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APPLICATION NUMBER:

208030Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

SUBMISSION NUMBER	NDA 208030
SUBMISSION DATE	11/17/2014
SUBMISSION TYPE	505(b)(1)
BRAND NAME	FERRIPROX
GENERIC NAME	Deferiprone (DP)
DOSAGE FORM	Oral Solution, 100 mg/mL
DOSAGE REGIMEN	75–99 mg/kg/day
INDICATION	Transfusional iron overload due to thalassemia syndromes
APPLICANT	ApoPharma Inc.
OND DIVISION	Division of Hematology Products
OCP DIVISION	Division of Clinical Pharmacology V
OCP REVIEWER	Sriram Subramaniam, Ph.D.
OCP TEAM LEADER	Bahru Habtemariam, Pharm.D.

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1. EXECUTIVE SUMMARY

ApoPharma submitted NDA application for deferiprone oral solution for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The application cross-references Apoharma's Ferriprox[®] (deferiprone) 500 mg film-coated tablets (NDA 021825), approved on October 14, 2011. The drug product in the current NDA is submitted for the same indication, dose, and route of administration, and has the same active ingredient (deferiprone) as that of the approved Ferriprox[®] tablets. The difference between the two drug products exists in the formulation: 100 mg/mL oral solution versus the marketed 500 mg tablet.

ApoPharma conducted a clinical pharmacology study in healthy subjects in order to determine whether the proposed oral solution formulation is bioequivalent to the marketed tablet formulation. The BE study results showed that ApoPharma's deferiprone oral solution and Ferriprox[®] tablet are bioequivalent.

1.1 RECOMMENDATIONS

This application is acceptable from a clinical pharmacology perspective. The Office of Clinical Pharmacology recommends approval of this NDA.

1.2 POST-MARKETING REQUIREMENT AND POST-MARKETING COMMITMENT

There are no additional clinical pharmacology requested PMRs or PMCs.

Signatures

Sriram Subramaniam, Ph.D.
Reviewer
Division of Clinical Pharmacology V

Bahru Habetmariam, Pharm.D.
Acting Team Leader
Division of Clinical Pharmacology V

Cc: DDOP: CSO - K Kolibab; MTL - K Robie Suh; MO – A Dmytrijuk
DCPV: Reviewer - S Subramaniam; Deputy DD - B Booth; DD - A Rahman

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

ApoPharma's to-be-marketed deferiprone oral solution in the current NDA is submitted for the same indication, dose, and route of administration, and includes the same active ingredient (deferiprone) as that of the approved Ferriprox[®] 500 mg film-coated tablets. The difference between the two drug products is limited to the dosage form (i.e., 100 mg/mL oral solution versus the marketed 500 mg tablet).

To assess the relative bioavailability (BA) of ApoPharma's deferiprone oral solution, the Applicant submitted a study comparing pharmacokinetic (PK) of the to-be-marketed oral solution against the marketed Ferriprox[®] tablet (Study LA21-BE).

Study LA21-BE demonstrated that the relative bioavailability of ApoPharma's to-be-marketed deferiprone oral solution is comparable to the currently marketed Ferriprox 500 mg tablet, in that the primary PK parameters C_{max}, AUC(0-t), and AUC(0-∞) for the test product demonstrated bioequivalence (BE) against the Ferriprox tablet (see table below).

Parameter (unit)	Least Squares Geometric Mean		Ratio of Test / Reference	90% Confidence Interval of Ratio
	Ferriprox Soln	Ferriprox [®] Tablet		
AUC _{0-t} (h*µg/mL)	48.26	47.94	1.01	98.00 – 103.41
AUC _{0-∞} (h*µg/mL)	49.35	49.15	1.00	97.77 – 103.13
C _{max} (µg/mL)	18.90	19.23	0.98	88.91-108.67

2. CLINICAL PHARMACOLOGY FINDINGS

Study LA21-BE was an open label, single-dose, randomized, two-treatment, two-period crossover study to compare the bioavailability of ApoPharma's to-be-marketed deferiprone oral solution (test) against the approved Ferriprox[®] 500 mg tablet (reference) under fasting conditions. A total of 42 healthy adult volunteers (29 males and 13 females) were recruited and 41 (28 males and 13 females) completed the study.

