803
Neck	0.75 (0.22)	0.31 (0.17)	-0.43 (-0.86, -0.01)	0.0465
Trunk	0.46 (0.22)	0.32 (0.17)	-0.14 (-0.56, 0.27)	0.5009
Left upper extremity	0.22 (0.19)	0.22 (0.15)	0.00 (-0.37, 0.37)	0.9995
Right upper extremity	0.43 (0.19)	0.34 (0.15)	-0.09 (-0.47, 0.29)	0.6422
Left lower extremity	0.54 (0.14)	0.26 (0.11)	-0.28 (-0.55, -0.01)	0.0391
Right lower extremity	0.54 (0.12)	0.30 (0.10)	-0.25 (-0.48, -0.01)	0.0435

Unified Parkinson's Disease Rating Scale

For all except Part I, where scores remained stable, patients worsened the mean UPDRS scores after 18 months, in both groups. None of the group differences were statistically significant.

Table 11.4 Change from baseline at Month 18 in UPDRS scores – mITT population

Test	Placebo Mean (SE)	DFP Mean (SE)	DFP-Placebo LSM Difference (95% CI)	P-value
UPDRS Part I Score	-0.07 (0.55)	-0.25 (0.43)	-0.18 (-1.20, 0.83)	0.7228
UPDRS Part II Score	2.36 (1.52)	1.09 (1.19)	-1.27 (-4.06, 1.52)	0.3677
UPDRS Part III Score	2.06 (2.79)	5.38 (2.20)	3.33 (-2.01, 8.67)	0.2182
UPDRS Part VI Score	-7.66 (3.85)	-2.17 (2.94)	5.49 (-2.50, 13.48)	0.1749

Functional Independence Measure

WeeFIM: No significant group differences were seen in the global score or in the domains of self-care or mobility, but a significant difference in favor of DFP (p=0.0324) was seen for cognition.

Table 11.6 Change from baseline at Month 18 in WeeFIM – mITT population

Test	Placebo (N=14) Mean (SE)	DFP (N=21) Mean (SE)	DFP-Placebo LSM Difference (95% CI)	P-value
Global score	-2.40 (5.42)	4.91 (5.30)	7.31 (-4.17, 18.79)	0.2026
Self-care score	-2.26 (3.11)	-2.11 (3.06)	0.15 (-5.64, 5.94)	0.9581
Mobility score	-0.69 (2.02)	-0.48 (2.03)	0.21 (-3.99, 4.42)	0.9175
Cognition score	-0.06 (2.63)	6.24 (2.56)	6.30 (0.57, 12.03)	0.0324

FIM:

None of the group differences at baseline and after 18 months were statistically significant.

Table 11.8 Change from baseline at Month 18 in FIM – mITT population

Test	Placebo Mean (SE)	DFP Mean (SE)	DFP-Placebo LSM Difference (95% CI)	P-value
Global score	0.69 (3.34)	5.40 (2.36)	4.71 (-1.81, 11.23)	0.1524
Self-care score	-0.75 (1.63)	1.72 (1.14)	2.47 (-0.70, 5.64)	0.1234
Mobility score	-0.81 (1.38)	0.28 (0.97)	1.09 (-1.57, 3.76)	0.4126
Communication/social cognition score	1.07 (1.42)	2.07 (1.02)	1.00 (-1.75, 3.75)	0.4668

Quality of Life
Comparisons between the treatment groups of the difference between Month 18 and baseline, revealed no statistically significant differences between the groups for either measure.

Table 11.10 Change from baseline at Month 18 in PedsQL – mITT population

Test	Placebo Mean (SE)	DFP Mean (SE)	DFP-Placebo LSM Difference (95% CI)	P-value
Patient self-report				
PedsQL total score	1.34 (4.49)	1.21 (3.68)	-0.13 (-8.66, 8.41)	0.9759
Physical health score	0.06 (5.17)	-1.45 (4.23)	-1.51 (-11.4, 8.40)	0.7616
Psychosocial health score	0.98 (5.04)	2.67 (4.14)	1.69 (-7.83, 11.21)	0.7229
Parent proxy-report				
PedsQL total score	-2.37 (4.90)	-4.90 (3.99)	-2.53 (-11.6, 6.57)	0.5781
Physical health score	1.54 (8.07)	-6.31 (6.52)	-7.85 (-23.2, 7.51)	0.3084
Psychosocial health score	-1.97 (4.82)	-1.97 (3.90)	-0.00 (-9.08, 9.08)	0.9997

Pittsburgh Sleep Quality Index
There was little change in either group over time: 0.14 points for placebo and 0.48 points for DFP at Month 18, and the group difference was not statistically significant (p=0.6323).

Table 14.2.2.19 PSQI score analysis with MMRM model - Least square mean (LSM) change in score from baseline to month 18 - mITT population

Test	Visit	Placebo Mean (SE)	DFP Mean (SE)	DFP-Placebo LSM Difference (95% CI)	P-value
PSQI Score	Change at Month 18	0.14 (0.80)	0.48 (0.61)	0.35 (-1.09, 1.78)	0.6323

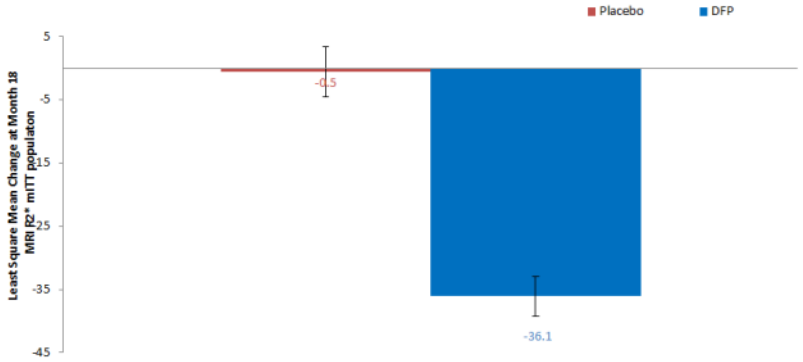
MRI R2* Score
Iron levels in the globus pallidus were measured in a subset of patients who were able to undergo this assessment at the start of the study (n=16 placebo, n=24 deferiprone) and at the end of the study (n=13 placebo, n=19 deferiprone).

There was no significant group difference at baseline (93.5 Hz for placebo, 96.6 Hz for DFP; p=0.7594). The mean change in iron content from baseline at Month 18: For placebo, there was virtually no change in iron content (a decrease of 0.50 Hz), while in the DFP group there was a decrease of 36.1 Hz, for a significant DFP-placebo difference of -35.6 Hz ($p < 0.0001$). There was no indication of a correlation between change in brain iron level and change in either the BAD score or the PGI-I score.

Table 14.2.2.6 MRI R2 analysis with MMRM model - Least square mean (LSM) change in score from baseline to month 18 - mITT population

Test	Visit	Placebo Mean (SE)	DFP Mean (SE)	DFP-Placebo LSM Difference (95% CI)	P-value
MRI R2*	Change at Month 18	-0.50 (3.97)	-36.1 (3.11)	-35.6 (-44.8, -26.3)	0.0000

Figure 11.10 Change from baseline to end of study in MRI R2* scores – mITT population



* Bars represent standard error

Likert Scale

Mean scores were consistently at the mid-point for both groups, with an unchanged mean of 2.7 at both baseline and Month 18 for the placebo group and a slight but significant decrease (improvement) from 2.8 to 2.4 (p=0.0185) in the DFP group. There was no significant difference between the treatment groups (p=0.4966).

Table 14.2.3.2 LK score analysis with MMRM model - Least square mean (LSM) change in score from baseline to month 18 - mITT population

Test	Visit	Placebo Mean (SE)	DFP Mean (SE)	DFP-Placebo LSM Difference (95% CI)	P-value
LK Score	Change at Month 18	-0.31 (0.32)	-0.48 (0.26)	-0.17 (-0.67, 0.33)	0.4966

Ancillary analyses

Subgroup Analyses

The statistical analysis plan specified that for the co-primary endpoints, analyses on the change from baseline to Month 18 were additionally to be conducted on subpopulations based on the following categories:

- age at onset of disease (< 6 years vs. ≥ 6 years, which differentiates between classic and atypical PKAN),
- use of a DBS device (yes vs. no),
- use of a baclofen pump (yes vs. no), and
- geographical region (Europe vs. USA).

Planned Subgroup Analyses on Total BAD Score

For patients with atypical PKAN, there was a statistically significant difference between the treatment groups of 2.19 points in favor of DFP (p=0.0187). In patients with classic PKAN, the group difference was only 0.81 points in favor of DFP and was not significant. Similar to what was seen for the overall population, there were no significant treatment differences with respect to the other subpopulations, but the differences were consistently in favor of deferiprone.

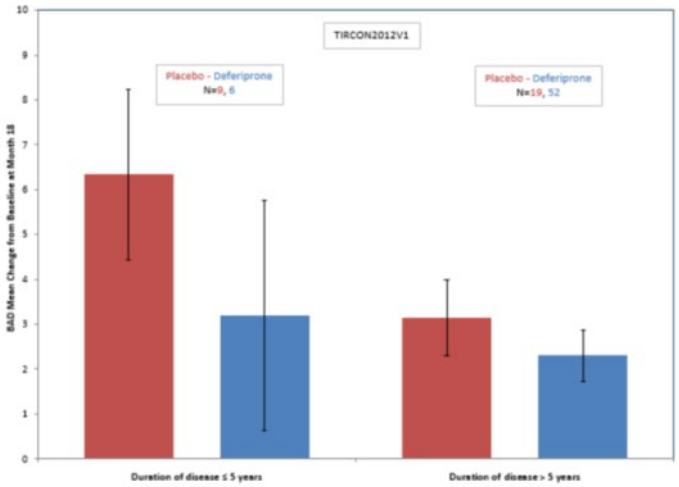
Planned Subgroup Analyses on PGI-I

Similar to what was seen for the overall population, no significant treatment group differences were seen for any subpopulations.

Post Hoc Subgroup Analysis on Primary Endpoints

BAD total score. No significant treatment group difference was seen for either subgroup. However, it is notable that among patients with a shorter duration of disease, those treated with deferiprone worsened by a mean of 3.14 points less than did those treated with placebo, and while this difference was not significant (p=0.3436), possibly due to the low number of patients, the difference between deferiprone and placebo was more pronounced than that detected in the overall group. Among patients with a longer disease duration, the treatment group difference in favor of DFP was just 0.86 points.

Figure 11.12 Change from baseline at Month 18 in BAD total score – disease duration subgroup analysis



Summary of main efficacy results

Title: **A randomized, double-blind, placebo-controlled trial of deferiprone in patients with pantothenate kinase-associated neurodegeneration (PKAN)**			
Studyidentifier	TIRCON2012V1		
Design	Multi-center, double-blind, randomized, placebo-controlled, 18-month study in patients with PKAN aged 4 years and older.		
	Durationofmainphase: Duration of extension phase (study TIRCON2012V1-EXT):	18 months 18 months	
Hypothesis	Superiority DFP vs. placebo		
Treatmentsgroups	Placebo - PL	Placebo, The duration of participation in the study for each patient was up to 20 months, includingthe screening period and the follow-up visit. 30 patients were randomized	
	Deferiprone - DFP	Deferiprone oral solution 80 mg/mL; up to 15 mg/kg b.i.d., for a total daily dosage of 30 mg/kg was used. The duration of participation in the study for each patient was up to 20 months, includingthe screening period and the follow-up visit. 59 patients were randomized	
Endpointsanddefinitions	Primary endpoints	BAD total core and PGI-I score at Month 18	• Change from baseline to Month 18 in BAD total score • PGI-I score at Month 18 The study was to be considered positive if group differences in both primary endpoints reached statistical significance.

	Secondary endpoints	Efficacy endopoints	• Proportion of patients with improved or unchanged BAD total score between baseline and Month 18 (responder analysis) • Change from baseline to Month 18 in BAD score per body region • Proportion of patients showing no change or an improvement on PGI-I at Month 18 (responder analysis) • Change from baseline to Month 18 in each of the UPDRS scores • Change from baseline to Month 18 in global WeeFIM or FIM score • Change from baseline to Month 18 in WeeFIM or FIM score per item • Change from baseline to Month 18 in PedsQL • Change from baseline to Month 18 in PSQI • Change from baseline to Month 18 in iron levels in the globus pallidus as measured by MRI R2* (subset of patients)
	Secondary endpoints	Pharmacokinetics endpoints	• Cmax, Tmax, Cmin, AUCSS, CL/F, T½, Vd/F
	Secondary endpoints	Safety endpoints	• Frequency of AEs • Frequency of SAEs • Number of discontinuations due to AEs
Databaselock	06 FEB 2017		

Results and Analysis

Analysisdescription	**PrimaryAnalysis**		
Analysispopulationandtimepointdescription	Intent-to-Treat (ITT), Modified Intent-to-Treat (mITT), Per Protocol (PP), Safety, a Pharmacokinetics. The mITT population represented the primary analysis population for evaluating the treatment groups on all efficacy endpoints. The co-primary efficacy endpoints were also analyzed for the PP population, which was the secondary analysis population.		
Descriptivestatisticsandestimate variability at month 18, mITT population	Treatmentgroup	PL	DFP
	Numberof subject	N=30	N=59
	BAD Total Score	20.5	21.5
	PGI-I	4.5	4.4
	UPDRS Part I Part II Part III Part IV	 1.8 25.5 38.4 41.5	 1.7 28.4 48.8 42.2
	FIM		

	WeeFIM	64.4	60.4
	PedsQL	53.3	51.0
	PSQI	5.5	6.3
	LK score (Likert score)	2.7	2.4
	MRI R2* Score	93.3	63.8
Effectestimate percomparison	BAD total score Least square mean (LSM), change in score from baseline to month 18 - mITT population	Comparison groups	Placebo vs DFP
		Point estimate (SE)	3.99 (0.82) vs. 2.48 (0.63)
		DFP-Placebo LSM Difference (95% CI)	-1.51 (-3.19, 0.16)
		P-value	0.0761
	Change in Patient's Global Impression of Improvement	Comparisongroups	Placebo vs DFP
		Point estimate (SE)	4.66 (0.38) vs 4.55 (0.30)
		DFP-Placebo LSM Difference (95% CI)	-0.12 (-0.80, 0.56)
		P-value	0.7279
	WeeFIM total score	Comparisongroups	Placebo vs DFP
		Point estimate	-2.40 (5.42) vs. 4.91 (5.30)
		DFP-Placebo LSM Difference (95% CI)	7.31 (-4.17, 18.79)
		P-value	0.2026
	FIM total score	Comparisongroups	Placebo vs DFP
		Point estimate	0.69 (3.34) vs. 5.40 (2.36)
		DFP-Placebo LSM Difference (95% CI)	4.71 (-1.81, 11.23)
		P-value	0.1524
	PedsQL Total Score	Comparisongroups	Placebo vs DFP
		Point estimate	1.34 (4.49) vs. 1.21 (3.68)
		DFP-Placebo LSM Difference (95% CI)	-0.13 (-8.66, 8.41)
		P-value	0.9759
	PSQI Score	Comparisongroups	Placebo vs DFP

		Point estimate	0.14 (0.80) vs. 0.48 (0.61)
		DFP-Placebo LSM Difference (95% CI)	0.35 (-1.09, 1.78)
		P-value	0.6323
	UPDRScale- Part I Part II Part III Part IV	Comparisongroups	Placebo vs DFP
		Point estimate	Part I -0.07 vs -0.25 Part II 2.36 vs 1.09 Part III 2.06 vs 5.38 Part IV -7.66 vs – 2.17
		DFP-Placebo LSM Difference (95% CI)	-018 (-1.20, 0.83) -1,27 9-4,06, 1.52) 3.33 (-2.01, 8,67) 5,49 (-2.5, 13.48)
		P-value	0.7228 0.3677 0.2182 0.1749
	LK score	Comparisongroups	Placebo vs DFP
		Point estimate	-0.31 (0.32) vs. -0.48 (0.26)
		DFP-Placebo LSM Difference (95% CI)	-0.17 (-0.67, 0.33)
		P-value	0.4966
	MRI R2* Score	Comparisongroups	Placebo vs DFP
		Point estimate	-0.50 (3.97) vs -36.1 (3.11)
		DFP-Placebo LSM Difference (95% CI)	-35.6 (-44.8, -26.3)
		P-value	0.0000

Long-term Safety and Efficacy Study of Deferiprone in Patients with Pantothenate Kinase-Associated Neurodegeneration (PKAN) - TIRCON2012V1EXT

Methods

This was an 18-month, multi-center, single-arm, open-label extension of an earlier placebo-controlled study, TIRCON2012V1. In the initial study, 89 patients with a diagnosis of PKAN were randomized in a 2:1 ratio to receive 18 months of treatment with either deferiprone or placebo, respectively, and were evaluated at specified time points for safety and efficacy. All participants who completed that study were offered the opportunity to continue for an additional 18 months in the extension study, with the final visit of the initial study being considered Visit 1 of the extension study. Patients who had been randomized to receive deferiprone in the initial studycontinued to receive it in the extension study (the DFP-DFP group), while thosewho had received placebo were switched to deferiprone (the placebo-DFP

group).Since the initial study was still in progress at the time that the first patientsentered the extension study, both patients and study staff remained blinded as towhich product had been taken previously.

