CHIESI CANADA CORP.
3800 Steeles Ave West, Suite 100E
Woodbridge, Ontario L4L 4G9
Canada
www.chiesi.com

09 September 2021

Re: EudraCT prematurely ended trial – sponsor declaration

EudraCT number	Sponsor code	Title
2013-002181-39 --- 2014-005685-30	LA38-0411 --- LA38-EXT	The efficacy and safety of Ferriprox® for the treatment of transfusional iron overload in patients with sickle cell disease or other anemias --- Long-term safety and efficacy study of Ferriprox® for the treatment of transfusional iron overload in patients with sickle cell disease or other anemias.

In 2013, ApoPharma Inc., now Chiesi Canada Corp., initiated studies LA38-0411 and LA38-EXT to determine the efficacy and safety of the use of deferiprone to treat iron overload in patients with sickle cell disease (SCD) or other more rare anemia. The primary objective of the study was to demonstrate non-inferiority of deferiprone to deferoxamine in controlling body iron load, as assessed by the liver iron concentration (LIC).
The original plan was to enroll 300 patients, 200 to receive deferiprone and 100 to receive deferoxamine.
Despite intense efforts involving reaching out to close to 500 potential sites over 5 years, recruitment proceeded very slowly, for reasons that included a lack of prospective patients, screen failures, and unwillingness by patients who were eligible to take part. Indeed, investigators from 34 treatment centers in 8 countries have been able to enroll 230 patients in 5 years. Even if the last enrollment rate could have been maintained by all investigators, enrollment of 300 patients would not have been achieved until 2022, and completion (i.e., last patient last visit) of the extension study LA38-EXT would not have occurred until 2025.
Such a delay in making the safety and efficacy data available to the medical community could have had a detrimental effect in SCD patients who could, in the meantime, require treatment with an iron chelator other than those currently available.

In light of the above, the available data were analyzed based on a pre-established Statistical Analysis Plan. The analysis demonstrated that the available data demonstrate non-inferiority of deferiprone to deferoxamine in controlling LIC, even with the lower than projected number

CHIESI CANADA CORP.
3800 Steeles Ave West, Suite 100E
Woodbridge, Ontario L4L 4G9
Canada
www.chiesi.com

of patients. An analysis of safety data was performed as well, and the safety profile was found consistent with the profile observed in previous ApoPharma studies in patients with systemic iron overload. Based on these results, ApoPharma submitted that the primary efficacy endpoint of study LA38-0411 has been met and enrollment of new patients was statistically futile as well as practically unachievable.

Furthermore, the independent Data Safety Monitoring Board (DSMB) that was overseeing both studies did not raised any safety concerns and issued the below recommendations: 1) because of the near certainty of failure to reach the projected enrollment despite extraordinary efforts, LA38-0411 should be terminated 2) there was insufficient merit in continuing the LA38-Extension study. The DSMB concluded that existing methods of surveillance of safety of deferiprone are as informative if not more informative than the extension study, and that the extension study should only be continued if the information to be gained is vital to reach a decision regarding approval of deferiprone (Ferriprox®) for patients with sickle cell disease.

Based on all the above, the ApoPharma/Chiesi Canada Corp LA38-0411 and LA38-EXT studies were terminated in April 2019.

Attached are the CSR synopses of LA38-0411 and LA38-EXT studies.

Sincerely,

Fernando Tricta

Fernando Tricta

Senior Vice President, Hematology & Immunology Programs

CHIESI CANADA CORP.

CHIESI CANADA CORP.
3800 Steeles Ave West, Suite 100E
Woodbridge, Ontario L4L 4G9
Canada
www.chiesi.com

Sharing Clinical Study Report Synopsis

This synopsis is part of the full Clinical Study Report (CSR), which is property of Chiesi Canada Corp.

Chiesi Canada Corp. makes the CSR Synopsis available, consistently with the need to protect the patient privacy, publication rights, and commercially confidential information, through appropriate redaction.