The study consisted of two treatment periods. The subjects were randomized to one of two sequences (test in Period 1 then reference in Period 2 or reference in Period I then test in Period II) for dosing. In each period, blood samples were collected at predose (0 hr), and at 0.083, 0.167, 0.333, 0.5, 0.75, 1, 1.333, 1.667, 2, 2.5, 3, 4, 5, 6, 8, and 10 hours postdose. Each treatment period was separated by a washout period of 7 days.

In each period, a dose of 1500 mg of deferiprone was administered. According to Apopharma, this dose does not exceed the usual recommended dose (75 mg/kg/day) for any subjects that weigh at least 50 kg, and was expected to yield quantifiable concentrations of deferiprone in serum throughout the sampling time.

Prior to the study, it was established that the peak concentration (C_{max}), area under the concentration time curve (AUC) to the last time point (AUC_{0-t}) and AUC_{0-∞} geometric mean ratio 90% confidence intervals should be contained within 80%-125%. Summary BE statistics and descriptive statistics of the pharmacokinetic (PK) parameters of deferiprone are presented in Table 1 and Table 2.

Table 1: Summary BE Statistics (Serum Deferiprone), Study LA21-BE (n=41)
(Reviewer's analysis)

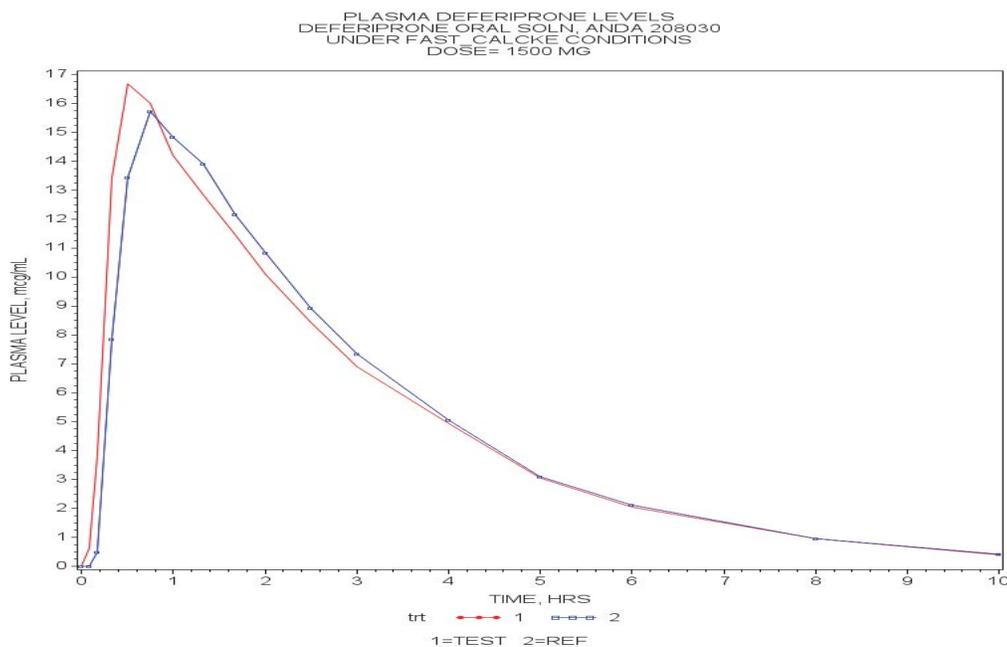
Parameter (unit)	Least Squares Geometric Mean		Mean Ratio % (Test / Reference)	90% Confidence Interval of Ratio
	Ferriprox Soln (Test product)	Ferriprox [®] Tablet (Reference Product)		
AUC _{0-t} (h*µg/mL)	48.26	47.94	1.01	98.00 – 103.41
AUC _{0-∞} (h*µg/mL)	49.35	49.15	1.00	97.77 – 103.13
C _{max} (µg/mL)	18.90	19.23	0.98	88.91-108.67

Table 2: Arithmetic PK Parameters of Deferiprone, Study LA21-BE

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUC _{0-t}	µhr/mL	49.451	23.03	29.91	83.70	49.244	24.40	32.93	87.07	1.00
AUC _{0-∞}	µhr/mL	50.609	23.47	30.58	87.86	50.498	24.49	33.47	90.06	1.00
C _{max}	µg/mL	19.729	31.03	10.60	38.50	20.456	38.17	11.60	43.80	0.96
T _{max}	hr	0.500	.	0.33	2.50	0.750	.	0.33	2.50	0.67
Ke	hr ⁻¹	0.409	12.83	0.32	0.54	0.408	13.96	0.32	0.55	1.00
THALF	hr	1.722	12.53	1.27	2.19	1.728	13.20	1.27	2.20	1.00