Study Participants

Main Inclusion Criteria

Patients were eligible to enroll in the study if they met all of the following criteria:

1. Completed study TIRCON2012V1
2. Sexually active females of childbearing potential, had to have a negative pregnancy test result. In addition, if applicable, they had to meet at least one of the following criteria:
   - Use an effective method of contraception during the study and within 30 days following their last dose of study medication, OR
   - Participate in a non-heterosexual lifestyle, OR
   - Have a male sexual partner who has been sterilized (supporting evidence required)

Female patients who were deemed to not be of childbearing potential did not need to practice contraception.

3. Fertile heterosexual males and/or their partners had to agree to use an effective method of contraception during the study and for 30 days following the last dose of study medication

Main Exclusion Criteria

Patients were excluded from enrollment if they met any of the following criteria:

1. Withdrew from the study TIRCON2012V1 for reasons of safety
2. Planned to participate in another clinical trial at any time from the day of enrolment until 30 days post-treatment in the current study
3. Presence of any medical, psychological, or psychiatric condition which in the opinion of the investigator would cause participation in the study to be unwise.
4. Pregnant, breastfeeding, or planning to become pregnant during the study period.

Treatments

All patients received deferiprone oral solution 80 mg/mL, at a dosage of up to 15 mg/kg twice daily for a total daily dosage of up to 30 mg/kg. In order to minimize the possible gastrointestinal upset that could result from starting deferiprone at too high a dose (and which might alert the former placebo recipients to the change in product), the dosing regimen was titrated weekly for the first 3 weeks. All patients, including those who had been on deferiprone initially, received 5 mg/kg deferiprone twice a day (b.i.d.) for the first week. If this dose was tolerated and there were no signs of toxicity, the dose was increased to 10 mg/kg b.i.d. for the next week, and if that dose was tolerated, it was increased the following week to 15 mg/kg b.i.d. for the remainder of the study. Individual dosages could have been adjusted downward if necessary at any time for reasons of safety or tolerability.

Selection of Doses in the Study

The dosage of deferiprone used in this study was the same as that used in the blinded trial TIRCON2012V1: up to 15 mg/kg b.i.d. for a total daily dosage of up to 30 mg/kg. The selection of this dose in the initial study had been established based on findings from two single-arm pilot studies and three case reports.

Objectives

Primary Objective

To evaluate the long-term safety and tolerability of deferiprone in patients with PKAN.

Secondary Objectives

• To evaluate the change in severity of dystonia over time in patients with PKAN treated with deferiprone.
• To evaluate global improvement over time in patients with PKAN treated with deferiprone

Outcomes/endpoints

Primary Endpoints
The safety endpoints were as follows:
• Adverse events (AEs): Frequency, severity, time to onset, duration, and relatedness to study product
• Serious adverse events (SAEs): Frequency, severity, time to onset, duration, and relatedness to study product
• Number of discontinuations due to AEs

Secondary Endpoints
The efficacy endpoints were as follows:
Between-group analyses:
• Change in the Barry-Albright Dystonia (BAD) scale total score from baseline to end of study, as assessed by central evaluation of videotapes
• Proportion of patients with improved or unchanged BAD scale total score between baseline and end of study (responder analysis)
• Change from baseline to end of study in BAD scale score per body region (eyes, mouth, neck, trunk, and each upper and lower extremity), as assessed by central evaluation of videotapes
• Score on the Patient Global Impression of Improvement (PGI-I) at end of study
• Proportion of patients reporting an improvement or no change on the PGI-I at end of study (responder analysis)

Within-group analyses:
• Change in BAD total score
• Proportion of patients with improved or unchanged BAD total score between the baseline and end of each study (responder analysis)
• Change in BAD score per body region
• PGI-I score at the end of each study
• Proportion of patients reporting an improvement or no change on the PGI-I at the end of each study (responder analysis)

Randomisation and blinding (masking)

This was an 18-month, multi-center, single-arm, open-label extension of an earlier placebo-controlled study, TIRCON2012V1. Patients who had been randomized to receive deferiprone in the initial study continued to receive it in the extension study (the DFP-DFP group), while those who had received placebo were switched to deferiprone (the placebo-DFP group). Since the initial study was still in progress at the time that the first patients entered the extension study, both patients and study staff remained blinded as to which product had been taken previously. This study was open-label.

Statistical methods

Safety Analysis
The incidences of AEs and SAEs were tabulated in two ways:
A consolidated summary of all AEs reported during deferiprone therapy: for the placebo-DFP group, only events that occurred during TIRCON2012V1-EXT; for the DFP-DFP group, all events that occurred from the start of TIRCON2012V1 up to the end of TIRCON2012V1-EXT

Separate summaries for each group: for the placebo-DFP group, AEs that occurred during TIRCON2012V1-EXT; for the DFP-DFP group, separate tabulations of the events that occurred during each study. Similar tables were produced for the severity of AEs and for their relationship to the study medication.

Efficacy Analysis

For the efficacy measure of the BAD (total score and by body region), the changes from baseline to each of the measurement time points were determined and summarized using descriptive statistics. The same was done for the PGI-I scores at each time point. A paired t-test was used to assess the statistical significance of the changes in these efficacy outcomes from baseline to end of study. For the BAD total score and for PGI-I, the proportions of patients determined to be responders at end of study were calculated and presented along with 95% confidence intervals.

For patients who received placebo in study TIRCON2012V1, a paired t-test was used to compare the change in BAD (total score and by body region) between the start and completion of the initial study to that between the start and completion of the extension study. The same was done for the PGI-I scores. For the BAD total score and for the PGI-I, McNemar's test was used to compare the proportion of responders in the initial study with the proportion of responders in the extension study.

Results

Participant flow

Table 10.1 Patient disposition – Safety population

	Placebo-DFP n (%)	DFP-DFP n (%)	Overall n (%)
Enrolled	24	44	68
Exposed	24 (100)	44 (100)	68 (100)
Completed	17 (70.8)	38 (86.4)	55 (80.9)
Withdrawn	7 (29.2)	6 (13.6)	13 (19.1)
Reason for withdrawal:			
Adverse event	2 (8.3)	1 (2.3)	3 (4.4)
Worsening of disease	1 (4.2)	1 (2.3)	2 (2.9)
Voluntary withdrawal	3 (12.5)	3 (6.8)	6 (8.8)
Lost to follow-up	0 (0.0)	1 (2.3)	1 (1.5)
Other	1 (4.2)	0 (0.0)	1 (1.5)

Baseline data

Table 10.2 Summary of demographics data at baseline – Safety population

	Placebo-DFP (N=24)	DFP-DFP (N=44)	Overall (N=68)	Placebo-DFP vs. DFP-DFP p-value*
Age (years) at baseline of TIRCON2012V1 study				
Mean (SD)	18.4 (13.0)	20.8 (9.7)	20.0 (10.9)	0.3855
(Minimum, Median, Maximum)	(5, 15, 55)	(4, 20, 46)	(4, 19, 55)	
Age (years) at baseline of TIRCON2012V1-EXT study				
Mean (SD)	19.9 (13.0)	22.4 (9.6)	21.5 (10.9)	0.3577
(Minimum, Median, Maximum)	(6, 17, 56)	(6, 22, 47)	(6, 21, 56)	
Sex: n (%)				
Female	14 (58.3)	16 (36.4)	30 (44.1)	0.1247
Male	10 (41.7)	28 (63.6)	38 (55.9)	
Racial Origin: n (%)				
Asian	1 (4.2)	3 (6.8)	4 (5.9)	0.5396
Multi-Racial; unknown	1 (4.2)	0 (0.0)	1 (1.5)	
White	22 (91.7)	41 (93.2)	63 (92.6)	
Ethnic Origin: n (%)				
Hispanic/Latino	5 (20.8)	2 (4.5)	7 (10.3)	0.0875
Other	19 (79.2)	42 (95.5)	61 (89.7)	

Table 10.4 Baseline characteristics according to age at start of each study – ITT population

Variable		Age at onset of motor symptoms			Age <6 vs. Age ≥6 p-value
		Age <6 (N=28)	Age ≥6 (N=34)	Overall (N=62)	
Age (years) at onset of motor symptoms	Mean (SD)	2.1 (1.5)	13.0 (3.7)	8.1 (6.2)	<0.0001
	(min, max)	(1, 5)	(6, 23)	(1, 23)	
Baseline of initial study					
Age (years) at baseline	Mean (SD)	13.8 (7.9)	24.7 (8.5)	19.8 (9.9)	<0.0001
	(min, max)	(4, 36)	(10, 46)	(4.0, 46)	
Duration of disease (years) at baseline	Mean (SD)	12.6 (7.5)	12.7 (8.1)	12.7 (7.7)	0.9607
	(min, max)	(4, 35)	(1, 34)	(1, 35)	
BAD score at baseline	Mean (SD)	20.0 (8.3)	16.9 (7.9)	18.3 (8.2)	0.1313
	(min, max)	(7.0, 31.0)	(1.0, 31.0)	(1.0, 31.0)	
Baseline of extension study					
BAD score at baseline	Mean (SD)	23.2 (6.9)	19.2 (8.0)	21.0 (7.7)	0.0434
	(min, max)	(7.0, 32.0)	(3.0, 31.0)	(3.0, 32.0)	

Demographics data of this extension study were consistent with those of the initial study. Overall, in the extension study, the population had a mean (SD) age of 21.5 (10.9) years (range 6-56 years), 55.9% of PKAN patients were male and the majority were white (92.6%).

Among the 62 patients evaluable for efficacy, the mean (SD) BAD score at baseline was 21.0 (7.7). Overall, 17 patients (27.4%) had a DBS system in place and 1 patient (1.6%) had an implanted baclofen pump. Of note, there were numerically more patients with DBS in the DFP-DFP group than in the placebo-DFP group at baseline for both initial and extension studies.

28 patients (45%) had the classic form of the disease, and 34 (55%) had the atypical form. For patients with classic PKAN, the mean (SD) BAD score at baseline was 23.2 (6.9) and for patients with atypical PKAN, BAD score at baseline was 19.2 (8.0). This difference was statistically significant (p=0.0434). These results suggest that patients with classic PKAN had more severe dystonia at baseline than patients with atypical PKAN, consistent with published literature on the disease.

Numbers analysed

Of the 76 participants who completed the placebo-controlled study, 68 enrolled in the extension study: 24 who had previously received placebo (the placebo-DFP group) and 44 who had previously received deferiprone (the DFP-DFP group). All 68 of these patients received at least 1 dose of study product. A total of 55 participants (80.9%) completed the extension study, and 13 withdrew: 7 (29.2%) in the placebo-DFP group and 6 (13.6%) in the DFP-DFP group. Reasons for withdrawal in the placebo-DFP group were adverse event (n=2), worsening of the disease (n=1), voluntary withdrawal (n=3), and other (n=1; inability to comply with the study requirements). The reasons in the DFP-DFP group were adverse event (n=1), worsening of the disease (n=1), voluntary withdrawal (n=3), and lost to follow-up (n=1). Of the 3 patients who withdrew due to AEs, 2 died: one (placebo-DFP) of aspiration pneumonia and multi-organ failure, and the other (DFP-DFP) of aspiration after vomiting. The third AErelated withdrawal (placebo-DFP) was due to cytomegalovirus infection and transaminitis.

Efficacy results

Change in BAD Total Score Across Studies for Both Treatment Groups

A comparison of the change in score after the first 18 months of deferiprone therapy in each group (i.e., 1.4 points in the placebo-DFP group vs. 1.9 points in the DFP-DFP group) found no significant difference (p=0.5821).

Change in BAD Total Score Across Studies for Each Treatment Group
Placebo-DFP Patients

Table 11.2 Change from baseline in BAD score at each visit of each study, placebo-DFP group - ITT population

Study Visit	Value	TIRCON (Placebo) (N = 19)	T-EXT (DFP) (N = 19)	T-EXT vs. TIRCON P-value
Baseline	Mean (SD)	15.9 (8.0)	20.4 (8.1)	0.0009
Month 6	Mean (SD)	2.8 (3.1)	0.8 (2.0)	0.0113
	p-value	0.0009	0.1094	
Month 12	Mean (SD)	3.4 (4.0)	0.9 (2.6)	0.0094
	p-value	0.0015	0.1492	
Visit 4 *	Mean (SD)	4.4 (4.8)	1.4 (3.7)	0.0206
	p-value	0.0009	0.1129	

DFP-DFP Patients

Table 11.3 Change from baseline in BAD score at each visit of each study, DFP-DFP group - ITT population

Study Visit	Value	TIRCON (DFP) (N = 43)	T-EXT (DFP) (N = 43)	T-EXT Vs. TIRCON P-value
Baseline	Mean (SD)	19.3 (8.1)	21.3 (7.6)	0.0003
Month 6	Mean (SD)	1.0 (2.4)	0.8 (2.0)	0.6049
	p-value	0.0079	0.0096	
Month 12	Mean (SD)	1.3 (2.6)	1.1 (2.2)	0.6237
	p-value	0.0015	0.0030	
Visit 4 *	Mean (SD)	1.9 (3.2)	1.4 (2.4)	0.2684
	p-value	0.0003	0.0004	

From these data, the applicant concluded that in the extension study, patients continuing deferiprone retained a similar rate of disease progression as assessed by the BAD scale, whereas progression in patients switching from placebo to deferiprone seemed to slow significantly. Given the uncontrolled nature of the study and the fact that no formal sample size and power calculations were carried out, these data should be interpreted with caution.

Change From Baseline in BAD Score Per Body Region

Comparison of BAD Body Region Scores Across Studies for Both Treatment Groups

Over the duration of the initial study, the patients on placebo worsened numerically more than did those on DFP for each body region, although the only group differences that reached significance were those for left and right lower extremities (p-values of 0.0221 and 0.0233, respectively). In contrast, over the duration of the extension study, when both groups were on deferiprone, the changes from baseline of the extension study to the end of the study were numerically similar between the groups, and there were no significant group differences in the worsening of scores of any body regions.

Comparison of BAD Body Region Scores Across Studies for Each Treatment Group
Placebo-DFP Group

The difference between the studies reached significance only for left and right lower extremities (p=0.0083 and p=0.0041, respectively).

DFP-DFP Group
For most body regions, progression was numerically slower during the extension study than during the initial study, with the difference reaching significance for mouth (p=0.0262). Exceptions were for the region of eyes, for which progression was slower during the initial study, and trunk and left upper extremity, for which it was the same in both studies.

Patient Global Impression of Improvement
Placebo-DFP Group. There was no significant difference between the final scores of the two studies (p=0.3306).

DFP-DFP patients. There was no significant difference between the final scores of the two studies (p=0.3079).

The PGI-I assessment in the extension study is consistent with the PGI-I assessment of the single pivotal study. There was no perceived change from baseline in PKAN symptoms after 18 months or 36 months of treatment with deferiprone.

PGI-I Responder Analysis
At the end of the extension study, the gap was smaller, with percentages of 52.6% and 65.1%, respectively. However, neither of these comparisons was statistically significant.

Ancillary analyses

Age at the onset
In the comparisons across studies, for the placebo-DFP group, patients with both types of PKAN did worse while they were on placebo treatment than they did while on deferiprone treatment. However, for those with classic disease, this difference was numerically smaller and was not statistically significant (p=0.6614), while for those with atypical disease, the mean BAD score increased (worsened) during the initial study but decreased (improved) during the extension study, for a numerically larger difference that was significant (p=0.0037). For the DFP-DFP group, in both studies, patients with classic disease worsened more than did those with atypical disease, but the difference across studies was not significant in either case, indicating that there was no loss of the drug effect over time.

Summary of main efficacy results

When patients who had received placebo in the randomized study were switched to the active drug, their rate of dystonia progression slowed to match that of the patients who had been on deferiprone from the start. For patients who received deferiprone in the randomized study, continuation of deferiprone treatment in the extension study showed no loss of effect in slowing down dystonia progression. The results of the PGI-I found that patients were unable to detect either a worsening or an improvement in their condition from baseline following treatment.