The CSR synopsis is supplied for information only, with the purpose of disclosing scientific data. Hence, it cannot be used, in parts or its entirety, for commercial purposes, nor distributed, published, reused or used for any other purpose without the express written permission of Chiesi Canada Corp.

Results reported in the CSR synopsis are related to a specific study and may not reflect the overall evidence obtained across the product development. Therefore, it is not aimed at providing an exhaustive analysis of all the data currently available on a particular drug. You can learn more about Chiesi Canada Corp. medicinal product consulting the approved product labelling, which may vary from country to country.

The CSR synopsis is not intended to promote any product or indication and is not intended to replace the advice of a health care professional.

2 SYNOPSIS

Name of Sponsor: ApoPharma **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of study:	The efficacy and safety of Ferriprox® for the treatment of transfusional iron overload in patients with sickle cell disease or other anemias
Study code:	LA38-0411
Phase of development:	Phase IV (United States), Phase IIIb (other countries)
Investigators:	Investigators are listed in Appendix 16.1.4 of the study report.
Study sites:	This study was conducted at 27 sites in Egypt, USA, Brazil, United Kingdom, Saudi Arabia, Tunisia, Canada, and Turkey. Sites are listed in Appendix 16.1.4 of the study report.
Publication (reference):	None
Date of first patient enrolled:	17 APR 2014
Date of study termination:	20 APR 2019
Objectives:	**Primary:** To determine the efficacy of deferiprone vs. deferoxamine in the treatment of iron overload in patients with sickle cell disease or other anemias. **Secondary:** • To evaluate the effect of deferiprone vs. deferoxamine on patients' quality of life • To evaluate the safety and tolerability of deferiprone vs. deferoxamine
Methodology:	LA38-0411 was a late-phase (Phase IV in the U.S., Phase IIIb in other countries), multi-center, randomized, open-label study comparing the efficacy and safety of the iron chelator deferiprone (DFP) vs. deferoxamine (DFO) in patients with sickle cell disease (SCD) or other transfusion-dependent anemias. Eligible patients were randomized in a 2:1 ratio to receive either DFP or DFO, respectively, for up to 12 months, using stratification to ensure maintenance of this ratio over the strata of disease category (SCD vs. other anemias) and transfusional iron input in the 3 months prior to baseline (less than or equal to vs. more than 0.3 mg/kg/day). Patients visited the study sites monthly for evaluations of efficacy and/or safety, and additionally underwent weekly or biweekly monitoring for hematology at a local laboratory. Safety assessments were performed at each site visit; serum ferritin (SF) was measured quarterly; and assessments of liver iron concentration (LIC), cardiac iron, and quality of life were carried out at baseline, Month 6, and Month 12. Patients who completed the 12 months of treatment were eligible to enroll in a 2-year extension study, LA38-EXT, in which all participants received deferiprone.