The 90% confidence intervals of the test-to-reference ratios of the geometric means for C_{max}, AUC_{0-t} and AUC_{0-∞} were within the acceptable BE limits of 80% to 125%. The sponsor's calculation was confirmed by the reviewer (Table 1, Figure 1). Therefore, the ApoPharma's to-be-marketed deferiprone oral solution and Ferriprox[®] tablets are bioequivalent.

Figure 1: Graphical Representation of DF Concentrations: Arithmetic Mean (Linear Scale)



Safety

From a safety perspective, this study did not appear to demonstrate any substantial differences between the formulations with regard to related adverse events (AEs) or serious AEs (Table 3). Following a 1500 mg dose, ten subjects (24%) had 26 AEs after administration of deferiprone solution and 6 subjects (14%) had 15 AEs after receiving deferiprone tablets. It should be noted that 9 of the 26 AEs following deferiprone oral solution belonged to Subject 42. Fatigue, headache, cold, somnolence and nausea were the commonly reported AEs for both formulations. However, fatigue was more common for solution formulation and headache was more frequent for the tablet formulation. According to the Ferriprox[®] tablet Package Insert¹, headache, abdominal pain, vomiting, and nausea are common AEs, and chills and somnolence were reported as post-marketing AEs. However, fatigue is not reported as an AE in the approved Package Insert. The AEs reported for subjects administered with the deferiprone oral solution were mild (85%) to moderate (15%), while AEs in subjects who received Ferriprox[®] tablets were all mild in Study LA21-BE. The incidence of drug-related AEs in the study was similar for the two formulations (77% vs. 80%). Subject 42 was withdrawn from the study due to vomiting at 4 minutes after receiving the solution formulation in Period 2. The subject later vomited at 17 minutes post-dose, and experienced chills, abdominal pain, hypoesthesia, dyspnea, and fatigue after 20 min to 1 hour post-dose. Blood in urine was detected after ~11 hours, and

¹ Ferriprox[®] tablet label dated 4/20/2012. Drugs@FDA

the subject was hyperventilating but vitals and oxymetry were normal. The AEs were reported as mild to moderate. All AEs, except blood in urine were resolved within 1-6 days. With the exception of blood in urine, all of Subject 42's AEs were considered related to the study medication. Refer to Clinical Review for more details with regards to safety evaluation of Subject 42. It is important to note that a reliable safety assessment cannot be made in a single, dose cross, over PK study due to the cross over study design and the short duration of study drug administration.

Table 3. Incidence of Adverse Events (all dose subjects, N=42)

Deferiprone oral solution

Ferriprox tablet

Body System Adverse event	Severity and relatedness to treatment						Total R+NR
	Mild		Moderate		Severe		
	R	NR	R	NR	R	NR	
Gastrointestinal disorders							
Abdominal discomfort	1 (4%) SN24	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Abdominal pain	1 (4%) SN42	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Nausea	0 (0%)	0 (0%)	1 (4%) SN42	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Vomiting	0 (0%)	0 (0%)	2 (8%) SN42	0 (0%)	0 (0%)	0 (0%)	2 (8%)
General disorders and administration site conditions							
Catheter site pain	0 (0%)	1 (4%) SN33	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Chills	1 (4%) SN42	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Fatigue	5 (19%) SN5 SN16 SN32 SN33 SN42	1 (4%) SN10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (23%)
Feeling cold	2 (8%) SN15 SN19	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)
Investigations							
Blood urine present	0 (0%)	1 (4%) SN42	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Nervous system disorders							
Disturbance in attention	0 (0%)	1 (4%) SN19	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Dizziness	2 (8%) SN42	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)
Headache	2 (8%) SN5 SN32	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)
Hypoesthesia	2 (8%) SN42	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)
Somnolence	0 (0%)	1 (4%) SN14	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Respiratory, thoracic and mediastinal disorders							
Dyspnoea	0 (0%)	0 (0%)	1 (4%) SN42	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Nasal congestion	0 (0%)	1 (4%) SN33	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)