Analysis performed across trials (pooled analyses and meta-analysis)

No analysis performed across trials have been performed.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	X	X	X
Non Controlled trials	X	X	X

Assessor's comment
No specific study in older subjects have been performed

Supportive study(ies)

No analysis performed across trials have been performed.

3.3.6. Discussion on clinical efficacy

Main clinical study (TIRCON2012V1)

The efficacy of deferiprone 80 mg/mL oral solution has been assessed in two clinical trials. TIRCON2012V1 was a Phase 3, multi-center, double-blind, randomized, placebo-controlled study conducted in patients with PKAN. Eligible participants were randomized in a 2:1 ratio to receive either deferiprone oral solution or placebo, with the dose titrated up to a maximum of 15 mg/kg b.i.d. for a total daily dosage of 30 mg/kg.

Participants received study product for up to 18 months, with efficacy evaluations conducted at baseline and Months 6, 12, and 18 or early termination. Of the 89 patients who were enrolled, 86 (28 placebo, 58 deferiprone) were evaluable for efficacy.

The trial duration of 18 months was questioned by the CHMP during Scientific Advice and it was recommended to consider whether it was appropriate for this neurodegenerative disorder or to extend the efficacy assessment period. The issue of trial duration is of particular importance since the natural history of PKAN differs between patients with typical and atypical PKAN. In typical PKAN, patients have early onset of disease and the most rapid rate of disease progression. In these patients, efficacy assessments planned after 18 months of treatment may be sufficient. In contrast, disease onset in atypical PKAN is in later childhood, adolescence and adulthood and the rate of progression is slower. In this case, an 18-month duration of treatment might not be sufficient for efficacy assessments.

The opportunity of extending the pivotal study duration was only partly taken into account with the long term extension study (TIRCON2012V1-EXT). It should be noted that efficacy was a secondary objective in the extension study and that the design was open label.

The key inclusion criteria were: males and females 4 years of age or older at screening visit, diagnosis of PKAN confirmed by genetic testing, and BAD total score ≥ 3 at screening visit.

The main exclusion criteria were: evidence of iron deficiency, conditions known to contra-indicate the use of deferiprone (history of agranulocytosis or recurrent episodes of neutropenia), disorders associated with neutropenia or thrombocytopenia in the 12 months preceding the initiation of the study medication, initiation or discontinuation of some dystonia and spasticity medications within a defined timeframe prior to baseline.

Study participants:

Patients included in the pivotal study were 47.2% women and 52.8% men, were white in 88.8% of cases, were enrolled in North America (35%) and in Europe (65%), and had a mean (SD) age of 20.3 (11.3) years. The mean (SD) age at onset of motor symptoms was 7.9 (6.2) years and 8.5 (7.2) years for placebo and deferiprone-treated patients, respectively. The average duration of disease at the time of enrolment was approximately 12 years in both treatment groups.

In the placebo and deferiprone groups, distribution of patients with classic and atypical PKAN was balanced.

The age of patients with PKAN ranged from 4 to 55 years with 23.6% patients aged 2-11 years, 14.6% of patients aged 12-16 years, 5.6% patients aged 17-18 years and 56.2% aged over 18 years.

Baseline values: Some statistically significant imbalances between placebo and deferiprone treatment groups were noticed when considering Parkinsonian symptoms (as assessed by UPDRS), in particular for part II (activities of daily living) of this scale, as well as for sub-scores of the BAD scale (mouth and left lower extremity). The applicant should discuss whether these imbalances may have had any impact on efficacy data. (**OC**)

Prior medications:

Some patients with PKAN were taking dystonia medications on a regular basis at baseline, including baclofen, trihexyphenidyl, benzodiazepines, tetrabenazine, botulinum toxin and tizanidine. Although the data provided by the applicant is informative, some level of details is currently missing, e.g. how many patients were on 1, 2, 3, 4 or more concomitant treatments for dystonia. The additional information provided by the applicant suggest some level of heterogeneity in the placebo and deferiprone-treated groups. In other words, the number of dystonia medications required to have similar dystonia BAD scores at baseline appears to be distributed differently between the 2 groups.

The estimation of sample size (TIRCON2012V1 study) according to the information from the applicant was carried out on the basis of Timmerman et al. It should be noted that in this study the study population consisted of patients not only from PKAN (14 patients), the remaining 7 patients had a different subtype NBIA. Therefore, the estimation of the sample size only on the basis of this study could be burdened with high uncertainty. It is not clear why other than PKAN-patients were also included in the sample size calculation. (**OC**)

Protocol amendments: Due to the progressive nature of the disease under investigation, changes in the condition of PKAN patients is expected during an 18-month study and it is acknowledged that a protocol amendment was necessary to allow the use of concomitant/rescue medication. Changes in DBS settings, baclofen pump settings or use of medications that have the potential to affect dystonia symptoms during the study, as well as their frequency of use may however confound the assessment of the treatment effect.

The applicant provided some of the required explanation on how the amendments submitted after the start of the study may have impacted data interpretation. More specifically:

- Amendment 5: 7 patients were included before implementation of Amendment 5 (27 Feb 2013).

Further analysis using listing 16.2.19 (listing of randomisation) and Appendix 16.7 (randomisation scheme) reveals that among these 7 patients, 4 were randomised to receive deferiprone and 3 to receive placebo. Based on the low number of patients included at the time of this amendment and their distribution among treatment groups, Amendment 5 is unlikely to have impacted data interpretation.

- The applicant reports that 87 patients (i.e. almost all patients) were enrolled after implementation of Amendment 6 (31 Jul 2013), which is not consistent with the number of patients randomised prior to Amendment 5 and the total of patients randomised (n=89) for this study.

After examination of listing 16.2.19 (listing of randomisation), n=70 patients were randomised after implementation of Amendment 6, representing 79% of the ITT population. Given that the majority of patients were included after Amendment 6 and that changes in DBS settings and use of rescue medications were added to the MMRM model as visit-dependent covariates to account for any potential confounding effect, this amendment is unlikely to have impacted data interpretation.

The population included in the study of patients with PKAN reflected two typical courses of the disease. At the beginning of symptoms before 6 years of age, usually with a faster and more severe course and at the beginning of symptoms after 6 years of age. Only patients with PKAN diagnosis were included in the study, which does not correspond to the proposed indication, which applies to all iron storage disorders (NBIA). Therefore, in the opinion of the assessor, the studied population could refer to an indication limited only to patients with PKAN.

Treatment/titration:

a.

In response to concerns regarding the 30 mL graduated measuring cup and the ability of such a device to appropriately measure volumes <5 mL in particular during the titration period, the applicant proposes to remove the measuring device from the product presentation and indicates that an appropriate dosing device will be provided to patients at the discretion of the Pharmacy.

The applicant intends Upkanz to be used in a wide population of patients: children, adolescents and adults, some of which may be underweight (due to nutritional and metabolic effects of the disease). For all patients, a titration period is planned until a maintenance dose of 30 mg/kg/day (maximum) taken in two divided doses is reached.

Considering the Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012, Rev.2) and based on the intended target population and posology, as well as the absence of demonstration that accurate dosing can be achieved with a range of commonly available measuring devices (e.g. spoons, measuring cups), the answer provided by the applicant is not considered acceptable and pharmacists should not bear the responsibility for providing measuring devices to patients.

The applicant is therefore asked to provide an appropriate measuring device for the administration of deferiprone. The choice of this measuring device should be in agreement with the EMA/CHMP/QWP/805880/2012, Rev.2 guideline. In the absence of a measuring device, this OC is upgraded to a MO (quality).

b. The Sponsor provided an explanation for the two different titration schedules of studies TIRCON2012V1 and TIRCON2012V1-EXT. The titration steps of 5 mg/kg (b.i.d) and 10 mg/kg (b.i.d) to reach a maintenance dose of 15 mg/kg (b.i.d) were shortened from 6 weeks to 1 week between the main study and the extension study, based on the fact that the safety profile was considered satisfactory during titration of study TIRCON2012V1.

Considering that the safety profile of deferiprone was similar during both titration schedules, the shorter duration of titration is considered acceptable.

The primary endpoints were:

- The change from baseline to end of study on the Barry-Albright Dystonia (BAD) scale (assessing the severity of dystonia),
- The score on the Patient Global Impression of Improvement (PGI-I), (assessing subjective impression of any change in disease since baseline).

Secondary efficacy endpoints included several changes from baseline on several measures of functional ability and activities of daily living (Unified Parkinson's Disease Rating Scale (UPDRS), Functional Independence Measure (FIM) or WeeFIM (pediatric version), Pediatric Quality of Life (PedsQL) scale, Pittsburgh Sleep Quality Index (PSQI), A Likert scale to evaluate the patient's state with regards to PKAN symptoms as well as changes in brain iron as measured by magnetic resonance imaging.

Selection of endpoints: Since patients with PKAN can present with impulsivity (especially in atypical PKAN), neuropsychiatric and behavioural assessments, which were recommended during Scientific Advice could have provided valuable data. However, The applicant explained that a choice was made to discard neuropsychiatric and behavioural testing in order to limit the number and duration of assessments, especially in fragile patients with more advanced disease.

Blinding:

a. Unintentional unblinding due to chromaturia is considered unlikely since the applicant reports that none of the patients in the placebo or deferiprone groups experienced chromaturia during the 18 months of the TIRCON2012V1 study.

b. Non-disclosure of MRI data by staff at the University of Newcastle who analysed all study MRI images until database lock to anyone else in order to avoid unblinding is acknowledged. Since one of the centre participating to the study was also located in Newcastle, the applicant was requested to further discuss measures that were in place to avoid unintentional blinding by MRI staff to investigators of the study in Newcastle. (**OC**) MRI data were pseudonymized to avoid unblinding, in addition to the MRI team signing non-disclosure agreements. More importantly, MRI data are available for 40 patients at baseline/32 patients at month 18 and the TIRCON2012V1 clinical study report (see Appendices – 16.2.20 Listing of MRI) indicates that MRI data from the UK site were only collected for 1 patient at baseline (patient 4006) and 2 patients at month 18 (patients 4005 and 4006) (out of the 8 patients

enrolled in that site). The risk of unintentional blinding and its subsequent impact on efficacy data is therefore considered unlikely.

Protocol deviations:

The analysis of the 68 major protocol deviations of the TIRCON2012V1 study remains broad. At this time, it is not possible to conclude whether protocol deviation categories revealed similar frequencies for deferiprone and placebo subjects. It would therefore be of particular interest to distinguish the number of placebo-treated patients and deferiprone-treated patients per type of deviation.

The range of analysed data seems acceptable, however, the applicant did not indicate what the difference in the scale of BAD is considered clinically significant. (**MO**)

After 18 months of treatment, the total BAD score in DFP-treated patients had worsened by 2.48 points compared with 3.99 points in the placebo group, for a difference of 1.51 points in favor of deferiprone. The difference did not reach significance (p=0.0761, m ITT population; p=0.1320 PP population). Similarly, no subjective change was detected as assessed by the PGI-I At Month 18, the LSmean scores were 4.66 for placebo and 4.55 for DFP, with no significant group difference (p=0.7279), indicating that, overall, patients did not detect either an improvement or a worsening in their condition from baseline.

The study showed no statistically significant differences in terms of both analysed primary endpoints (BAD and PGI-I scales). No differences were found in both the mITT and PP populations. It should be noted that according to the protocol, the results of the study may be considered positive if there is a significant difference between the two scales analysed. It is worth noting that the PP population analysis did not show any improvement in statistical significance. Therefore, the results of the study cannot be a sufficient proof of a positive effect of deferiprone therapy on the progress of PKAN symptoms. (**MO**)

Responder analysis: In order to better understand the responder analyses that were carried out on the co-primary endpoints, the applicant should provide a table summarising the following information: number of patients with improvement, no change, worsening for each of the treatment groups (placebo and deferiprone), and mean BAD and PGI-I scores for each of these categories.(**OC**)

BAD scores per body region and WeeFIM:

a. BAD total scores have been shown to demonstrate high inter-rater reliability, which is not the case of individual items. In the TIRCON2012V1 study, BAD assessments were videotaped and sent for central assessment to neurologists. With regards to the issue described above, the applicant indicates that videotapes of BAD assessments were assessed by a central assessment team, which consisted of two raters that reviewed videotapes together and at the same time. According to the applicant, both of them reached consensus in all cases, thereby ensuring high inter-reliability of BAD scores.

However, listing 16.2.8 of the CSR indicates a single rater for 31 patients (corresponding to 36.0% of the mITT population) with regards to assessments of BAD scales at baseline and/or month 18.

More specifically, a single rater was observed at both baseline and month 18 for n=15 patients, and a single rater was observed for n=16 patients at either baseline and/or month 18. The answer provided by the applicant therefore appears questionable.

b.

No significant differences between studied groups were seen in the findings of any of the other efficacy measures including UPDRS score, FIM measure (besides WeeFIM – cognition score p=0.0324), PedsQL scale, PSQI index, and Likert scale .

The significant change observed in the study was a reduction in the level of iron in the globus pallidus, as assessed by MRI R2* in participants who received deferiprone. In the placebo group, there was virtually no change in iron content (a mean decrease of 0.50 Hz), while in the DFP group there was a mean decrease of 36.1 Hz, for a significant group difference of -35.6 Hz ($p < 0.0001$). It is worth noting, however, that the population in which the reduction of iron content in globus pallidus was

demonstrated was not the mITT population. Patients who were able to undergo this assessment at the start of the study (16 placebo, 24 DFP) and end of the study (13 placebo, 19 DFP) were analyzed.

Due to a high number of major protocol violations, just 37 patients fulfilled the criteria for being included in the per protocol (PP) population (N=13 for placebo, N=24 for DFP). A subset of 13 patients who were included in the pharmacokinetics (PK) population (N=4 for placebo, N=9 for DFP) was even smaller. However, considering the severity of symptoms of the illness, the limited PK data can be considered acceptable.

MRI results: Patients who underwent MRI at baseline (n=40) and 18 months (n=32) were a sub-group of the study population. The data did not demonstrate any evidence of a statistical and clinical relationship between iron levels in the globus pallidus, as measured by MRI and a change in patient's condition, as measured by the BAD scale and PGI-I at 18 months.

Use of DBS during the study:

a. The applicant reported that among the 19 deferiprone-treated patients with DBS devices, 3 had their settings changed on one occasion each. However, in listing 16.2.35 of DBS/baclofen pump changes, five patients receiving deferiprone are listed as having changes in DBS settings during the study (001005, 001020, 002002, 002033 and 004002). Patient 001005 had his settings changed on more than one occasion. After review by a neurologist, DBS changes were considered significant for only 3 deferiprone-patients (out of 5). Since changes for these 3 patients may have had an impact on efficacy results, these 3 patients were included in the statistical model, which explains the discrepancy in reporting.

b. Reasons underlying DBS settings changes in deferiprone-treated patients should be discussed. (**OC**)

Post-hoc analyses on primary endpoints: Post-hoc analyses, based on the MMRM model, were done on BAD and PGI-I data that excluded the deferiprone-treated patient whose BAD total score was 32 at baseline and hence could not worsen. However, in the description of baseline data, the applicant mentioned that one patient in the deferiprone group had the maximum score of 32 at baseline and another patient in the placebo group had a score of 31 at baseline. For both of these patients, the applicant indicated that no further worsening or minimal worsening could be detected using this scale. The applicant demonstrated that post-hoc analysis with exclusion of the deferiprone patient with a BAD=32 and the placebo patient with a BAD=31 did not lead to a change of overall efficacy results on BAD total score at 18 months.

Dystonia represents one of the main symptoms in PKAN, but patients with atypical PKAN also often develop Parkinsonian symptoms. No statistically significant changes in Parkinsonian symptoms at 18 months were observed on UPDRS parts I, II and III in deferiprone-treated patients when compared to placebo-treated patients (all PKAN, classic PKAN and atypical PKAN patients).

A statistically significant difference is seen in patients 6 years or less as compared to those 6 years and over for the BAD total score. The equivalent for PGI-I is not found in the reports. This should be discussed by the applicant. Furthermore, the reliability of the BAD scale in adolescents and adults and in individual regions should be confirmed. (**OC**)

Supportive study (TIRCON2012V1-EXT)

TIRCON2012V1-EXT was a Phase 3, multi-center, single-arm, open-label extension of theTIRCON2012V1. All participants who completed the placebo-controlled study wereoffered to receive treatment for an additional 18 months. Patients who had beenrandomized to receive placebo were switched to deferiprone in the extension study (the placebo-DFP group), while those who had received deferiprone continued to receive it (the DFP-DFPgroup).