Name of Sponsor: ApoPharma **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Methodology (cont'd):	DFP is taken orally as 3 doses approximately 8 hours apart, while DFO is administered as a subcutaneous infusion over 8–12 hours, 5 to 7 days a week. The dosage of both products is calculated in terms of milligrams per kilogram of body weight (mg/kg) and depends on the patient's transfusional iron input and severity of iron load. In this study, participants with lower iron input over the last 3 months and less severe iron load were prescribed either DFP at a daily dosage of 75 mg/kg divided t.i.d. (25 mg/kg per dose) or DFO at a daily dosage of 20 mg/kg (children) or 40 mg/kg (adults), while those with higher iron input and/or more severe iron load received DFP at a dosage of 99 mg/kg divided t.i.d. (33 mg/kg per dose) or DFO at a dosage of up to 40 mg/kg (children) or 50 mg/kg (adults). For DFP, the dosage was titrated over the first 4 weeks up to the assigned dose. With both products, the lower dosage could be increased during the study if the mean daily transfusional iron input increased to > 0.3 mg/kg body weight for at least 3 consecutive months or if the patient showed less than 10% improvement by Month 6 in any of the measures indicative of iron overload. Conversely, dosages could be reduced at any time during the study if a patient experienced adverse reactions deemed to be possibly dose-dependent. Rescue medication was not allowed: if iron overload symptoms became intolerable for a patient despite dose adjustment, that patient was to be withdrawn from the study. It was originally planned to enroll 300 patients in this study: 200 to receive DFP and 100 to receive DFO. However, despite intense efforts involving reaching out to close to 500 potential sites over 5 years, recruitment proceeded very slowly, for reasons that included a lack of prospective patients, screen failures, and unwillingness by patients who were eligible to take part. Accordingly, a new power analysis was done that used the data of completed and withdrawn patients plus the projected data of ongoing ones to determine whether the number of participants already randomized was sufficient to meet the primary endpoint. As the results indicated that this number was indeed sufficient, an interim analysis was conducted; and based on its results, the decision was made to terminate the study. Enrollment was halted on 30 NOV 2018, with 17 DEC 2018 used as the cut-off for efficacy data to be included in the interim analysis. Based on the results of the interim analysis, the decision was made to terminate the study, and the last patient visit took place on 20 APR 2019. Ongoing patients who had not yet completed 12 months of treatment by that date were considered to have been withdrawn. Two separate analyses were conducted on the efficacy measures of iron overload: the initial analysis, which included the data of just those patients who were evaluable as of the cut-off date of 17 DEC 2018, and a final analysis, which included the data of all evaluable patients up to the date of study termination on 20 APR 2019. The results of the initial analysis, which was used as the basis for the decision to terminate the trial and which as per the Statistical Analysis Plan is considered the pivotal efficacy analysis for the study, are provided in the body of the report, and the results of the final analysis are provided in an appendix.

Name of Sponsor: ApoPharma **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Number of patients:

	DFP	DFO	Total
Planned	200	100	300
Randomized	152	78	230
Exposed	152	76	228
Completed	106	58	164
Withdrawn [1]	46	18	64
Included in the pivotal efficacy analyses for LIC and cardiac iron [2]	122	63	185
Included in the pivotal efficacy analysis for serum ferritin [2]	133	67	200
Included in the final efficacy analyses for LIC and cardiac iron [3]	133	69	202
Included in the final efficacy analysis for serum ferritin [3]	143	74	217

1 Includes 10 patients who were ongoing on the date of study termination and were withdrawn by the sponsor

2 Patients who had either completed or withdrawn from the study by 17 DEC 2018 and had provided at least one post-baseline efficacy assessment. The numbers are greater for serum ferritin than for LIC and cardiac iron since the first post-baseline SF assessment was done at Month 3 whereas the others were done at Month 6.

3 Patients who had either completed or withdrawn from the study by 20 APR 2019 and had provided at least one post-baseline efficacy assessment. The numbers are greater for serum ferritin than for LIC and cardiac iron since the first post-baseline SF assessment was done at Month 3 whereas the others were done at Month 6.

Diagnosis and main criteria for inclusion:

Main inclusion criteria:

- Male or female ≥ 2 years of age
- Diagnosis of sickle cell disease or other condition with iron overload from repeated blood transfusions
- Baseline LIC >7 but ≤ 30 mg/g dry weight (dw)
- Receipt of at least 20 red blood cell transfusions, including at least one per year in the past 2 years, and expected to have a continuing requirement for the duration of the trial

Main exclusion criteria:

- Diagnosis of thalassemia syndrome, myelodysplastic syndrome, myelofibrosis, or Diamond Blackfan anemia
- Primary bone marrow failure
- Cardiac MRI T2* < 10 ms