Source data: Tables 10.3.1.1, 10.3.1.2, 10.3.1.3, 10.3.1.4, Appendix 12.2.2.2
 N = Total number of AEs in this treatment group
 R = Related to study treatment
 NR = Not related to study treatment
 SN = Subject number

Body System Adverse event	Severity and relatedness to treatment						Total R+NR
	Mild		Moderate		Severe		
	R	NR	R	NR	R	NR	
Eye disorders							
Abnormal sensation in eye	0 (0%)	1 (7%) SN37	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Gastrointestinal disorders							
Nausea	1 (7%) SN9	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
General disorders and administration site conditions							
Fatigue	2 (13%) SN5 SN18	1 (7%) SN9	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (20%)
Feeling cold	3 (20%) SN5 SN9 SN18	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (20%)
Nervous system disorders							
Headache	5 (33%) SN5 SN27 SN34	1 (7%) SN37	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (40%)
Somnolence	1 (7%) SN37	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)

Source data: Tables 10.3.1.1, 10.3.1.2, 10.3.1.3, 10.3.1.4, Appendix 12.2.2.2
 N = Total number of AEs in this treatment group
 R = Related to study treatment
 NR = Not related to study treatment
 SN = Subject number

In summary, the bioequivalence study LA21-BE demonstrates that the tablet and oral solution are bioequivalent with respect to AUC and Cmax. Also, no substantial differences in related AEs or serious AEs were seen between the two formulations.

Study LA20-BA:

During formulation development, Apopharma conducted an open label, single-dose, three-way crossover relative bioavailability study of Ferriprox (deferiprone) 500 mg tablets (3 x 500 mg dose) under fasting and fed conditions and earlier formulation of Deferiprone 100 mg/mL oral solution (1500 mg dose) under fasted conditions in 15 healthy subjects. This study was submitted and reviewed as part of NDA 021825 (DARRTS 09/24/2009). Compared to the oral solution formulation in Study LA21-BE, the oral solution formulation in Study LA20-BE used different flavors (b) (4) instead of sucralose cherry favor) and higher amount of glycerin (Module 3.2.P.2, SDN 1). Per ApoPharma, they subsequently

decided to develop a commercial liquid formulation of deferiprone based on the one used in the LA20-BA study. Therefore, the study LA20-BA is not the pivotal study for the current NDA.

3 INTRINSIC FACTORS

3.1 *What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response?*

The PK of deferiprone has not been studied in geriatric or pediatric populations, and the influences of race, gender, or obesity have not been established. The effects of renal and hepatic impairment on the PK and safety of deferiprone were reviewed previously following submission under NDA 021825 (DARRTS Reference ID 3694553). Renal impairment and mild to moderate hepatic impairment do not affect PK of deferiprone and its metabolite. The effect of severe hepatic impairment has not been studied. The renal and hepatic impairment sections of the Labeling were updated to reflect the renal and hepatic impairment study findings.

4 EXTRINSIC FACTORS

4.1 *Is there an in vitro basis to suspect in-vivo drug-drug interactions?*

Yes. Deferiprone is primarily eliminated via metabolism to the 3-*O*-glucuronide. Phenylbutazone, a UDP glucuronosyltransferase (UGT) 1A6 inhibitor, reduced the *in vitro* glucuronidation of deferiprone by 78% (N021825 DARRTS Reference ID 3109780). Since, there is no clinical data to support a dose reduction or enhanced safety monitoring, concomitant use of UGT1A6 inhibitors should be avoided with deferiprone.

5 GENERAL ATTRIBUTES

5.1 GENERAL BIOPHARMACEUTICS

The proposed formulation is an oral solution containing deferiprone at strength of 100 mg/mL, compared to the Ferriprox 500 mg tablet reference product.