Of the 76 participants who completed the initial trial, 68 enrolled in the extensionstudy, 24 of whom had previously received placebo and 44 of whom had previously receiveddeferiprone; and of these, 62 (19 in the placebo-DFP group, 43 in the DFP-DFP group) wereevaluable for efficacy.

Among the eight patients who did not enrol in the extension study, five were treated by deferiprone and three were treated by placebo during the main part of the study (TIRCON2012V1). While a lack of efficacy and subsequent decline to continue onto a long-term open-label study may be expected for placebo-treated patients, reasons given for not participating to the extension study by deferiprone-treated patients ("not interested", "poor condition and worsening of the disease", "worsening of dystonia") (3 out of 5 patients, or 60%) suggest a lack of efficacy of deferiprone for these patients.

The number of protocol deviations and their nature during the long-term open-label study may suggest a weak efficacy of deferiprone leading to non-compliance, withdrawal prior to end of the study or/and a need for rescue or prohibited medications.

In this study, the only efficacy measures used were the BAD scale andthe PGI-I. Evaluations were carried out at Months 6, 12, and 18.Over the 18 months of the initial study, the patients on placebo had had a mean increase in BAD score of 4.4 points while those ondeferiprone had had a mean increase of 1.9 points, for a treatment group difference of 2.5 pointsthat fell just short of significance (p=0.0500). Over the course of the extension study, when allpatients received deferiprone, both groups increased by the same amount, 1.4 points: there was no group difference (p=0.9781). In a comparison that looked at progression during thefirst 18 months of deferiprone therapy in each group, there was no significant difference betweenthe increase of 1.9 points seen in the DFP-DFP group in the TIRCON2012V1 study and theincrease of 1.4 points seen in the placebo-DFP group in the TIRCON2012V1-EXT study(p=0.5821). As in the TIRCON2012V1 study, patients in both groups reported little perception of change intheir PKAN symptoms as indicated by their score on the PGI-I.

Patients who have completed TIRCON2012V1study were included to extension study. Patients had to have a diagnosis of PKAN. The choice of study participants is acceptable.In the extension study, deferiprone administration was continued in the dose used in pivotal study TIRCON2012V1. The selection of this dose in the initial study had been established based on findings from two single-arm pilot studies and three case reports. There were no significant differences between the treatment groups on any characteristics at the baseline of the study (age at baseline, sex, rac), including BAD score. It is of note however that baseline characteristics according to age at onset of motor symptoms differed significantly in the context of age at onset of symptoms, age at baseline of initial study as well as BAD score at baseline of extension study.

Given the design of the TIRCON2012V1-EXT study (single arm open-label, efficacy as secondary objective) and the fact that this study is the extension of a single pivotal study who failed to meet its primary endpoints, no firm conclusions can be drawn from its results. This extension study is however of interest for the long term safety assessment, with a total exposure of patients reaching 36 months.

3.3.7. Conclusions on clinical efficacy

In the light of the negative results for both primary endpoints as well as for almost all secondary endpoints of the pivotal study, the clinical data presented do not sufficiently support the proposed indication. Long-term extension of the pivotal study, due to its nature (open-label study without control group), and mostly negative outcomes, also does not provide sufficient support.

In conclusion, from a clinical point of view, there is currently no data available to justify acceptance of the proposed product in the intended indication.

3.3.8. Clinical safety

Patient exposure

In the Study TIRCON2012V1in the DFP group (N=58), total exposure was 77.86 person-years,with a mean of 1.34 years (SD=0.39).In the placebo group (N=30), total exposure to study product was 41.58 person-years, with amean of 1.39 years.

Of the 76 participants who completed thestudy TIRCON2012V1 (both from placebo and DFP groups), 68 were enrolled in the extension study (Study TIRCON2012V1-EXT): 24 who had previously received placebo (the placebo-DFP group) and 44 who had previously received deferiprone (the DFP-DFPgroup). All 68 of these patients received at least 1 dose of study product.

A total of 55 participants (80.9%) completed the extension study, and 13 withdrew: 7 (29.2%) in

the placebo-DFP group and 6 (13.6%) in the DFP-DFP group. Reasons for withdrawal in theplacebo-DFP group were adverse event (n=2), worsening of the disease (n=1), voluntarywithdrawal (n=3), and other (n=1; inability to comply with the study requirements). The reasonsin the DFP-DFP group were adverse event (n=1), worsening of the disease (n=1), voluntarywithdrawal (n=3), and lost to follow-up (n=1).Of the 3 patients who withdrew due to AEs, 2 died: one (placebo-DFP) of aspiration pneumoniaand multi-organ failure, and the other (DFP-DFP) of aspiration after vomiting. The third AErelatedwithdrawal (placebo-DFP) was due to cytomegalovirus infection and transaminitis.

The applicant sponsored a compassionate use program in patients with PKAN, TIRCON2012V1-COMP (*TheCompassionate Use of Deferiprone in Patients with Pantothenate Kinase-AssociatedNeurodegeneration*). TIRCON2012V1-COMP is offered to patients who have completed TIRCON2012V1-EXT and who wish to remain on deferiprone treatment. 21 patients have been included, 12 have withdrawnand 9 are ongoing.

Table 4.2.1. Patient exposure

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Placebo-controlled	58	58	58	53 (≥ 6 months)/51 (≥12 months)
Open studies	68#	68	55	17 (≥12 months)
Compassionate use	21	9	9	9

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

24 (from the placebo-DFP group in the Study TIRCON2012V1) and 44 from the DFP-DFP group in the Study TIRCON2012V1

According to the RMP Table 3 "Number of NBIA patients exposed to deferiprone, by age and sex" that represents demographic data from TIRCON2012V1 and TIRCON2012V1-EXT studies (therefore PKAN patients and not NBIA patients as mentioned in the title), among the 89 patients:

- 21 (23.6%) patients were 2 to 11 year-old;

-13 (14.6%) patients were 12 to 16 year-old;

- 5 patients were 17 to 18 year-old;

- 50 (56.2%) patients were 19 to 79 year-old.

Adverse events

Analysis of adverse events in deferiprone- and placebo-treated patients in the Study TIRCON2012V1

All but one patient reported at least one adverse event (AE). An overall summary of AEs isprovided in Table 4.3.1. Rates were similar between the placebo and deferiprone (DFP)groups for any AEs(100.0%

vs. 98.3%, respectively), serious AEs (33.3% vs. 31.0%), and severeAEs (26.7% vs. 29.3%), but were higher in the DFP group for AEs related to study treatment(43.3% vs. 79.3%) and AEs leading to withdrawal from the study (0.0% vs. 6.9%). The onlycategory that reached significance was that of AEs related to treatment (p=0.0015).

The applicant was requested to discuss the safety profile by age groups, by treatment duration and by PKAN population (classical versus atypical).

The analysis by age range (2-11 year-old, 12-17 year-old and ≥ 18 year-old) confirms that:

- Neutropenia is reported in all category of ages.

- Dystonia is the AEs the most reported whatever the catory of age.

- Regarding anemia, the number of associated PTs of anaemia, Blood iron decreased, Serum ferritin decreased and Iron deficiency seems to be higher in the younger population if we consider the classification by age of patients provided in the RMP: 14/21 (67%) in patients Age 2-11 versus 5/13 or 5/18 (38% or 28%) in patients Age 12-17 and versus 24/50 or 24/55 (48% or 43%).

The analysis by PKAN population (classical versus atypical) confirms that:

- Dystonia is the AEs most reported for both populations;

- Anemia Blood iron decreased, Serum ferritin decreased and Iron deficiency are more reported in DFP arm than in PCB arm as expected. Of note, the number of Associated PTs of anaemia, Blood iron decreased, Serum ferritin decreased and Iron deficiency seems to be higher in the classical PKAN population (Age <6) compared to atypical PKAN population (Age ≥6).

- Neutropenia is a safety concern in both populations.

Regarding the analysis by treatment duration (e.g. 6, 12, and 18 months), there is no discernable correlation noted between incidence of AEs and duration of DFP treatment. That confirms the importance to regularly monitor patients all along DFP treatment especially regarding anemia and neutropenia risks.

Table 4.3.1. Overall summary of adverse events (Source: CSS Table 2.7.4-4)

Number of patients with at least one:	Placebo (N=30) % (n)	DFP (N=58) % (n)	P-value (Fisher's exact test)
Adverse event	100.0 (30)	98.3 (57)	1.0000
Serious adverse event	33.3 (10)	31.0 (18)	0.8146
Severe adverse event	26.7 (8)	29.3 (17)	1.0000
Adverse event related to study treatment	43.3 (13)	79.3 (46)	0.0015
Death	0.0 (0)	0.0 (0)	NA
Adverse event leading to withdrawal	0.0 (0)	6.9 (4)	0.2947

Of the 362 events reported in theplacebo group15 (4.1%) were rated as severe.Of the 670 events reported in the DFP group58 (8.7%) were rated as severe (see Table 4.4.1).Severe events of dystonia were reported in 10.0% (3) of placebo patients and 13.8% (8) of DFP patients; severe events of condition aggravated in 10.0% (3) and 3.4% (2), respectively; andsevere events of laceration in 3.4% (2) DFP patients. All other AEs that were rated as severewere seen in only 1 patient.

Table 4.3.2. Summary of intensity ratings of all adverse events (Source: Table 14.3.1.17)

Intensity Ratings	Deferiprone number of events=670 n (%)	Placebo number of events=362 n (%)
Mild	362 (54.0)	243 (67.1)
Moderate	250 (37.3)	104 (28.7)
Severe	58 (8.7)	15 (4.1)

Table 4.3.3. lists AEs that occurred in at least 10% of patients in DFP and placebo group.
In both groups, the most commonly reported adverse event was dystonia (46.7% in theplacebo group, 43.1% in the DFP group), followed by pyrexia (43.3% placebo, 27.6% DFP).
There was a significant group difference for two events: DFP patients had a significantly higherrate of anaemia (0% placebo vs. 20.7% DFP; p=0.0067), and placebo patients had a significantlyhigher rate of the PKAN-associated AE of freezing phenomenon (10.0% placebo vs. 0.0% DFP;p=0.0370). There was no significant group difference in the rates of any other event.

Table 4.3.3. Summary of adverse events seen in ≥10% of patients – Safety population (Source: Study TIRCON2012V1 Report - Table 12.3)

Preferred Term	Placebo (N=30) % (n)	DFP N=58) % (n)	P-value (Fisher's exact test)
Dystonia	46.7 (14)	43.1 (25)	0.8225
Pyrexia	43.3 (13)	27.6 (16)	0.1567
Serum ferritin decreased	16.7 (5)	32.8 (19)	0.1341
Headache	30.0 (9)	22.4 (13)	0.4478
Nasopharyngitis	20.0 (6)	19.0 (11)	1.0000
Anaemia *	0.0 (0)	20.7 (12)	0.0067
Condition aggravated	30.0 (9)	17.2 (10)	0.1827
Neutrophil count decreased	10.0 (3)	17.2 (10)	0.5294
Pain in extremity	13.3 (4)	17.2 (10)	0.7641
Cough	16.7 (5)	17.2 (10)	1.0000
Vomiting	26.7 (8)	15.5 (9)	0.2580
Iron deficiency	10.0 (3)	15.5 (9)	0.7442
Oropharyngeal pain	10.0 (3)	15.5 (9)	0.7442
Upper respiratory tract infection	13.3 (4)	13.8 (8)	1.0000
Arthralgia	3.3 (1)	13.8 (8)	0.1579
Bronchitis	6.7 (2)	12.1 (7)	0.7124
Laceration	10.0 (3)	10.3 (6)	1.0000
Ear pain	10.0 (3)	1.7 (1)	0.1127
Abdominal pain upper	16.7 (5)	6.9 (4)	0.2637
Constipation	13.3 (4)	3.4 (2)	0.1746
Diarrhoea	10.0 (3)	6.9 (4)	0.6860
Gastrointestinal infection	10.0 (3)	5.2 (3)	0.4058
Freezing phenomenon	10.0 (3)	0.0 (0)	0.0370

* Includes the preferred terms of anaemia, hypochromic anaemia, iron deficiency anaemia, microcytic anaemia, and normochromic normocytic anaemia.

Table 4.3.4. presents just those adverse events that were deemed to be related to PKAN.
Thepercentage of patients reporting at least one such AE was slightly higher in the placebo group (66.7%, 20 patients) than in the DFP group (56.9%, 33 patients), but the difference was

notsignificant(p=0.4915). The only PKAN-related AE for which the group difference reachedstatistical significance was freezing phenomenon (10.0% in the placebo group vs. none in theDFP group; p=0.0370).

Table 4.3.4. Summary of adverse events related to PKAN – Safety population (Source: StudyTIRCON2012V1 Report - Table 12.4)

Preferred Term	Placebo (N=30) % (n)	DFP (N=58) % (n)	P-value (Fisher's exact test)
Dystonia	46.7 (14)	43.1 (25)	0.8225
Condition aggravated	26.7 (8)	15.5 (9)	0.2580
Abasia	6.7 (2)	3.4 (2)	0.6030
Aphasia	3.3 (1)	5.2 (3)	1.0000
Drooling	6.7 (2)	3.4 (2)	0.6030
Freezing phenomenon	10.0 (3)	0.0 (0)	0.0370
Balance disorder	0.0 (0)	3.4 (2)	0.5455
Blepharospasm	3.3 (1)	1.7 (1)	1.0000
Dysarthria	0.0 (0)	3.4 (2)	0.5455
Gait disturbance	3.3 (1)	1.7 (1)	1.0000
Musculoskeletal stiffness	3.3 (1)	1.7 (1)	1.0000
Tongue biting	0.0 (0)	3.4 (2)	0.5455
Tremor	0.0 (0)	3.4 (2)	0.5455
Fall	3.3 (1)	0.0 (0)	0.3409
Hypertonia	0.0 (0)	1.7 (1)	1.0000
Hypotonia	3.3 (1)	0.0 (0)	0.3409
Mastication disorder	0.0 (0)	1.7 (1)	1.0000
Oromandibular dystonia	0.0 (0)	1.7 (1)	1.0000
Pain in extremity	0.0 (0)	1.7 (1)	1.0000
Postural reflex impairment	3.3 (1)	0.0 (0)	0.3409
Staring	0.0 (0)	1.7 (1)	1.0000
Walking aid user	0.0 (0)	1.7 (1)	1.0000

Intensity of Treatment Emergent Adverse Events

Of the 670 events reported in the DFP group, 362 (54.0%) were rated as mild, 250 (37.3%) as moderate, and 58 (8.7%) as severe.

Of the 362 events reported in theplacebo group, 243 (67.1%) were rated as mild, 104 (28.7%) as moderate, and 15 (4.1%) as severe.

Severe events of dystonia were reported in 10.0% (3) of placebo patients and 13.8% (8) of DFPpatients; severe events of condition aggravated in 10.0% (3) and 3.4% (2), respectively; andsevere events of laceration in 3.4% (2) DFP patients. All other AEs that were rated as severewere seen in only 1 patient.

Of the AEs rated as moderate, the most common were dystonia, reported in 20.0% (6) of placebopatients and 20.7% (12) DFP patients; pyrexia in 26.7% (8) and 10.3% (6), respectively;condition aggravated in 10.0% (3) and 8.6% (5), respectively; pain in extremity in 6.7% (2)and 8.6% (5), respectively; serum ferritin decreased in 6.7% (2) and 12.1% (7), respectively;headache in 6.7% (2) and 6.9% (4), respectively; aphasia in 6.7% (2) and 5.2% (3), respectively;and arthralgia in 0.0% and 8.6% (5), respectively. No other moderate AE was seen in more than4 patients, and most were seen in only one.

Drug Relationship of Treatment Emergent Adverse Events

Adverse events that were considered to be at least possibly related to study product wereidentified as adverse drug reactions (ADRs). Forty-four (12.2%) of the 362 AEs in the placebogroup and 143 (21.3%) of the 670 AEs in the DFP group were considered to be ADRs.

The majority were in theSOCs of Blood and lymphatic system disorders, where ADRs were reported by 10.0% (3) ofplacebo patients and 31.0% (18) DFP patients; Investigations, with 23.3% (7) and (43.1% (25),respectively; and Metabolism and nutrition disorders, with 10.0% (3) and 19.0% (11), respectively.