Name of Sponsor: ApoPharma **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Diagnosis and main criteria for inclusion (cont'd):	• Unable or unwilling to undergo a 7-day washout period if currently being treated with an iron chelator • Previous discontinuation of treatment with deferiprone or deferoxamine due to adverse events • Treated with hydroxyurea within 30 days • Evidence of abnormal liver function (serum ALT > 5 times upper limit of normal or creatinine levels >2 times upper limit of normal at screening) • Presence of a medical condition that in the investigator's opinion might increase safety risks or interfere with interpretation of the results of the trial • Unable to undergo MRI
Investigational product:	Product: Ferriprox® (deferiprone) 500 mg tablets OR deferiprone 80 mg/mL oral solution Dose: 75 or 99 mg/kg/day, divided t.i.d. Mode of administration: Oral [redacted]
Reference product:	Product: Deferoxamine 2 g vial Dose: 20 or 40 mg/kg (children); 40 or 50 mg/kg (adults) Mode of administration: Subcutaneous infusion [redacted]
Duration of participation:	The duration of participation for each patient was up to 12 months.
Criteria for evaluation:	**Efficacy:** *Primary:* The change from baseline to Month 12 in liver iron concentration, as measured by MRI *Secondary:* • Change from baseline to Month 12 in cardiac MRI T2* • Change from baseline to Month 12 in serum ferritin • Change from baseline to Month 12 in patient-reported quality of life, as assessed by the SF-36 (adults) or Child Health Questionnaire (minors)

Name of Sponsor: ApoPharma **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Criteria for evaluation (cont'd):	**Safety:** • 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
Statistical methods:	The primary efficacy endpoint was the change from baseline to Month 12 in LIC. The treatment groups were compared using an analysis of covariance (ANCOVA) model, with treatment as the main factor and overall average transfusional iron input during the study, baseline LIC, and stratification factors (disease category and transfusional iron input in the 3 months prior to baseline) as covariates. The 96.01% confidence interval (CI) of the difference between the treatment groups in the change in LIC from baseline to Month 12 was computed. (The 96.01% was determined by $1 - \alpha$, where $\alpha = 0.0399$ based on the Pocock's α spending function for the interim analysis.) For the demonstration of non-inferiority, the upper limit of the 96.01% CI could be no more than 2 mg/g dw. The SAS MIXED procedure was used to produce the differences in Least Squares (LS) Mean of change in LIC at Month 6 and Month 12 between the DFP and DFO groups and the corresponding 96.01% confidence intervals. In the mixed model, AR (1) (autoregressive of order 1) was used for the covariance structure, and Kenward and Roger's method was used to estimate the denominator degrees of freedom (SAS model statement option, DDFM = KR). Similar ANCOVA models were used for the secondary efficacy endpoints of changes in cardiac MRI T2* and serum ferritin. For cardiac MRI T2*, the data were log-transformed, as stipulated in the statistical analysis plan for normalization of the data, before any statistical evaluation were done. The safety data for continuous variables were summarized using descriptive statistics, and the safety data for discrete variables were presented as frequency tables.

Name of Sponsor: ApoPharma **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

RESULTS

PATIENT POPULATION

A total of 230 patients were randomized in the study. Two patients who were assigned to the DFO group withdrew before receiving any treatment. Completion rates in the groups were similar: 69.7% of DFP patients vs. 74.4% of DFO patients (p=0.5388). In both groups, the most common reasons for withdrawal were patient request (8.6% in the DFP group, 9.0% in the DFO group), protocol deviation (7.2% and 5.1%), and adverse event (5.9% and 3.8%); and 10 (4.3%) ongoing patients were withdrawn by the sponsor when the decision was made to terminate the study. There were no significant group differences in the overall withdrawal rate or in any of the reasons for withdrawal. For 6 of the 12 patients who withdrew due to adverse events, the events were considered to be related to study product: in the DFP group, 1 case of agranulocytosis, 2 of neutropenia, and 2 of both abdominal pain and vomiting; and in the DFO group, 1 case of nausea.