Name: Deferiprone Oral Solution; Active ingredient: deferiprone

Formulation: Solution, Strength: 100 mg/mL

Manufacturer: (b) (4) Batch No.: (b) (4) Expiry Date: (b) (4)

Table 4. Description and Composition of the Proposed Deferiprone Oral Solution

Component and Quality Standard (and Grade, if applicable)	Function	Quantity per bottle (500 mL fill size)	Strength: 100 mg/mL (b) (4)	
				% (w/v)
Deferiprone (In-house)	Active drug substance	50.00 g**		10.0
Hydroxyethyl cellulose (b) (4) (NF/EP/BP)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Glycerin/Glycerol (USP/EP)				
Hydrochloric acid (NF/EP)				
Sucralose (NF/EP)				
Artificial cherry flavour (b) (4) (In-house)				
Peppermint oil (In-house)				
FD&C Yellow No. 6* (In-house)				
Purified water (USP/EP)				
Total		571.0 g (500 mL)		

(b) (4)

Reference Product

Name: Ferriprox®: USA marketed product; Active ingredient: deferiprone
 Formulation: Tablet, Strength: 500 mg
 Manufacturer: Apotex, Inc., Batch No.: GW4454, Expiry Date: April 2007

ANALYTICAL

5.2.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Deferiprone, the primary active moiety, was assessed in the serum of subjects in the clinical study. An analytical method (AA20080-VTL) was developed and validated for the quantification of deferiprone in human serum over the range of 2 µg/mL to 50 µg/mL. The sponsor states the method validation had met the acceptance criteria as stipulated in the standard operating procedures of the Bioanalytical Services Division. Samples with concentration levels above the ULOQ (up to 100 µg/ml) may be analyzed by applying a maximum of a 2-fold dilution.

5.2.2 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The method demonstrates suitable accuracy, precision, and linearity (2 µg/mL to 50 µg/mL, and up to 100 µg/mL with 2-fold dilution) for the assessment of deferiprone in human serum. This linear range of the standard curve adequately meets the needs of clinical studies for deferiprone.

The method also quantitates L1-glucuronide, metabolite of deferiprone. However, L1 glucuronide is not measured in Study LA21-BE.

5.2.3 What are the lower and upper limits of quantification (LLOQ/ ULOQ)?

The lower limits of quantification (LLOQ) and the upper limits of quantification (ULOQ) for deferiprone were 2 µg/mL and 50 µg/mL, respectively.

5.2.4 What are the accuracy, precision and selectivity at these limits?

The accuracy, precision, and selectivity parameters for the determination of deferiprone are summarized in the table below (Table 5).

Table 5. Method Validation Summary for Quantitation of Deferiprone in Human Serum

Analyte	APO-066		
Matrix (Anticoagulant)	Human Serum		
Internal Standard	APO-066 analogue		
SOP Number	LMS-S-8152-01		
Assay Method	High performance liquid chromatographic mass spectrometric method		
Detector	AB/MDS Sciex API 4000		
Assay Volume Required	0.075 mL		
Standard Curve Range	0.200 – 50.0 µg/mL		
Regression Type	Linear (1/concentration)		
Quantitation Method	Peak Area Ratio		
Quality Control Samples		Precision (%)	Accuracy (%)
Inter-batch	LLOQ	10.3	1.0
	Low	3.0	7.2
	Medium	3.3	0.7
	High	3.8	1.0
Intra-batch	LLOQ	6.9-12.2	-0.5-3.5
	Low	2.0-3.50	5.8- 9.0
	Medium	2.3-4.1	-1.3 -2.0
	High	2.8 - 4.7	-1.5 -2.3
Recovery		Recovery (%)	
Analyte	Low	103.2	
	Medium	107.4	
	High	111.7	
Internal Standard		105.3	
Dilution Integrity	up to 100 µg/mL		
Long-term Stability	91 days at -80°C		
Short-term Stability	19.6 hours at ambient temperature under UV shielded light conditions		
Freeze and Thaw Stability	4 cycles at -80°C		
Post-preparative Stability	166.3 hours at ambient temperature		
Stock Solution Stability	90 days at 5.00 µg/mL in 10% acetonitrile/water at -80°C		
	501 days at 2.50 mg/mL in 10% acetonitrile/water at -80°C		
Internal Standard Stock Stability	140 days at 1.00 mg/mL in 10% acetonitrile/water at -80°C		
Processed Sample Integrity	85.5 hours at ambient temperature		

5.2.5 What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)

Long-term stability of deferiprone in human serum was validated by assaying previously prepared stability samples at high and low QC concentrations after storage at approximately -80 °C for a period of 91 days against a freshly prepared calibration curve. Stability of the QCs was within 15 % of the nominal concentrations. The serum samples in Study LA21-BE were stored for 74 days (first sample collection to last day of analysis: (b) (4)) which is within the validated long-term storage stability (91 days). One predose sample (Subject 24, Period 2) was reanalyzed on (b) (4) (Run 36), which is 118 days after sample collection and exceeds validated long-term stability (original analysis was BLQ in Run 22, but was rejected). Nonetheless, this is not likely a significant issue as this encompasses just one study sample.