ADRs that were reported by more than 1 patient are listed in Table 4.3.5. The most common were decreased serum ferritin, in 16.7% (5) of the patients in the placebo group and 32.8% (19) in the DFP group; and iron deficiency, in 10.0% (3) and 15.5% (9), respectively. The only ADR forwhich the group difference was statistically significant was anaemia (p=0.0136).

Table 4.3.5. Summary of most common (>5%) adverse drug reactions – Safety population (Source: Study TIRCON2012V1 Report - Table 12.5)

Preferred Term	Placebo (N=30) % (n)	DFP (N=58) % (n)	P-value (Fisher's exact test)
Serum ferritin decreased	16.7 (5)	32.8 (19)	0.1341
Iron deficiency	10.0 (3)	15.5 (9)	0.7442
Anaemia *	0.0 (0)	19.0 (11)	0.0136
Neutrophil count decreased	6.7 (2)	13.8 (8)	0.4838
Diarrhoea	3.3 (1)	5.2 (3)	1.0000
Pyrexia	0.0 (0)	5.2 (3)	0.5481
Neutropenia	6.7 (2)	8.6 (5)	1.0000
Blood iron decreased	6.7 (2)	5.2 (3)	1.0000
Headache	6.7 (2)	5.2 (3)	1.0000

* Includes the preferred terms of anaemia, hypochromic anaemia, iron deficiency anaemia, microcytic anaemia, and normochromic normocytic anaemia.

Rates of AEs between DFP and placebo groups were comparable, however, higher for DFP group for AEs related to study treatment (43.3%vs 79.3%, p=0.0015) and AEs leading to withdrawal from treatment (0.0% vs 6.9%). The most commonly observed AEs were dystonia and pyrexia. Statistically significant differences between placebo and DFP groups were shown for two AEs: anemia (0% in placebo group and 20.7% in DFP group, p=0.0067) and freezing phenomenon (10% in placebo group and 0% in DFP group, p=0.037)

There were more ADRs in the DFP treated group than in the placebo group. 44 (12.2%) in the placebo group and 143 (21.3) in the DFP group were considered to be ADRs.

The applicant was requested to further justify AEs to be considered related or not to DFP. Events not known to be associated with DFP should not be mentioned in the SmPC. The proposal to update the SmPC with ADR that occurred in at least 3 patients could be acceptable if different Tabulated lists of ADRs are considered (one taking into post marketing data and the known safety profile of DFP and one with specific ADR following safety results in TIRCON studies).

All PTs that are not known with Ferriprox® and are not considered related to DFP should be deleted (OC).

Regarding neutropenia and agranulocytosis risk, the applicant has revised the SmPC of Upkanz to have the same warnings & precautions regarding neutropenia and agranulocytosis risks that are approved in the SmPC of Ferriprox® as requested. The applicant is not aware of any change to add the same contraindications as for Ferriprox® regarding this risk as no episodes of agranulocytosis were reported in TIRCON studies. The applicant refers to the well-known article of Tricta and al 2016. Of note this article was thoroughly assessed in previous PSUSA (for example, please see EMEA/H/C/PSUSA/00000940/201608) of DFP and contraindications and precaution of use were still considered important to be maintained for Ferriprox®. In the TIRCON studies, CBC was performed weekly (Total WBC, absolute neutrophil count, platelet count, and hemoglobin). Such monitoring and taking into account discontinuation rules might explain the absence of agranulocytosis. Clinical Trial conditions do not reflect post marketing conditions. More than 20 years of post-marketing experience with DFP should be taken into account regarding agranulocytosis risk. Therefore, a contra-indication in section 4.3 is still requested **(OC)**.

Analysis of adverse events in deferiprone in the Study TIRCON2012V1-EXT

Table 4.3.6 lists summary of adverse events by intensity and Table 4.3.7 lists the AEs for which events of either moderate or severe intensity were reported bymore than 1 patient in a group. In all cases, the AEs with the highest rate of both moderate andsevere occurrences were dystonia and condition aggravated, both of which are related to PKAN.

Other AEs for which moderate and/or severe events were reported in at least 2 patients in anyone group included the PKAN-related events of dysphagia, aphasia, balance disorder,oromandibulardystonia, and muscle spasticity. Moderate events of decreased serum ferritin wereseen in 3 (6.8%) DFP-DFP patients in each study. The rate of moderate or severe events did notdiffer significantlyacross the two studies for any AE for the DFP-DFP patients.

Table 4.3.6. Summary of adverse events by intensity – safety population

Intensity of adverse events	All patients, both studies (N=68)	Placebo-DFP (N=24)	DFP-DFP (N=44)	
		T-EXT study	TIRCON study	T-EXT study
Total number of AEs (N)	1068	206	505	357
Mild (%)	56.3	57.8	56.8	54.6
Moderate (%)	35.3	34.0	34.9	36.7
Severe (%)	8.4	8.2	8.3	8.7

Table 4.3.7. Summary of most commonly reported moderate and severe adverse events – safety population

Preferred Term	All patients, both studies (N=68) % (n)		Placebo-DFP (N=24) % (n)		DFP-DFP (N=44) % (n)			
			T-EXT study		TIRCON study		T-EXT study	
	Moderate	Severe	Moderate	Severe	Moderate	Severe	Moderate	Severe
Dystonia	11 (16.2)	20 (29.4)	7 (29.2)	5 (20.8)	5 (11.4)	5 (11.4)	5 (11.4)	11 (25.0)
Condition aggravated	11 (16.2)	5 (7.4)	3 (12.5)	2 (8.3)	4 (9.1)	2 (4.5)	7 (15.9)	1 (2.3)
Laceration	5 (7.4)	2 (2.9)	1 (4.2)	0 (0.0)	3 (6.8)	2 (4.5)	2 (4.5)	0 (0.0)
Agitation	1 (1.5)	2 (2.9)	0 (0.0)	1 (4.2)	0 (0.0)	1 (2.3)	1 (2.3)	0 (0.0)
Aphasia	3 (4.4)	2 (2.9)	0 (0.0)	1 (4.2)	3 (6.8)	0 (0.0)	1 (2.3)	1 (2.3)
Balance disorder	3 (4.4)	2 (2.9)	1 (4.2)	0 (0.0)	0 (0.0)	1 (2.3)	2 (4.5)	1 (2.3)
Dysphagia	4 (5.9)	2 (2.9)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.8)	2 (4.5)
Pyrexia	5 (7.4)	1 (1.5)	2 (8.3)	1 (4.2)	3 (6.8)	0 (0.0)	0 (0.0)	0 (0.0)
Oromandibular dystonia	3 (4.4)	1 (1.5)	2 (8.3)	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.3)	0 (0.0)
Pain in extremity	5 (8.8)	1 (1.5)	0 (0.0)	0 (0.0)	4 (9.1)	0 (0.0)	3 (6.8)	1 (2.3)
Arthralgia	4 (5.9)	1 (1.5)	1 (4.2)	0 (0.0)	2 (4.5)	1 (2.3)	1 (2.3)	0 (0.0)
Muscle spasms	4 (5.9)	1 (1.5)	1 (4.2)	0 (0.0)	2 (4.5)	0 (0.0)	2 (4.5)	1 (2.3)
Pain	4 (5.9)	1 (1.5)	1 (4.2)	0 (0.0)	3 (6.8)	1 (2.3)	0 (0.0)	0 (0.0)
Weight decreased	3 (4.4)	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Muscle spasticity	2 (2.9)	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	3 (4.4)	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Upper respiratory tract infection	4 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	4 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	5 (8.8)	0 (0.0)	1 (4.2)	0 (0.0)	4 (9.1)	0 (0.0)	3 (6.8)	0 (0.0)
Contusion	4 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (9.1)	0 (0.0)
Serum ferritin decreased	6 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.8)	0 (0.0)	3 (6.8)	0 (0.0)
Syncope	4 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	3 (6.8)	0 (0.0)
Viral infection	4 (5.9)	0 (0.0)	1 (4.2)	0 (0.0)	3 (6.8)	0 (0.0)	0 (0.0)	0 (0.0)

Treatment Emergent Adverse Events

A total of 1068 AEs were reported during deferiprone treatment: 206 in 22 placebo-DFPpatients in the extension study, 505 in 44 DFP-DFP patients in the initial study, and 357 in42 DFP-DFP patients in the extension study.

For both treatment groups, the SOCs in which the most patients reported at least one type of AEwere Nervous system disorders (85.3% of patients overall), Infections and infestations (64.7%),General disorders and administration site conditions (63.2%), Gastrointestinal disorders (48.5%),Investigations (48.5%), Musculoskeletal and connective tissue disorders (47.1%), and Injury,poisoning and procedural complications (42.6%). For the DFP-DFP group, there was nosignificant difference across studies in the rate of any SOCs (all p-values > 0.05).

Table 4.3.8. lists those AEs that occurred in at least 10% of patients in a group. For both groups,the most commonly reported event was dystonia (58.8% overall). In the DFP-DFP group, thereappeared to be a significantly higher rate in the initial study for two events, nasopharyngitisand oropharyngeal pain, with the difference reaching a p-value less than 0.05 in both cases(0.0264 and 0.0298, respectively). However, since there was no adjustment of p-value formultiplicity, it is uncertainwhether these differences were indeed significant. Of note, none of the nasopharyngitis or the oropharyngeal pain events were considered to be related todeferiprone use. For all other events, there was no significant difference inthe rate across studies.

Table 4.3.8 Summary of adverse events seen in ≥10% of patients – safety population'

Preferred Term	All patients, both studies (N=68) % (n)	Placebo-DFP (N=24) % (n)	DFP-DFP (N=44) % (n)		
		T-EXT study	TIRCON study	T-EXT study	T-EXT vs. TIRCON p-value
Dystonia	58.8 (40)	54.2 (13)	34.1 (15)	47.7 (21)	0.2783
Pyrexia	33.8 (23)	33.3 (8)	25.0 (11)	25.0 (11)	1.0000
Headache	29.4 (20)	25.0 (6)	27.3 (12)	15.9 (7)	0.3001
Condition aggravated	26.5 (18)	25.0 (6)	18.2 (8)	18.2 (8)	1.0000
Serum ferritin decreased	26.5 (18)	12.5 (3)	13.6 (6)	27.3 (12)	0.1855
Pain in extremity	20.6 (14)	8.3 (2)	20.5 (9)	11.4 (5)	0.3827
Upper respiratory tract infection	19.1 (13)	16.7 (4)	15.9 (7)	11.4 (5)	0.7574
Cough	19.1 (13)	8.3 (2)	20.5 (9)	11.4 (5)	0.3827
Anaemia *	17.6 (12)	0.0 (0)	20.5 (9)	13.6 (6)	0.5719
Vomiting	16.2 (11)	16.7 (4)	11.4 (5)	6.8 (3)	0.7133
Arthralgia	16.2 (11)	16.7 (4)	9.1 (4)	6.8 (3)	1.0000
Nasopharyngitis	16.2 (11)	4.2 (1)	22.7 (10)	4.5 (2)	0.0264
Iron deficiency	16.2 (11)	0.0 (0)	15.9 (7)	9.1 (4)	0.5210
Oropharyngeal pain	14.7 (10)	4.2 (1)	18.2 (8)	2.3 (1)	0.0298
Neutrophil count decreased	14.7 (10)	4.2 (1)	13.6 (6)	9.1 (4)	0.7387
Bronchitis	11.8 (8)	8.3 (2)	13.6 (6)	9.1 (4)	0.7387
Laceration	11.8 (8)	8.3 (2)	11.4 (5)	4.5 (2)	0.4336
Somnolence	10.3 (7)	12.5 (3)	2.3 (1)	6.8 (3)	0.6162

* Includes the preferred terms of anaemia, hypochromic anaemia, iron deficiency anaemia, and normocytic anaemia

Drug Relationship of Treatment Emergent Adverse Events

For the placebo-DFP group, 19(9.2%) of the 206 reported AEs were considered to be ADRs, while for the DFP-DFP group,these numbers were 85 (16.8%) of the 505 AEs in the initial study and 49(13.7%) of the 357AEs in the extension study.

The SOC with the highest number of related events was Investigations, in which ADRs wererereported by 20.8% (5) of the placebo-DFP patients, (27.3% (12) of the DFP-DFP patients in theinitial study, and 40.9% (18) of the DFP-DFP patients in the extension study. The majority ofother ADRs were inthe SOC of Nervous system disorders, for 12.5% (3) of the placebo-DFPpatients and 6.8% (3) of the DFP-DFP patients in the initial study; Blood and lymphatic systemdisorders, for 27.3% (12) of the DFP-DFP patients in the initial study and 9.1% (4) in theextension study; and Metabolism andnutrition disorders, for 15.9% (7) of the DFP-DFP patientsin the initial study and 9.1% (4) in the extension study.

ADRs that were seen in more than one patient in a group in either study are shown in Table 4.3.9

In the placebo-DFP group, the most frequent ADR was decreased serum ferritin, seen in 12.5% (3)

of the patients. In the DFP-DFP group, the most frequent ADR in the initial study was anemia,seen in 18.2% (8) of the patients, followed by iron deficiency in 15.9% (7) and decreasedserum ferritin in 13.6% (6); in the extension study, the most frequent was decreased serumferritin in 27.3% (12). With the exception of decreased serum ferritin, the rate of each ADRamong the DFP-DFP patients was lower in the extension study than in the initial study, but noneof the differences were statistically significant (all p-values > 0.05).

Table 4.3.9. Summary of adverse drug reactions seen in >5% of patients in any group – safety population

Preferred Term	All patients, both studies (N=68) % (n)	Placebo-DFP (N=24) % (n)	DFP-DFP (N=44) % (n)		
		T-EXT study	TIRCON study	T-EXT study	T-EXT vs. TIRCON p-value
Serum ferritin decreased	26.5 (18)	12.5 (3)	13.6 (6)	27.3 (12)	0.1855
Iron deficiency	16.2 (11)	0.0 (0)	15.9 (7)	9.1 (4)	0.5210
Anemia*	14.7 (10)	0.0 (0)	18.2 (8)	9.1 (4)	0.3521
Neutrophil count decreased	13.2 (9)	4.2 (1)	11.4 (5)	9.1 (4)	1.0000
Neutropenia	5.9 (4)	4.2 (1)	4.5 (2)	2.3 (1)	1.0000
Haemoglobin decreased	2.9 (2)	8.3 (2)	0.0 (0)	0.0 (0)	--
Somnolence	2.9 (2)	8.3 (2)	0.0 (0)	0.0 (0)	--

Frequency of serum ferritin decrease was doubled DFP-DFP group in T-EXT study compared to TIRCON study. However, no statistical significance was shown between groups. Numerical increase in rates of dystonia and serum ferritin decrease were observed between studies TIRCON and T-EXT in patients treated with DFP-DFP. However, this could be related to a long observation period.

Additional safety data from studies in patients with localized brain iron accumulation

The safety of deferiprone in patients with local brain iron overload has been assessed in otherApoPharma-sponsored clinical studies including LA29-0207 and LA29-0207-EXT, whichenrolled patients with Friedreich's ataxia (FRDA) and LA-04/06B, a compassionate useprogram, whereby patients with NBIA (including PKAN) and superficial siderosis participated.

The general profile of adverse events observed from these patients was consistent with the known adverse event profile in patients with NBIA.

Nausea, vomiting, abdominal pain, asthenia, fatigue, pyrexia, nasopharyngitis , serum ferritin decrease, arthralgia, dizziness, headache, cough and oropharyngeal pain were observed in more than 15% of patients treated with DFP. No clinically relevant differences in safety profile of DFP were observed among patients with Friedrich's ataxia, superficial siderosis and NBIA enrolled into supportive studies**.**

Neutropenia was an only SAE observed in ≥5% of patients. However, the applicant clarified that no clinically relevant clinical consequences of neutropenia were observed in these patients.

Serious adverse events and deaths

No patients died during the TIRCON2012V1 study

In case of both deaths autopsy was not performed. While death in **Case 2017AP006499** seems not related to study product (treatment was discontinued 17 days before the patient died), **Case 2017AP007118**concerns a fatal report of vomiting and aspiration of patients on study treatment. The underlying reason for vomiting was not specified, however, it was confirmed that food was not the reason.

In TIRCON2012V1 study, 72 SAEs were reported: 23 SAEs in placebo arm and 49 SAEs in DFP arm. 72 SAEs were reported as 88 patients were in included in the study.

- 23 SAEs were reported in 10 patients in PCB arm. 33% (10/30) in placebo arm reported at least one SAE.

- 49 SAEs were reported in 18 patients in DFP arm. 31 % (18/58) in DFP arm reported at least one SAE.