The mean age was 16.9 years in both groups, with an overall range from 3 to 59 years. The ratio of females to males was exactly 50:50 in the DFO group, but there were more males (54.6%) than females in the DFP group. The majority of participants were white (77.2%), with the remainder identifying as black or multi-racial, and were ethnically non-Hispanic (93.0%). There were no significant group differences in any demographic measures.

EFFICACY

Efficacy was assessed by comparing the treatment groups on the changes from baseline in measures of iron load (liver iron concentration, cardiac iron, and serum ferritin) and of patient-assessed quality of life. For each of the iron load measures, the key evaluation was to test for non-inferiority of deferiprone to deferoxamine at Month 12. The results of the interim analysis conducted on the data of patients who were evaluable as of the cut-off date of 17 DEC 2018 were pre-defined as the pivotal efficacy findings.

Primary Efficacy Endpoint

Liver Iron Concentration

A total of 185 patients (122 DFP, 63 DFO) were included in the pivotal analysis for the study's primary endpoint. There were no significant treatment group differences at baseline or at either of the post-baseline time points (all p-values >0.05). The mean change from baseline was very similar between the groups (-4.13 for DFP, -4.38 for DFO), and the upper limit of the 96.01% confidence interval (CI) was 1.48. This met the pre-defined criterion for non-inferiority, which specified that the upper limit of the CI had to be $\leq$ 2 mg/g dw.

Separate analyses were conducted on the subpopulations of patients with SCD vs. other anemias. Of the 185 patients evaluable for LIC, 155 (104 DFP, 51 DFO) had SCD, and 30 (18 DFP, 12 DFO) had other anemias. In both subpopulations, there were no significant treatment group differences at baseline or at either of the post-baseline time points (all p-values >0.05). Non-inferiority of DFP to DFO was demonstrated for the SCD subpopulation (upper limit of the 96.01% CI = 1.86). For the subpopulation with other anemias, the reduction of

LIC at Month 12 was numerically larger for the DFP group, but due to the relatively small sample size, the non-inferiority criterion was not met (upper limit of the 96.01% CI = 2.21).

Secondary Efficacy Endpoints

The secondary efficacy endpoints were the changes from baseline to Month 12 in cardiac iron as measured by MRI T2*, in the level of serum ferritin, and in measures of patient-reported quality of life.

Cardiac Iron

A total of 185 patients (122 DFP, 63 DFO) were included in the pivotal analysis for this endpoint. There were no significant treatment group differences at baseline or at either of the post-baseline time points (all p-values >0.05). The mean change from baseline at Month 12 in the log-transformed cardiac MRI T2* (ms) was very similar between the groups (approximately -0.02 for both) and the 96.01% CI was (-0.0543, 0.0537). This supports the non-inferiority of DFP to DFO, as the 96.01% CI contains zero (0) which indicates no significant difference between the two treatment groups.

Separate analyses were conducted on the subpopulations of patients with SCD vs. other anemias. Of the 185 patients evaluable for cardiac iron, 155 (104 DFP, 51 DFO) had SCD, and 30 (18 DFP, 12 DFO) had other anemias. In both subpopulations, there were no significant treatment group differences at baseline or at either of the post-baseline time points (all p-values >0.05). Support for non-inferiority of DFP to DFO at Month 12 was demonstrated in both cases, with a 96.01% CI of (-0.0727, 0.0418) for the SCD patients and of (-0.0697, 0.2531) for the patients with other anemias.

Serum Ferritin

Serum ferritin (SF) was measured quarterly, with data obtained at baseline and at Months 3, 6, 9, and 12. A total of 200 patients (133 DFP, 67 DFO) underwent at least one post-baseline assessment for SF and were included in the pivotal analysis for this endpoint. Whereas in the DFO group the mean SF level went down at each time point except Month 12, in the DFP group it increased at Month 3, and while it began to decrease after that, it was still above baseline at Month 6, resulting in significant group differences at both these time points (p=0.0133 and p=0.0472, respectively). The level continued to go down, and no significant group differences were seen at Months 9 and 12 (both p-values >0.05). The 96.01% CI at Month 12 was (-261, 1011). As with cardiac iron, the 96.01% CI contains zero (0), thereby supporting non-inferiority of DFP to DFO.