Also, the sponsor reports that the period 2 samples for all subjects (pre-dose up to 4h) were stored at -63°C for one hour in Study LA21-BE. However, this is not likely to impact sample integrity as short-term stability was validated for 19.6 hours at room temperature.

Stability for the analyte is indicated over 4 freeze-thaw cycles. Plasma samples spiked with deferiprone at high and low QC concentrations were stored frozen at approximately -80°C were thawed unassisted at room temperature, and this was repeated for 3 additional cycles. After four freeze-thaw cycles, the samples were assayed against a set of freshly prepared calibration standards. The results met the required acceptance criteria. During the study LA21-BE, samples were reanalyzed only a maximum of 2 times.

Short-term stability for the deferiprone in human serum was validated for 19.6 hours (under UV protected conditions) at high and low QC concentrations against freshly prepared calibration curve. The results met the required acceptance criteria.

Extract sample stability was validated over a period of 166 hours against a freshly extracted calibration curve under UV protected conditions. On-instrument/post-preparative stability of the analyte is validated for 85.5 hours.

5.2.6 What is the QC sample plan?

Quality control (QC) samples were prepared by spiking known quantities of deferiprone stock solutions to blank serum (according to SOP LMS-S-8152-02). QCs were prepared at 0.600 µg/mL (QC A), 15.0 µg/mL (QC B) and 40.0 µg/mL (QC C) and stored at -80°C in Study LA21-BE. Following, the first 3 analytical runs, 5.00 µg/mL QC (QC D) was added to the rest of the analytical runs.

QC acceptance criteria: at least 67% (2/3) of all the QC samples must be within ±15% of their respective nominal values. At least 50% (1/2) of the replicates at each concentration level must be within ±15% of their respective nominal value. The overall inter-run accuracy and precision during the study LA21-BE was 96.8-102.5% and 4.6-10%, respectively.

A total of 34 analytical runs were analyzed in the study. About 12% of the runs (4 of 34) did not meet QC acceptance criteria. The samples from the rejected runs were reanalyzed later in different analytical runs.

In addition, about 2% (30 of 1428) of the samples were reanalyzed for analytical reasons (removal of LLOQ standard, abnormal IS response and lost in processing). Sponsor reported no reanalysis for non-analytical reasons.

5.3 OFFICE OF SCIENTIFIC INVESTIGATION INSPECTION

(b) (4) portions of bioequivalence study LA21-BE was conducted at (b) (4). The Office of Scientific Investigation (OSI) was requested to inspect (b) (4) sites for study LA21-BE. The OSI did not audit the study LA21-BE at (b) (4), but concluded that the study was acceptable without an on-site inspection of (b) (4) for the following reasons (DARRTS Reference ID 3708642):

- The study was conducted in (b) (4) which was outside the time period (b) (4) (b) (4) when (b) (4) was engaged in (b) (4).
- The OSI inspections of other studies conducted in (b) (4) or later at this (b) (4) facility did not show any objectionable significant findings.
- (b) (4) has since closed down. Therefore, an on-site inspection of the source electronic records is not possible.
- Based on the applicant's information, the hardcopy of the study records are archived at (b) (4). However, per OSI, audit of these records would provide limited information in the absence of full access to electronic source records.

In addition, based on the submitted data, the OCP reviewer did not find any evidence of issues concerning assay validation or in-study assay conduct that would invalidate the results of the study LA21-BE.

6 APPENDIX (in red are additions, strikethroughs are deletions of clinical pharmacology-related sections of the 04/30/2015 draft label)

2 Dosage and Administration

2.2 Interactions with Foods, Vitamins and (b) (4) -Drugs

Allow at least a 4-hour interval between Ferriprox FERRIPROX and other medications or supplements containing polyvalent cations such as iron, aluminum, and zinc. Avoid concomitant use of UGT1A6 inhibitor (e.g. diclofenac, probenecid, or silymarin (milk thistle)) with FERRIPROX. [see (b) (4) Drug Interactions (7.2, 7.3)].