As AEs, SAEs were not presented by age, classical/atypical PKAN neither by treatment duration. This was done, as requested. It appears that more SAEs and especially SAEs leading to hospitalization or prolongation of the hospitalization were reported in classical PKAN population. This is in line with classical PKAN condition which is a very severe disease. As for AEs, there is no discernable correlation noted between incidence of SAEs and duration of DFP treatment. That confirms the importance to regularly monitor patients all along DFP treatment regarding anemia and neutropenia risks.

The applicant considered that 9/72 SAEs reported in 8 patients were possibly related to medicinal product (7 in DFP arm, 2 in placebo arm)

- In DFP arm, 7 SAEs were reported in 6 patients. Neutropenia was reported in 6/7 SAEs.

Those 7 SAES included 3 adults (neutropenia) and 3 children (3 SAE neutropenia and 1 SAE dystonia). 2 SAEs of neutropenia were reported for the same 13 y-o patient.

- In placebo arm: 2 SAEs were reported in 2 children (neutropenia).

In the safety population, the applicant considered that 40 SAEs were reported in this safety population (82 patients) and 13 were considered related (7 in TIRCON2012-V1 already discussed above and 6 in TIRCON2012V1EXT).

Regarding the 6 SAEs reported in TIRCON2012V1EXT that were considered to be possibly related to study product by the applicant: 5 neutropenia and 1 one aggravated dystonia were reported. These SAEs were reported in 3 patients according to the applicant.

- 14-year-old female reported an aggravated dystonia 4 months after the start of DFP.
- 1 female child who reported 2 SADR of neutropenia respectively at 7 and 8 year-old (e.g. neutropenia 1 month after the start. The patient stopped DFP recovered and restarted DFP and another episode of neutropenia was reported 14 months after the start). This patient reported a neutropenia in PCB arm also in the pivotal study.
- 1 adult (36 yo male) reported the 3 other SAEs of neutropenia

As for the pivotal study, the other SAEs that were reported in the TIRCON2012V1 EXT are not discussed since there are considered as not related to DFP according to the applicant. Indeed, most of the cases can be considered to be related to the progression of the disease (at least 10 patients the SAEs reported was aggravated dystonia) or underlying condition (such as medical device issue, gastrostomy and tracheostomy) due to the dramatic condition of the patients.

Laboratory findings

Hematology

Total WBC count was lower in patients treated with deferiprone. However, although the total WBC was lower in the patients who received deferiprone than in those who received placebo, the counts were within the normal reference range and there was no difference in the incidence of neutropenia between the two study arms.

The applicant was requested to justify why eosinophilia, thrombocytopenia were considered as ADRs taking into account safety results of both TIRCON studies and also the known safety profile of deferiprone. Events not known to be associated with DFP should not be mentioned in the SmPC. The proposal to update the SmPC with ADR that occurred in at least 3 patients could be acceptable if the applicant proposes in the SmPC two Different Tabulated lists of ADRs: one taking into post marketing data and the known safety profile of DFP and one with specific ADR following safety results in TIRCON studies (OC).

The mean values at the end of study (EOS) did not differ significantly fromthe mean baseline values in either treatment group for any of these parameters. The difference between the treatment groups in the trend over time from baselineto EOS was statistically significant for ANC ($p=0.0001$) and total WBC ($p < 0.0001$), but not for hemoglobin or platelets.

Biochemistry:
Decreases in the following parameters were reported: LDH, serum ferritin, amylase and potassium. Serum ferritin decrease is expected as previously mentioned.

Regarding LDH decrease, amylase decrease and potassium decrease, these parameters are not listed in the SmPC of Ferriprox®. The applicant has discussed the decrease of the followings laboratory findings results: LDH decrease, amylase decrease and potassium decrease as requested. Mean levels of these parameters remained within normal levels and none of the changes were considered of clinical significance. There were no adverse events LDH decrease, amylase decrease or potassium decrease during deferiprone use.

ALT, AST, and bilirubin:
One placebo patient had values of both ALT and AST that were > 3 times the upper limit ofnormal(ULN) at Month 18, one DFP patient had ALT > 3 x ULN at Month 6, and one DFPpatient had AST > 3 x ULN at Month 18.There were no cases of total bilirubin >2 x ULN.

Statistically significant differences were observed in DFP group for albumin (decrease, $p=0.047$), GGT (increase, $p=0.0002$) and glucose (increase, $p=0.0416$) in the Study TIRCON2012V1. Furthermore, in the extension study, statistically significant differences were observed for AST (increase in both PLB-DFP and DFP-DFP groups, $p=0.0128$ and $p=0.083$, respectively), potassium (decrease, $p=0.0041$), total protein ($p<0.001$).

<u>Impact of deferiprone on prolactin levels</u>

LA54-0116 and LA56-0117 were proposed to assess the effects of deferiprone on prolactin levels, based on the findings of increased prolactin values in non-clinical study (rats).

A transient increase of prolactin was reported following the administration of DFP (in single dose or dose repeated in healthy volunteer). The effect has no clinical impact according to the applicant. The applicant was requested to further discuss this reaction taking into account the age of the patient (children) and the impact of this increase in such population. The applicant has discussed the relevance of prolactin data collected in studies LA54-0116 and LA56-0117 with regards to the disease under

investigation (neurodegeneration with brain iron accumulation, pantothenate kinase-associated neurodegeneration), population (female patients, children) and duration of treatment (long-term administration).

- Risks in patients with hepatic and renal impairment

Risk in patient with renal and hepatic impairment was assessed in study LA39-0412 and LA40-0412. Of note, one SAE of severe acute liver injury and severe acute renal failure was reported (2 days following administration of deferiprone and recovered around 2 weeks after the stop of DFP.

Both studies (LA39-0412 and LA40-0412) were already assessed in the Type II variation (EMEA/H/C/000236/II/0126/G CHMP opinion on 31.01.2019) for Ferriprox® and a warning was proposed to consider those data. Therefore, the same information is in the SmPC of Upkanz, as expected.

QT risk with DFP

LA37-1111, study was conducted in 2012 (last subject completed in Dec 2012). This study was already assessed in the context of a Type II variation in 2015 (EMEA/H/C/000236/II/0089/G) for Ferriprox® and information was added in section 5.1 to present main results of this study. As requested, the same information appears in the SmPC of Upkanz® as in Ferriprox® in section 5.1.

Use in pregnancy and lactation

There were no reported pregnancies in TIRCON2012V1 and TIRCON2021V1-EXT.

No formal studies of the safety of deferiprone in pregnant women or nursing mothers have been conducted by ApoPharma. Reproductive studies in animals show that deferiprone is teratogenic and embryotoxic in non-iron-overloaded rats and rabbits.

As of 31 Aug 2018, ApoPharma had been informed of 44 pregnancies in deferiprone-treatedwomen: 37 with known outcomes (7 abnormal and 30 normal), 6 with unknown outcomes, andone ongoing.

One of these pregnancies led to the delivery, at full-term, of a male infant who was diagnosedafter birth with anal atresia, nephroptosis, ventricular septal defect, hemivertebra, and urethralfistula. This infant had been exposed to deferiprone *in utero* for less than three months. Sixpregnancies resulted in spontaneous abortion; the *in utero* exposure to deferiprone during threepregnancies was unknown, one was less than 2 weeks, one was 17 days, and one wasapproximately 5 weeks.
Thirty pregnancies have been reported to result in the delivery of healthy infants: 11 delivered atfull-term; nine delivered by Caesarian section at 33, 34, 36 (n=2), 37, 38 (n=2), 39 weeks and full-term; and the gestation age at delivery of 10 pregnancies was not reported. One of those 30pregnancies resulted in a healthy infant (delivered via C-section at 38 weeks), but with transient neonatal tachypnea. The *in utero* exposure of 14 of these infants to deferiprone varied, but was limited to the first trimester for 12 infants and greater than 12 weeks for two infants. Seven of the women had discontinued deferiprone use prior to becoming pregnant, and the *in utero* exposures of nine infants are unknown.
As of the data cut off date, the outcome of six pregnancies is unknown and one pregnancy is ongoing, with no complications reported to date.
Based on the available information, deferiprone use is contraindicated during pregnancy orbreastfeeding. Deferiprone was measurable in milk samples collected from a lactating womantreated with deferiprone (ApoPharma data). Women of childbearing potential are advised toavoid pregnancy or to stop taking deferiprone immediately if they become pregnant or are tryingto become pregnant, and while breastfeeding.

The information in the SmPC of Upkanz is the same as in Ferriprox®, which is considered acceptable.

According to the SmPC: ”Caution must be exercised in patients with end stage renal disease or severe hepatic dysfunction. Renaland hepatic function should be monitored in these patient populations during deferiprone therapy. Ifthere is a persistent increase in serum alanine aminotransferase (ALT), interruption of deferipronetherapy should be considered”. This is considered acceptable.

Deferiprone use is contraindicated during pregnancy orbreastfeeding.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

The potential for pharmacokinetic drug interactions is low, given deferiprone’s low plasmaprotein binding (<20%)(REF) and its lack of inhibition of human CYP450 isoforms.

Given the mechanism of action of deferiprone, i.e., chelation of iron (III), pharmacodynamicdrug-drug interactions are expected to be rare. However, since deferiprone binds to metalliccations, the potential exists for interactions between deferiprone and trivalent cation-dependentmedicinal products such as aluminum-based antacids. Therefore, there’s a recommendationagainst concomitant ingestion of aluminum-based antacids and deferiprone.

Also, due to unknown mechanism of deferiprone-induced neutropenia, there is arecommendation against concomitant use of medicinal products known to be associated with neutropenia or those that can cause agranulocytosis.

Discontinuation due to AEs

Twelve patients withdrew from TIRCON2012V1. Of these 12 patients, 4 were due to AEs, alloccurring in the DFP group. Three of the events were neutropenia: one was of moderateintensity, so the patient was withdrawn as per protocol; the other two were of mild intensity, butthe patient was withdrawn in each case due to the duration of the events (11 days in one case, 22days in the other). The fourth event was pneumonia with fever, where the patient was unable totravel back to the site for end-of-study procedures.

Thirteen patients withdrew from TIRCON2012V1-EXT. Of these 13 patients, 3 were due toAEs: one placebo-DFP patient hadcytomegalovirus infection and transaminitis, one placebo-DFP patient had aspiration pneumoniaand multi-organ failure leading to death, and one DFP-DFP patient had aspiration leading todeath. None of these AEs were considered to be related to study product.

During the acompassionate use program in patients with PKAN 14 patients have withdrawn (up to 09 Jan 2020).

During both studies TIRCON2012V1 and TIRCON2012V1-EXT 7 patients discontinued due to AEs. Three of the events were neutropenia.

The applicant was requested to clarify if withdrawals from the compassionate use program (14 patients in total, up to 09 Jan 2020) were due to AEs**.** The main reasons for withdrawal seem not to be due to AEs, but overall, all the provided reasons might suggest lack of efficacy of deferiprone in these patients (14/23).

Post marketing experience

Deferiprone is not marketed for the treatment of NBIA.

In addition to TIRCON2012V1 and TIRCON2012V1-EXT, ApoPharma sponsored acompassionate use program in patients with PKAN, TIRCON2012V1-COMP (*The Compassionate Use of Deferiprone in Patients with Pantothenate Kinase-Associated Neurodegeneration*). TIRCON2012V1-COMP is offered to patients who have completedTIRCON2012V1-EXT and who wish to remain on deferiprone treatment. Participants continueto receive deferiprone at no charge and are followed locally by their own neurologist or otherspecialist, who must have agreed to provide ApoPharma with data as specified in the protocol.

Patients are provided with deferiprone oral solution 80 mg/mL at the same dose they wereprescribed in the extension study (up to 15 mg/kg b.i.d., for a maximum daily dose of 30 mg/kg).

The first patient in this program was enrolled in Mar 2016. As of 31 Aug 2018, 21 patients have

received deferiprone, for an overall exposure of 28.3 patient years, 12 have withdrawn, and 9 are

ongoing . The program is open-ended with respect to the completion date. A total of 13 SAEs were reported in 8 patients enrolled in TIRCON2012V1-COMP (Table 4.10.1). None of the SAEs wereassessed as related to deferiprone.

Table 4.10.1 SAEs experienced by TIRCON2012V1-COMP patients (Source CSS Table 2.7.4-16)

	DFP (from TIRCON-COMP)	
	Exposure: 28.31 yrs** **n subjects exposed=21** **Total events=13** **n subjects reporting=8**	
SOC **PT**	**N subjects (%)***	**N Events** **(Rate/100 patient years)**
Gastrointestinal disorders	**2 (9.5)**	**2 (7.06)**
Abdominal pain	1 (4.8)	1 (3.53)
Small intestinal obstruction	1 (4.8)	1 (3.53)
General disorders and administration site conditions	**1 (4.8)**	**1 (3.53)**
Pyrexia	1 (4.8)	1 (3.53)
Infections and infestations	**2 (9.5)**	**2 (7.06)**
Cellulitis	1 (4.8)	1 (3.53)

Pneumonia	1 (4.8)	1 (3.53)
Injury, poisoning and procedural complications	**1 (4.8)**	**1 (3.53)**
Laryngeal injury	1 (4.8)	1 (3.53)
Metabolism and nutrition disorders	**1 (4.8)**	**1 (3.53)**
Malnutrition	1 (4.8)	1 (3.53)
Nervous system disorders	**1 (4.8)**	**1 (3.53)**
Dystonia	1 (4.8)	1 (3.53)
Respiratory, thoracic and mediastinal disorders	**2 (9.5)**	**2 (7.06)**
Pneumonia aspiration	1 (4.8)	1 (3.53)
Respiratory distress	1 (4.8)	1 (3.53)
Surgical and medical procedures	**2 (9.5)**	**3 (10.60)**
Gastrostomy	2 (9.5)	2 (7.06)
Medical device implantation	1 (4.8)	1 (3.53)

3.3.9. Discussion on clinical safety

The size of the primary safety database is considered limited, however can be considered adequate regarding that PKAN is an orphan disease. The pooled TIRCON2012V1 and TIRCON2012V1-EXT population include 82 PKAN patients exposed to deferiprone. Of these, 68 patients has been exposed to deferiprone for ≥ 12 months, and 54 for ≥18 months, respectively. This data is supplemented by 72 patients with FRDA (65 patients) and superficial siderosis (3 patients), NBIA (2 patients) and 2 patients with PKAN. 82 patients were considered in the safety population (58 in DFP-DFP arm and 24 in PCB-DFP arm). The majority of patients were treated during 1 year (68/82 (82.9%) and 42 (51.2 %) patients were exposed ≥ 24 months. Regarding the analysis by treatment duration (e.g. 6, 12, and 18 months), there is no discernable correlation noted between incidence of AEs neither SAEs and duration of DFP treatment. That confirms the importance to regularly monitor patients all along DFP treatment especially regarding anemia and neutropenia risks.

Rates of adverse events (AE) in the pivotal study were similar between the placebo and deferiprone (DFP) groups for any AEs (100.0% vs. 98.3%, respectively), serious AEs (33.3% vs. 31.0%), and severe AEs (26.7% vs. 29.3%), but were higher in the DFP group for AEs related to studytreatment (43.3% vs. 79.3%) and AEs leading to withdrawal from the study (0.0% vs. 6.9%). The only category that reached significance was that of AEs related to treatment (p=0.0015).

Of the 362 events reported in the placebo group 15 (4.1%) were rated as severe. Of the 670 events reported in the DFP group 58 (8.7%) were rated as severe. Severe events of dystonia were reported in 10.0% (3) of placebo patients and 13.8% (8) of DFP patients; severe events of condition aggravated in 10.0% (3) and 3.4% (2), respectively; and severe events of laceration in 3.4% (2) DFP patients. All other AEs that were rated as severe were seen in only 1 patient.

In both groups, the most commonly reported adverse event was dystonia (46.7% in the placebo group, 43.1% in the DFP group), followed by pyrexia (43.3% placebo, 27.6% DFP).

There was a significant group difference for two events: DFP patients had a significantly higher rate of anaemia (0% placebo vs. 20.7% DFP; p=0.0067), and placebo patients had a significantly higher rate of the PKAN-associated AE of freezing phenomenon (10.0% placebo vs. 0.0% DFP; p=0.0370). There was no significant group difference in the rates of any other event.

Adverse events that were considered to be at least possibly related to study product were identified as adverse drug reactions (ADRs). Forty-four (12.2%) of the 362 AEs in the placebo group and 143 (21.3%) of the 670 AEs in the DFP group were considered to be ADRs. The most common were decreased serum ferritin, in 16.7% (5) of the patients in the placebo group and 32.8% (19) in the DFP group; and iron deficiency, in 10.0% (3) and 15.5% (9), respectively. The only ADR for which the group difference was statistically significant was anaemia (p=0.0136).