Separate analyses were conducted on the subpopulations of patients with SCD vs. other anemias. Of the 200 patients evaluable for serum ferritin, 168 (113 DFP, 55 DFO) had SCD, and 32 (20 DFP, 12 DFO) had other anemias. For the SCD subpopulation, similar to the overall patient population, SF levels in the DFP-treated group increased from baseline at both Month 3 and Month 6, resulting in a significant difference from the DFO group at both these time points, but then dropped, resulting in no significant group difference at Months 9 and 12. In contrast, for the patients with other anemias, SF levels in the DFP group decreased throughout the study and did not differ from those in the DFO group at any time point. Support for non-inferiority at Month 12 was demonstrated for both the SCD patients, for which the 96.01% CI was (-84.85, 1387.01), and the patients with other anemias, for which it was (-1858.12, 70.61).

Quality of Life

QoL was assessed by administering the SF-36, the CHQ-CF87, and the CHQ-PF50 questionnaires to adult, minors, and parents of minors, respectively, at baseline, Month 6, and end of study (Month 12 or early termination). Unlike the pivotal analyses for the iron load endpoints, for QoL, the data from all evaluable patients up to the date of study termination were analyzed.

Name of Sponsor: ApoPharma	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Deferiprone		
Name of Active Ingredient: 3-hydroxy-1,2-dimethylpyridin-4-one		

The SF-36 provides scores on 8 individual scales plus 2 summary scores that are computed from weighted combinations of the results from the individual scales (Physical Summary and Mental Summary), and the CHQ-PF50 provides scores on 10 individual scales plus 2 summary scores (Physical Summary and Psychosocial Summary). There are no summary scores for the CHQ-CF87. No statistically significant differences between the two treatment groups were seen in any of these comparisons (all p-values > 0.05). For all three QoL questionnaires, the results of the analyses based on the subgroup of SCD patients and the subgroup of patients with low baseline transfusional iron input were consistent with those based on the full patient population.

SAFETY

Of the 230 randomized patients, 228 received at least one dose of study product and were included in the Safety population. The percentage of patients who experienced at least one adverse event (AE) of any type was exactly the same in both groups (88.2%), and the rates did not differ significantly for serious AEs, AEs related to study treatment, or AEs leading to withdrawal (p>0.05). However, a higher percentage of patients in the DFP group reported AEs rated as severe (16.4% vs. 6.6%; p=0.0393).

Adverse Events

Overall, 134 (88.2%) DFP patients reported a total of 1014 AEs, and 67 (88.2%) DFO patients reported a total of 445 AEs. In the DFP group, the most commonly reported events were pyrexia, abdominal pain, bone pain, headache, and vomiting; in the DFO group, they were bone pain, pyrexia, back pain, pain in extremity, oropharyngeal pain, and cough.

Within the subset of the study population with sickle cell disease, 89.8% (115) of the DFP patients reported a total of 905 AEs, and 90.6% (58) of the DFO patients reported a total of 409 AEs. The frequencies of rates of each type of AE were comparable to those seen in the overall study population.

Severity of Adverse Events

The severity (intensity) of adverse events was rated as mild, moderate, or severe. Of the 1014 events reported in the DFP group, 66.6% (675) were rated as mild, 27.0% (274) as moderate, and 6.3% (64) as severe. (No rating was provided for one event, an occurrence of spontaneous abortion.) Of the 445 events reported in the DFO group, 69.0% (307) were rated as mild, 29.7% (132) as moderate, and 1.3% (6) as severe.