7 DRUG INTERACTIONS

7.2 UDP-Glucuronosyltransferases (UGTs)

A clinical study to evaluate the effect of coadministration of UGT1A6 inhibitor with FERRIPROX on the systemic exposure of deferiprone has not been conducted. However, in the presence of the (b) (4)

(b) (4) DP glucuronosyltransferase (UGT) 1A6 inhibitor, phenylbutazone, the *in vitro* (b) (4) glucuronidation of deferiprone is (b) (4) reduced by (b) (4) 78%.

Therefore, avoid concomitant use of UGT1A6 inhibitors (b) (4) (e.g. diclofenac, (b) (4) probenecid, or silymarin (milk thistle)) with FERRIPROX.

[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3)].

8.6 Renal Impairment

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired renal function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of FERRIPROX Ferriprox. Subjects were categorized into 4 groups based on estimated glomerular filtration rate (eGFR): healthy volunteers (eGFR ≥ 90 mL/min/1.73 m²), mild renal impairment (eGFR 60–89 mL/min/1.73 m²), moderate renal impairment (eGFR 30–59 mL/min/1.73 m²), and severe renal impairment (eGFR 15–29 mL/min/1.73 m²). Renal function does not influence the pharmacokinetics of deferiprone and deferiprone 3-*O*-glucuronide. (b) (4)

8.7 Hepatic Impairment

(b) (4)

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired hepatic function on the (b) (4) pharmacokinetics of a single 33 mg/kg oral dose of FERRIPROX (feriprone). Subjects were categorized into 3 groups based on the Child-Pugh classification score: healthy volunteers, mild hepatic impairment (Class A: 5– 6 points), and moderate hepatic impairment (Class B: 7– 9 points). **Mild and moderate hepatic impairment do not influence the pharmacokinetics of** (b) (4)

deferiprone and deferiprone 3-*O*-glucuronide (b) (4)

One subject with moderate hepatic impairment experienced a serious adverse event of acute liver and renal injury. The pharmacokinetics of deferiprone and deferiprone 3-*O*-glucuronide have not been evaluated in patients with severe hepatic impairment (Child Pugh Class C; 10-15 points).

12 Clinical Pharmacology

12.3 Pharmacokinetics

Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract, appearing in the blood within 5 to 10 minutes of oral administration. Peak serum concentrations occur approximately 1 hour after a single dose in fasted healthy subjects and patients, and up to 2 hours after a single dose in the fed state. Administration with food decreased the **mean maximum concentration (C_{max})** of deferiprone by 38% and **the area under the concentration-time curve (AUC)** by 10%. (b) (4) **The magnitude of the exposure change does not warrant dose adjustment.**

In healthy subjects, the mean (b) (4) (C_{max}) of deferiprone in serum was **about 20 mcg/mL**, and the mean (b) (4) (AUC) was **about 50 (b) (4) mcg·h/mL** following oral administration of a 1,500 mg dose of FERRIPROX (b) (4) tablets **or oral solution** in the fasting state. Dose proportionality over the labeled dosage range of 25 to 33 mg/kg three times per day (75 to 99 mg/kg per day) has not been studied.

~~The elimination half-life (b) (4) of deferiprone (b) (4) hours.~~ (b) (4)

(b) (4)

(b) (4)

The elimination half-life of deferiprone is approximately 2 hours. Following oral administration, 75% to 90% of the administered dose is recovered in the urine in the first 24 hours, primarily as metabolite. In humans, the majority of the deferiprone is metabolized, primarily by UGT1A6. The contribution of extrahepatic (e.g., renal) UGT1A6 is unknown. The major metabolite of deferiprone is the 3-*O*-glucuronide, which lacks iron binding capability.

In a bioequivalence study, the rate (C_{max}) and the extent (AUC) of drug absorption of the solution and tablet formulations were shown to be equivalent. (b) (4)

Special populations

The pharmacokinetics of deferiprone has not been studied in geriatric or pediatric populations, and the influence of race, gender, or obesity has not been established.

Drug Interactions

Deferiprone is primarily eliminated via metabolism to the 3-*O*-glucuronide. *In vitro* UGT1A6 is primarily responsible for the glucuronidation of deferiprone which can be reduced up to 78% in the presence of the UGT1A6 inhibitor phenylbutazone.

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/s/

SRIRAM SUBRAMANIAM
08/13/2015

BAHRU A HABTEMARIAM
08/13/2015