A total of 1068 AEs were reported during deferiprone treatment in the extension study: 206 in 22 placebo-DFP patients in the extension study, 505 in 44 DFP-DFP patients in the initial study, and 357 in 42 DFP-DFP patients in the extension study. For both treatment groups, the SOCs in which the most patients reported at least one type of AE were Nervous system disorders (85.3% of patients overall), Infections and infestations (64.7%), General disorders and administration site conditions (63.2%), Gastrointestinal disorders (48.5%), Investigations (48.5%), Musculoskeletal and connective tissue disorders (47.1%), and Injury, poisoning and procedural complications (42.6%). For the DFP-DFP group, there was no significant difference across studies in the rate of any SOCs (all p-values > 0.05).

For the placebo-DFP group, 19 (9.2%) of the 206 reported AEs were considered to be ADRs, while for the DFP-DFP group, these numbers were 85 (16.8%) of the 505 AEs in the initial study and 49 (13.7%) of the 357 AEs in the extension study.

Numerical increase in rates of dystonia and serum ferritin decrease were observed between studies TIRCON and T-EXT in patients treated with DFP-DFP. The applicant clarified that this was related to long term observation period.

In the pivotal study as in the safety population, infections were reported especially bronchitis, Influenza, Nasopharyngitis, pneumonia and Upper respiratory tract infection. If note, such infection may be expected taking into account that PKAN patients may have infectious complications, mainly secondary to pulmonary aspiration in the context of dysphagia or infections related to underlying conditions such as use of deep brain stimulation and use of a baclofen pump. The applicant proposes to add in section 4.8 of the SmPC in this SOC, the PT Rash pustular and PT skin infection. Both AEs were reported once and are not considered as ADR with Ferriprox® at the time being.

Regarding the ADRs that are proposed in the table of adverse reactions in section 4.8 of the SmPC, different Tabulated lists of ADRs may be considered (one taking into post marketing data and the known safety profile of DFP and one with specific ADR following safety results in TIRCON studies).

All PT that are not known with ferriprox® and are not considered related to DFP should be deleted

The applicant was also requested to consider how to manage patients with iron deficiency before to start DFP as patients with iron deficiency (e.g. defined by Fe:TIBC ratio <15%, or serum ferritin <12 ng/mL) were excluded from TIRCONV12012 studies, contraindications may be considered. The applicant proposes to include a recommendation in the Upkanz SmPC to consider dose reduction if anemia and/or decreased serum ferritin values are not resolved with iron supplementation. The SmPC has also been modified to advise the prescribers to check the patient's body iron load based on the serum ferritin values and in cases of iron deficiency (serum ferritin values < 12ng/mL) to correct the body iron with iron supplementation prior to initiation of Upkanz. The proposal is partially acceptable :

- The SmPC should be more descriptive and clearly mentioned that the management of anaemia that is proposed is based on clinical trial experience.

- The frequency of the monitoring of patient's body iron load (Monitoring of serum ferritin and for signs of anaemia) could be clearly mentioned in the SmPC: before treatment start and then regularly (a frequency might be clearly proposed by the applicant instead of "regularly").

- Initiation of DFP treatment should be considered only in patients who do not present anemia. This should be clearly written in the SmPC

- Dose reduction recommendation cannot be proposed without the detailed methods of reduction (which dose, how long) and without insurance of efficacy of a reduced dose. The stop of DFP should be considered instead of a dose reduction. (**OC**)

The applicant was requested to consider a regular monitoring of the CBC (including neutropenia risk and anemia) overall. The applicant has revised section 4.4 subsection "Neutropenia/Agranulocytosis" of the Upkanz SmPC including the black box. It is aligned with the Ferriprox® SmPC. Contraindications should be added as it is mentioned in the SmPc of Ferriprox® (**OC**).

Frequency of severe AE was higher in DFP group compared to placebo group (8,7% vs 4,1 %, respectively). Severe events of dystonia were reported in 10.0% (3) of placebo patients and in 13.8% (8) of DFP patients; severe events of condition aggravated in 10.0% (3) and 3.4% (2),respectively; and severe events of laceration in 3.4% (2) of DFP patients. All other AEs that were rated as severe were seen in only 1 patient.No patients died during the study.

There were a total of 72 SAEs in the TIRCON2012V1 study: 23 in 10 (33.3%) patients in the placebo group, and 49 in 18 (31.0%) patients in the DFP group.Most SAEs were seen in only 1 patient. Those that were seen in more than one were neutropenia (2 patients in the placebo group, 5 in the DFP group), dystonia (2 and 3, respectively), medical device battery replacement (1 and 2, respectively), bronchitis and pneumonia (2 each in the DFP group), and vomiting, syncope, pneumonia aspiration, and gastrointestinal tube insertion (1 patient in each group). There was no significant group difference ($p > 0.05$) in the rate of any SAE.

Nine SAEs, 2 events in 2 placebo patients and 7 events in 6 DFP patients, were deemed to be at least possibly related to study product. In the placebo group, 2 patients each had 1 occurrence of neutropenia, while in the DFP group, 1 patient had an event of moderate dystonia, 4 patients each had 1 event of neutropenia, and 1 patient had 2 events of neutropenia. There were no significant group differences in the rates of any of these SAEs.

All other SAEs were considered to not be related to study product. Apart from 1 patient in the DFP group who had aspiration pneumonia, all patients recovered without sequalae.

During the extension study TIRCON2012V1-EXT 6 serious adverse drug reaction were observed during the study. None of the cases was classified as severe.

No patients died during the TIRCON2012V1 study. Two patients died during TIRCON2012V1-EXT: one patient (placebo-DFP) of aspiration pneumonia and multi-organfailure, and the other (DFP-DFP) of aspiration after vomiting. Neither of the deaths was considered to be related to study treatment.

Statistically significant differences were observed in DFP group for albumin (decrease, p=0.047), GGT (increase, p=0.0002) and glucose (increase, p=0.0416) in the Study TIRCON2012V1. Furthermore, in the extension study, statistically significant differences were observed for AST (increase in both PLB-DFP and DFP-DFP groups, p=0.0128 and p=0.083, respectively), potassium (decrease, p=0.0041), total protein ($p<0.001$).

During both studies TIRCON2012V1 and TIRCON2012V1-EXT 7 patients discontinued due to AEs. Three of the events were neutropenia. The applicant was requested to clarify if withdrawals from the compassionate use program (14 patients in total) were due to AEs**.** The main reasons for withdrawal do not seem to be due to AEs, but overall, all the provided reasons might suggest lack of efficacy of deferiprone in these patients (14/23).

3.3.10. Conclusions on clinical safety

The risks for adverse events and other safety parameters do not appear to be a safety concern as most of the reported AEs can be considered as expected taking into account the known safety profile of deferiprone (Ferriprox®). Of note, the most serious adverse event with Ferriprox® is agranulocytosis. However, no cases of agranulocytosis were reported with Upkanz. This risk cannot be excluded as this is idiosyncratic, unpredictable and not dose-dependent.

Many adverse events related to neurologic disorders potentially due to the progression of the disease were reported. The main AEs reported were dystonia and condition aggravated.

Overall, the AE profile is consistent with what is known for deferiprone in other indication (e.g. Ferriprox® in thalassemia patients, 75 mg/kg/day), despite the lower recommended dose (30mg/kg/day in PKAN) with no unexpected findings. Some safety related concerns are still pending and outlined in the LoOI. These safety issues could be resolved if the applicant updates the SmPC.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

Summary of safety concerns:	
Important identified risks	Use in pregnancy Neutropenia
Important potential risks	Agranulocytosis
Missing information	Patients with iron deficiency Off-label use Long-term safety data

3.4.2. Discussion on safety specification

The applicant agrees with Rapporteurs' requests to provide a new version of RMP taking into account the summary of safety specification that was proposed by the Rapporteurs during the initial assessment.

Further amendments to the safety specifications are requested. Considering that no specific risk is targeted with "off-label use" safety concern, it should be removed from the RMP but closely monitored through PSURs. Also, the safety concern "Use in pregnancy" should be renamed "Teratogenicity", since teratogenicity was identified as a risk.

The summary of safety concerns should be updated to:

Summary of safety concerns:	
Important identified risks	Teratogenicity Neutropenia
Important potential risks	Agranulocytosis
Missing information	Patients with iron deficiency Long-term safety data

Summary of safety concerns might be acceptable depending on outcome of the marketing authorisation by the CHMP.

3.4.3. Conclusions on the safety specification

In view of the proposed indication, the safety specification should be updated in line with the known profile of deferiprone:

Summary of safety concerns:	
Important identified risks	Teratogenicity Neutropenia
Important potential risks	Agranulocytosis
Missing information	Patients with iron deficiency Long-term safety data

3.4.4. Pharmacovigilance plan

The applicant considers that routine pharmacovigilance activities are sufficient in the post-authorization setting for deferiprone beyond adverse reactions reporting and signal detection. The applicant also proposes a follow-up questionnaire for agranulocytosis and neutropenia to collect detailed information about each event.

Summary of planned additional PhV activities from RMP

No additional pharmacovigilance studies (category 1-3) are planned or ongoing for deferiprone.

However, due to the limited number of patients included in TIRCON studies for a short period of time, additional PhV activities will be needed to further characterize the safety profile of the product in the PKAN population. Collection of safety data through a specific existing registry is needed to further investigate all safety concerns in the PKAN population.

Regarding routine pharmacovigilance activities in case of a favourable outcome of the marketing authorization by the CHMP, post-marketing monitoring through PSURs with a 3-year frequency is not considered appropriate, considering the lack of data in this particular population. The EURD list necessitates revision and separated assessment of deferiprone for thalassemia and PKAN indications with a 1-year frequency submission for Upkanz, which has been accepted by the applicant. Indeed, since PKAN is a rare disease, a PSUR frequency of 1 year is considered to be a better option than a 6-month frequency since few patients would benefit from this treatment.

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is not sufficient to identify and characterise the risks of the product in the PKAN population. Due to the limited number of patients included in TIRCON studies for a relatively short period of time, collection of long term data through a PASS in an existing registry is needed in case of favorable outcome from the CHMP to further monitor all safety concerns in the PKAN population.

In addition, separated assessment of safety data of deferiprone for thalassemia and PKAN indications in post-marketing through PSUR is needed.

Finally, the applicant commits to update the pharmacovigilance plan according to revised safety specification.

3.4.5. Risk minimisation measures

Routine Risk Minimisation Measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Teratogenicity	Routine risk minimisation measure: • SmPC sections 4.3, 4.6, 5.3 Additional risk minimisation measure: • Patient/carer reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for agranulocytosis and neutropenia. • Real-time reviews of single cases. • Scheduled reviews of aggregate data from ARGUS to identify relevant changes in reporting frequency or patterns of adverse events. • Aggregate reviews, at pre-specified intervals, of product quality complaint cases with associated adverse events and lot numbers, to identify safety signals related to product quality and manufacturing. • Analysis of the MAH's nonclinical, clinical and epidemiological study results. Additional pharmacovigilance activities: None.
Neutropenia	Routine risk minimisation measures: • SmPC section 4.4	
Agranulocytosis	Routine risk minimisation measures: • SmPC section 4.4 Additional risk minimisation measures: • Patient/carer reminder card	
Lactation toxicity	Routine risk minimisation measure: • SmPC sections 4.3 and 4.6	
Patients with iron deficiency	Routine risk minimisation measures: • SmPC section 4.4	
Patients currently taking other iron chelators	Routine risk minimisation measures: • SmPC section 4.4	
Long-term safety data	No risk minimisation measure	

Additional risk minimisation measures

The applicant proposes to include a wallet-sized, tear-away, patient/carer cards within the Labelling and Packaging Leaflet (Annex III) for the risk Agranulocytosis. This card is proposed in order to increase patient awareness of the importance of regular monitoring of the neutrophil count during treatment with Upkanz and of the significance of any symptoms of infection while taking Upkanz. The patient reminder card is also proposed for the important identified risk Use in pregnancy.

As it is already in place for Ferriprox, deferiprone marketed in thalassemia indication, the proposal for a patient card to reduce the risk of agranulocytosis and use in pregnancy is endorsed. The need of such a card is increased in PKAN patients which are at higher risk of infectious complications mainly

aspiration pneumonia in a context of dysphagia and also local infections of implantable devices (cerebral stimulation system or intraventricular baclofen pump).

This card would also reduce the risk of use in pregnancy in a sub population of PKAN patients who are sexually active since pregnancy is contra-indicated in the product information. Of note, a stand-alone format not attached with the PIL may be considered regarding the patient card (Annex IID).

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the PKAN indication with minor revisions.

PRAC Outcome

During its plenary meeting held from 11-14th May, overall the PRAC supported the assessment of the pharmacovigilance plan and risk minimisation measures as detailed in the assessment report.

However, the PRAC suggested to CHMP that "Off-label use" should be removed from the summary of safety concerns. "Off-label use" is not per se a safety concern as it needs to be linked to a corresponding risk resulting for the patient treated with deferiprone and it will be challenging to collect information during a post-authorization study, outside of the approved indication. In addition, relevant data on off-label use will be collected and assessed in the remit of PSURs.

The PRAC also suggested to CHMP to rename the safety concern "Use in pregnancy" to "Teratogenicity", since "use in pregnancy" is usually included as missing information and in this specific case teratogenicity was identified as a risk.

The PRAC supported the need to further study the product in an existing registry and the inclusion of a patient card as risk minimisation measure to increase patients' awareness and deliver the key risk minimisation messages for the safe use of the medicinal product. The patient card should be distributed as a stand-alone card by the prescribing physician in order to facilitate discussions at the time of prescription.

In conclusion, the RMP for Upkanz (deferiprone) in the proposed indication is not acceptable and satisfactory responses to the questions detailed in the D180 LoOI assessment report (AR) should be submitted.

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.1 is not acceptable. The applicant commits to implement the revisions requested at D120 in an updated RMP version in a next round after the assessment of the CHMP.

3.5. Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

Based on lack of data in PKAN population, the PRAC Rapporteur is of the opinion that a separate entry in the EURD list for deferiprone is needed, as it cannot follow the already existing entry. The

requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The PSUR cycle for deferiprone used in PKAN population should follow a yearly frequency.

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of genetic disorders characterized by the focal accumulation of iron in the brain, usually in the basal ganglia. Pantothenate kinase-associated neurodegeneration (PKAN) is a rare disease that accounts for 30-50% of NBIA cases. Despite the different underlying genetic causes, many of the clinical manifestations of these disorders are similar, and in all cases, there is iron overload in a brain. However, no genetic or other specific therapies are available for this condition. There is, therefore, an urgent need for a therapy that could interrupt the pathologic process and slow the progression of the disorder.

4.1.2. Available therapies and unmet medical need

There are currently no approved disease-modifying therapies for NBIA and PKAN. Pharmacological and surgical interventions are aimed at palliation of symptoms. For many of the interventions that offer improvement of clinical symptoms, the period of benefit is however limited.

Pharmacological symptomatic treatments include anticholinergics, benzodiazepines and other anti-spasticity agents, alone or in combination to relieve spasticity and dystonia.

Deep brain stimulation (DBS) can also be used to relieve dystonia. Numerous case reports and series that include mixed NBIA etiologies report benefit in the first year or years with placement in the globus pallidus interna. However, benefit usually is not sustained as disease advances. Thalamotomy and pallidotomy have been performed in PKAN patients, sometimes with good symptomatic relief, for patients with severe disabling dystonia that is refractory to medical management. These ablative procedures have been largely replaced by DBS.

Tics, chorea and myoclonus are usually treated with noradrenergic agents, such as clonidine, guanfacine or atomoxetine.

It is acknowledged that there is an unmet medical need for the treatment of NBIA, including PKAN

4.1.3. Main clinical studies

The main evidence of efficacy submitted is a single Phase 3, multi-center, double-blind, randomized, placebo-controlled study conducted in patients with PKAN. Eligible participants were randomized in a 2:1 ratio to receive either deferiprone oral solution or placebo, with the dose titrated up to a maximum of 15 mg/kg b.i.d. for a total daily dosage of 30 mg/kg.

4.2. Favourable effects

The significant change observed in the study was a reduction in the level of iron in the globus pallidus, as assessed by MRI R2* in participants who received deferiprone. In the placebo group, there was virtually no change in iron content (a mean decrease of 0.50 Hz), while in the DFP group there was a mean decrease of 36.1 Hz, for a significant group difference of -35.6 Hz ($p < 0.0001$).