In the DFP group, the AEs with the most frequent ratings of moderate or severe were sickle cell crisis (5.9% of patients with moderate events, 7.2% with severe events), abdominal pain (7.9% and 3.3%, respectively), pyrexia (7.9% and 2.0%), vomiting (6.6% and 1.3%), bone pain (11.2% and 0.7%), pain in extremity (5.9% and 0.0%), back pain (3.9% and 0.7%), increased AST (3.3% and 0.7%), and acute chest syndrome (0.0% and 2.0%). In addition, severe events of sepsis, encephalopathy, and deep vein thrombosis were each experienced by 2 patients (1.3%), and moderate events of arthralgia, pain, oropharyngeal pain, pneumonia, and decreased neutrophil count were experienced by between 6 (3.9%) and 3 (2.0%) patients. No other AEs were reported as severe in more than 1 (0.7%) patient or as moderate in more than 2 (1.3%) patients.

In the DFO group, the severe events were occurrences of toothache, pulmonary embolism, nausea, pneumonia, road traffic accident, and pyrexia in 1 (1.3%) patient each. Events rated as moderate were reported for bone pain (26.3% of patients), back pain, sickle cell crisis and pyrexia (7.9% each), headache (6.6%), and abdominal

Name of Sponsor: ApoPharma	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Deferiprone		
Name of Active Ingredient: 3-hydroxy-1,2-dimethylpyridin-4-one		

pain and injection site pain (3.9% each). No other AEs were reported as moderate in more than 2 (2.6%) patients.

Drug Relationship of Adverse Events

Adverse events that were considered to be at least possibly related to study product were identified as adverse drug reactions (ADRs). ADRs were reported in 51.3% (78) of the DFP patients and in 39.5% (30) of the DFO patients (p=0.1215). With respect to number of events, 257 (25.3%) of the 1014 AEs in the DFP group and 66 (14.8%) of the 445 AEs in the DFO group were considered to be ADRs.

In the DFP group, ADRs that were seen in at least 5% of patients were abdominal pain, vomiting, pyrexia, increased ALT, increased AST, decreased neutrophil count, nausea, and chromaturia; in the DFO group, they were pyrexia and injection site pain.

In the subset of patients with SCD, 50.0% (64) of patients in the DFP group and 40.6% (26) of those in the DFO group reported at least one ADR. In the DFP group, the most common ADRs were abdominal pain, vomiting, increased ALT, increased AST, and pyrexia, and in the DFO group they were pyrexia and injection site pain.

Serious Adverse Events

A total of 134 SAEs occurred in the study: 94 events in 40 (26.3%) patients in the DFP group, and 40 events in 14 (18.4%) patients in the DFO group. There were two deaths, deemed not related to study treatment: a pair of siblings, one in each treatment group, who were killed together in a motor vehicle accident. The most frequent SAE was sickle cell crisis, experienced by 10.5% (16) of DFP patients and 5.3% (4) of DFO patients; followed by pyrexia in 3.3% (5) and 3.9% (3), respectively; neutropenia in 2.6% (4) and 1.3% (1), abdominal pain in 2.0% (3) and 1.3% (1), and acute chest syndrome in 2.0% (3) and 0.0% (0). No other SAE was seen in more than 2 patients, and the majority (45) were seen in only one.

In the subset of patients with SCD, SAEs were reported for 25% (32) of DFP recipients and for 18.8% (12) of DFO recipients. As with the overall population, the most commonly reported SAE was sickle cell crisis, experienced by 12.5% (16) and 6.3% (4) patients, respectively. Additionally, in the DFP group, SAEs of pyrexia were reported in 3.1% (4) patients, and abdominal pain and acute chest syndrome in 2.3% (3) each. No other SAEs were seen in more than 2 patients in either treatment group.