4.3. Uncertainties and limitations about favourable effects

After 18 months of treatment, the total BAD score in DFP-treated patients had worsened by 2.48 points compared with 3.99 points in the placebo group, for a difference of 1.51 points in favor of deferiprone. The difference did not reach significance (p=0.0761, m ITT population; p=0.1320 PP population).

Similarly, no subjective change was detected as assessed by the PGI-I At Month 18, the LSmean scores were 4.66 for placebo and 4.55 for DFP, with no significant group difference (p=0.7279), indicating that, overall, patients did not detect either an improvement or a worsening in their condition from baseline. No significant differences between studied groups were seen in the findings of any of the other efficacy measures including UPDRS score, FIM measure (besides WeeFIM – cognition score p=0.0324), PedsQL scale, PSQI index, and Likert scale.

Deferiprone demonstrated an activity by decreasing iron levels in a brain region relevant for PKAN patients (globus pallidus) at 18 months. This activity was however not associated with an improvement in dystonia or a global improvement of patients, as assessed by the BAD and PGI-I scales (co-primary endpoints). Furthermore,the population in which the reduction of iron content in globus pallidus was demonstrated was not the mITT population. Patients who were able to undergo this assessment at the start of the study (16 placebo, 24 DFP) and end of the study (13 placebo, 19 DFP) were analyzed.

In both groups, a worsening in BAD score was noticed after 18 months of treatment with a LS mean (LSM) change from baseline of +2.48 points for the deferiprone group and LSM change from baseline of +3.99 points for the placebo group. A numerical advantage was observed for the deferiprone-treated group. With regards to PGI-I, no change or a minimal worsening was noticed after 18 months of treatment in both groups, with a LSM change from baseline of 4.55 points for the deferiprone group and LSM change from baseline of 4.66 points for the placebo group.

None of the group differences for both co-primary endpoints (change from baseline to month 18 for the BAD total score and the PGI-I score at month 18) reached statistical significance in the pre-defined efficacy analyses (MMRM model, mITT), which was defined as a p-value less than 0.05. The PP analysis and the sensitivity analysis using an ANCOVA model were consistent with the mITT analysis.

With regards to clinical relevance of the first co-primary endpoint, the observed difference of -1.51 points (-3.19, 0.16) on BAD total score was almost 70% lower than the expected planned treatment effect (≥ 5-point reduction).

In the 18-month extension study, BAD total scores continued to worsen over time in both groups (placebo-DFP and DFP-DFP) with a similar progression (1.4 points).

Responders were defined as patients in whom the BAD total score or PGI-I score either improved or remain unchanged at 18 months. Using this definition, the percentage of responders at 18 months for BAD total score was 14.3% in the placebo group and 36.4% in the deferiprone group. The deferiprone versus placebo odds ratio (95% CI) was 3.17 (0.84-12.02). With regards to PGI-I, the percentage of responders at 18 months was 39.3% in the placebo group and 52.7% in the deferiprone group. The deferiprone versus placebo odds ratio (95% CI) was 1.60 (0.59-4.34). The percentages of responders at 18 months for BAD total score and PGI-I were numerically higher in the deferiprone group than in the placebo group but differences were not statistically significant.

No statistically significant changes in Parkinsonian symptoms were observed at 18 months on UPDRS parts I, II, III and VI in deferiprone-treated patients when compared to placebo-treated patients.

When considering functional scales (WeeFIM, FIM), no statistically significant changes in overall functional abilities at 18 months were observed in deferiprone-treated patients when compared to placebo-treated patients.

No statistically significant changes were observed in Parkinsonian symptoms at 18 months, as assessed by UPDRS parts I, II, III and VI in deferiprone-treated patients when compared to placebo-treated patients, nor were there statistically significant changes in quality of life (as assessed by PedsQL) or sleep quality and disturbances (as assessed by PSQI) at 18 months in deferiprone-treated patients when compared to placebo-treated patients.

The applicant also carried out subgroups analyses in classic/atypical PKAN. In both placebo and deferiprone groups, classic PKAN and atypical PKAN patients worsened on dystonia from baseline to month 18, as assessed by BAD total score. The LSM difference (95% CI) between groups for classic PKAN patients was -0.81 points (-3.68, 2.06), which was not statistically different. In contrast, the applicant reported that the LSM difference (95% CI) between groups for atypical PKAN patients was -2.19 points (-4.00, -0.38), which was statistically significant (p=0.0187). These data would suggest that patients with atypical PKAN and treated with deferiprone display a significant decrease in dystonia from baseline to month 18 when compared to patients treated with placebo. No subgroup analyses pertaining to neuropsychiatric symptoms, which are more prominent in atypical PKAN patients were carried out. In addition,no statistically significant changes in Parkinsonian symptoms at 18 months were observed for atypical PKAN on UPDRS parts I, II and III in deferiprone-treated patients when compared to placebo-treated patients.

4.4. Unfavourable effects

Generally safety database is considered rather limited. In the Study TIRCON2012V1in the DFP group (N=58), total exposure was 77.86 person-years, with a mean of 1.34 years (SD=0.39). Of the 76 participants who completed the study TIRCON2012V1 (both from placebo and DFP groups), 68 were enrolled in the extension study (Study TIRCON2012V1-EXT): 24 who had previously received placebo (the placebo-DFP group) and 44 who had previously received deferiprone (the DFP-DFP group).

The pooledTIRCON2012V1 and TIRCON2012V1-EXT population include 82 PKAN patients exposed to deferiprone. Of these, 68 patients has been exposed to deferiprone for ≥ 12 months, and 54 for ≥18 months, respectively. This data is supplemented by 72 patients with FRDA (65 patients) and superficial siderosis (3 patients), NBIA (2 patients) and 2 patients with PKAN.

Among the common AEs reported in the 82 PKAN patients treated with deferiprone weregastrointestinal disorders such as nausea, abdominal pain upper, vomiting and diarrhoea, as wellas arthralgia and neutropenia. The most commonly reported ADRwas serum ferritin decreased (29.3%), followed by neutrophil count decreased (14.6%). The events related to body iron reduction, such as decreased serum ferritinand anaemia were also reported as ADRs. Neutropenia was reported in 8.5% (7) patients treated with deferiprone and in 2 (6.7%) placebo patients from TIRCON2012V1 and TIRCON2012V1-EXT. There were no occurrences of agranulocytosis in TIRCON2012V1 and TIRCON2012V1-EXT studies. No events of agranulocytosis were also observed in deferiprone-treated PKAN patients who participated in TIRCON2012V1-COMP, in patients with localized brain iron overload (NBIA and superficial siderosis) from LA-04/06B, and in patients with Friedreich's ataxia from LA29-0207 and LA29-0207-EXT. No events of neutropenia occurred in TIRCON2012V1-COMP. Six events of neutropenia occurred in 6 patients who participated in the LA29-0207 and LA29-0207-EXT studies.

In the pivotal study rates of AEs were similar between the placebo and DFP groups for any AEs (100.0% vs. 98.3%), serious AEs (33.3% vs. 31.0%), and severe AEs (26.7%vs. 29.3%), but were

higher in the DFP group for AEs related to study treatment (43.3% vs. 79.3%)and AEs leading to withdrawal from the study (0.0% vs. 6.9%). The only category that reachedsignificance was that of AEs related to treatment (p=0.0015).

4.1% (15) and 8.7% (58) of events reported in theplacebo and DFP groups, respectively, were rated as severe.Severe events of dystonia were reported in 10.0% (3) of placebo patients and 13.8% (8) of DFPpatients; severe events of condition aggravated in 10.0% (3) and 3.4% (2), respectively; andsevere events of laceration in 3.4% (2) DFP patients. All other AEs that were rated as severewere seen in only 1 patient. Statistically significant difference between There was a significant group difference for two events: DFP patients had a significantly higher rate of anaemia (0% placebo vs. 20.7% DFP; p=0.0067), and placebo patients had a significantly higher rate of the PKAN-associated AE of freezing phenomenon (10.0% placebo vs. 0.0% DFP; p=0.0370).

Forty-four (12.2%) of the 362 AEs in the placebo group and 143 (21.3%) of the 670 AEs in the DFP group were considered to be ADRs. The most common were decreased serum ferritin, in 16.7% (5) of the patients in the placebo group and 32.8% (19) in the DFP group; and iron deficiency, in 10.0% (3) and 15.5% (9), respectively. The only ADR for which the group difference was statistically significant was anaemia (p=0.0136).

A total of 1068 AEs were reported during deferiprone treatment in the extension study: 206 in 22 placebo-DFP patients in the extension study, 505 in 44 DFP-DFP patients in the initial study, and 357 in 42 DFP-DFP patients in the extension study. For both treatment groups, the SOCs in which the most patients reported at least one type of AE were Nervous system disorders (85.3% of patients overall), Infections and infestations (64.7%), General disorders and administration site conditions (63.2%), Gastrointestinal disorders (48.5%), Investigations (48.5%), Musculoskeletal and connective tissue disorders (47.1%), and Injury, poisoning and procedural complications (42.6%). For the DFP-DFP group, there was no significant difference across studies in the rate of any SOCs (all p-values > 0.05).

For the placebo-DFP group, 19 (9.2%) of the 206 reported AEs were considered to be ADRs, while for the DFP-DFP group, these numbers were 85 (16.8%) of the 505 AEs in the initial study and 49 (13.7%) of the 357 AEs in the extension study.

Frequency of severe AE was higher in DFP group compared to placebo group (8,7% vs 4,1 %, respectively). Severe events of dystonia were reported in 10.0% (3) of placebo patients and in 13.8% (8) of DFP patients; severe events of condition aggravated in 10.0% (3) and 3.4% (2), respectively; and severe events of laceration in 3.4% (2) of DFP patients. All other AEs that were rated as severe were seen in only 1 patient. No patients died during the study.

Two patients died during TIRCON2012V1-EXT: one patient (placebo-DFP) of aspiration pneumonia and multi-organfailure, and the other (DFP-DFP) of aspiration after vomiting.

Statistically significant differences were observed in DFP group for albumin (decrease, p=0.047), GGT (increase, p=0.0002) and glucose (increase, p=0.0416) in the Study TIRCON2012V1. Furthermore, in the extension study, statistically significant differences were observed for AST (increase in both PLB-DFP and DFP-DFP groups, p=0.0128 and p=0.083, respectively), potassium (decrease, p=0.0041), total protein (p<0.001).

4.5. Uncertainties and limitations about unfavourable effects

The majority of patients enrolled in TIRCON2012V1 (85.4% overall; 83.1% in the DFP group) and TIRCON2012V1-EXT (80.9%) completed all 18 months of treatment.

In both groups (placebo and DFP), the most commonly reported adverse event was dystonia (46.7% in the placebo group, 43.1% in the DFP group), followed by pyrexia (43.3% placebo, 27.6% DFP).

Two patients died during TIRCON2012V1-EXTbut autopsy was not performed. While death in Case 2017AP006499 seems not related to study product (treatment was discontinued 17 days before the patient died), Case 2017AP007118 concerns a fatal report of vomiting and aspiration of patients on study treatment, which requires further justification in terms of potential relation to deferiprone.

No data regarding changes of prolactin level in patients with PKAN were presented.

4.6. Effects Table

Table 4.6.1. Effects Table for Upkanz the treatment of neurodegeneration with brain iron accumulation.

Effect	Short Description	Unit	Treatment Upkanz (SE)	Control Placebo (SE)	Uncertainties/ Strength of evidence	References
Favourable Effects						
MRI R2* Score			-0.50 (3.97)	-36.1 (3.11)		1
Unfavourable Effects						
AEs related to study treatment		%	79.3	43.3	P=0.0015	1
Rate of AEs leading to withdrawal from the study		%	6.9	0	Not significant	1
Rate of anaemia		%	20.7	0	P=0.0067	1

Abbreviations:
Notes:
1. Clinical study report - TIRCON2012V1.

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Deferiprone demonstrated an activity by decreasing iron levels in a region relevant for PKAN patients (globus pallidus) after 18 months of treatment. This decrease is consistent with the activity of an iron chelating agent that crosses the blood brain barrier. However, the population in which the reduction of iron content in globus pallidus was demonstrated was not the mITT population.

The clinical relevance of a decrease in iron levels in the globus pallidus of PKAN patients in this study could however be questioned. Indeed, whether accumulation of iron is a direct cause of neurodegeneration still remains debated (see reviews: Hayflick and Hogarth, 2011, Rouault, 2013, Schneider et al, 2013, Meyer et al, 2015, Jabeen and Fu, 2017).

In keeping with this, previous pilot studies demonstrated that administration of deferiprone at similar doses (25-30 mg/kg/day) for 6 to 12 months resulted in decreases in iron contents in the globus

pallidus and provided weak evidence with regards to improvement in clinical symptoms of the disease, including dystonia (Abbruzzese et al, 2011, Zorzi et al, 2011, Cossu et al, 2014).

In the TIRCON2012V1 study, the decrease in iron levels in the globus pallidus of the subgroup of patients who underwent MRI is not associated with an improvement in dystonia or a global improvement of patients, as assessed by the BAD and PGI-I scales (co-primary endpoints).

More specifically, the statistical significance was not considered compelling in this single pivotal study since the two co-primary endpoints were not met. In other words and according to the statistical analysis plan of the applicant, the null hypothesis of no difference was not rejected at a 2-sided level of significance for both co-primary endpoints and therefore, the study is considered negative. The PP analysis and the sensitivity analysis using an ANCOVA model were consistent with the mITT analysis.

In the 18-month extension study, BAD total scores continued to worsen over time in both groups (placebo-DFP and DFP-DFP) and with a similar progression (1.4 points). The PGI-I assessment in the extension study was also consistent with the PGI-I assessment of the single pivotal study, with no perceived change in PKAN symptoms after 18 months or 36 months of treatment.

With regards to clinical relevance of the first co-primary endpoint, the observed difference of -1.51 points (-3.19, 0.16) on BAD total score was almost 70% lower than the expected planned treatment effect (≥ 5-point reduction). As a result, the clinical relevance can be considered doubtful.

Secondary endpoints demonstrated weak evidence of an efficacy for deferiprone. Due to the number of secondary criteria, results that may favour deferiprone over placebo are confounded by multiplicity issues and lack of methods to control the overall type I error.

Responders were defined as patients in whom the BAD total score or PGI-I score either improved or remain unchanged at 18 months. This definition could be questioned. Indeed, a recent review reported that clinical stabilisation may be a misleading outcome measure in PKAN patients since the clinical progression in the atypical (late onset) form is non-linear with rapid deterioration in the first five years and relative stabilisation after that (Dusek et al, 2016). Given that patients with atypical PKAN represented 52% of the studied population (45/86, with 16 patients receiving placebo and 29 receiving deferiprone) and that the average duration of disease was 12 years, pooling patients with improved and unchanged BAD scores at 18 months may lead to a responder analysis that is not the most clinically relevant.

Patients with atypical PKAN (later onset, slower progression of disease) treated with deferiprone had a statistically significant decrease in dystonia at month 18 when compared to atypical PKAN patients treated by placebo, as assessed by BAD total score. Such evidence may considered weak when considering that subgroups analyses have a supportive or exploratory role after the primary objective has been accomplished, which was not the case in this study.

For some scales under investigation (BAD, WeeFIM, FIM), the applicant carried out subscale analyses when total scores for these scales did not reach significance. The relevance of statistically significant differences between groups on these subscales appears questionable.

From a clinical point of view, there is currently no data available to justify acceptance of deferiprone in the proposed indication.

Moreover, the pharmacokinetic study programme did not include any studies carried out with the proposed drug form. Individual studies concerned: LA20-BA study (500 mg film coated tablets and solution 100mg/ml); LA21-BE study (500 mg film coated tablets and solution 100mg/ml), LA39-0412 study (500 mg film coated tablets), LA40-0412 study (500 mg film coated tablets), LA54-0116 study (500 mg film coated tablets), LA56-0117 study (600 mg delayed release tablets). Given the absence of a study that would demonstrate bioequivalence between the solution of deferiprone 80 mg/ml and

other forms of deferiprone, it is currently not possible to extrapolate the results of studies conducted with the other forms to the requested form.

4.7.2. Balance of benefits and risks

The efficacy of Upkanz is considered not to outweigh the risks for the treatment of patients with PKAN, on the basis of efficacy and safety shown in the pivotal study and extension study

4.7.3. Additional considerations on the benefit-risk balance

n/a

4.8. Conclusions

The overall B/R of Upkanz in the treatment of the treatment of neurodegeneration with brain ironaccumulation (including PKAN) is currently negative.

5. Biosimilarity assessment

N/A