A total of 12 patients had SAEs that were considered at least possibly related to study treatment: 5.9% (9) in the DFP group and 3.9% (3) in the DFO group. In the DFP group, related or possibly related SAEs of neutropenia were seen in 4 patients, increased transaminases in 2, and agranulocytosis, sickle cell crisis, epididymitis, propionibacterium infection, bacterial sinusitis, vascular device infection, and migraine in 1 each. In the DFO group, the possibly related SAEs were abdominal pain, arthritis, and headache, seen in 1 patient each. Of the neutropenia events in the DFP group, 2 patients experienced mild events for which no action was taken; 1 patient experienced a moderate event that led to stopping treatment temporarily (in fact, this event was mild based on the pre-established criteria for classifying neutropenia, but had been incorrectly classified as moderate by the investigator); and 1 experienced 2 mild events of which the second led to study discontinuation because of its duration. All 4 patients recovered. The event of agranulocytosis led to withdrawal; the patient in that case recovered as well.

Name of Sponsor: ApoPharma	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Deferiprone		
Name of Active Ingredient: 3-hydroxy-1,2-dimethylpyridin-4-one		

Other Significant Adverse Events

Twelve of the 64 withdrawals from the study, 9 in the DFP group and 3 in the DFO group, were due to adverse events. The rate did not differ significantly between the groups (5.9% vs. 3.9%; p=0.7550). Seven of the 12 events, 5 in the DFP group and 2 in the DFO group, and including the two fatalities, were considered to be unrelated to study treatment. Of the 5 cases considered to be at least possibly related, 4 were in the DFP group: 1 event of agranulocytosis, 1 of mild neutropenia that lasted beyond 14 days, and 2 of abdominal pain and vomiting (both moderate in one patient, both severe in the other). The one case in the DFO group was due to severe nausea. All patients recovered.

CONCLUSIONS

Efficacy: The efficacy of deferiprone for the treatment of iron overload in patients with sickle cell disease or other rare anemias is non-inferior to that of deferoxamine, as assessed by changes in iron load.

Safety: The safety profile of deferiprone is acceptable and is consistent with that previously seen in patients with thalassemia syndromes.

Date of the report: 20 SEP 2019

2 SYNOPSIS

Name of Sponsor: ApoPharma Inc. **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of study:	Long-term safety and efficacy study of Ferriprox® for the treatment of transfusional iron overload in patients with sickle cell disease or other anemias
Study code:	LA38-EXT
Phase of development:	Phase IV (United States), Phase IIIb (other countries)
Investigators:	Investigators are listed in Appendix 16.1.4 of the study report.
Study sites:	This study was conducted at sites in Egypt, USA, United Kingdom, Saudi Arabia, and Canada. Sites are listed in Appendix 16.1.4 of the study report.
Publication (reference):	Kwiatkowski, JL et al. Randomized Controlled Trial of the Efficacy and Safety of Deferiprone in Iron-Overloaded Patients with Sickle Cell Disease or Other Anemias. Presentation at 61st American Society of Hematology Annual Meeting & Exposition, December 2019.
Date of first patient enrolled:	21 MAY 2015
Date of study termination:	30 APR 2019
Objectives:	**Primary:** To evaluate the long-term safety and tolerability of deferiprone in iron-overloaded patients with sickle cell disease or other anemias **Secondary:** To evaluate the efficacy of deferiprone in the treatment of iron overload in patients with sickle cell disease or other anemias who have received deferiprone for up to 3 years
Methodology:	LA38-EXT was a 2-year prospective, multi-center, single-arm, open-label extension of study LA38-0411 in which patients with sickle cell disease or certain other transfusion-dependent anemias had been randomized to receive either deferiprone (DFP) or deferoxamine (DFO) for 12 months. Patients who completed the initial study were offered the opportunity to take part in in the extension study for 2 years, with the final visit of LA38-0411 being Visit 1 of LA38-EXT. Patients who had been treated with deferiprone during LA38-0411 (the DFP-DFP group) continued to receive deferiprone, while those who had been treated with deferoxamine (the DFO-DFP group) were switched to deferiprone. The dosage of deferiprone was based on transfusional iron input and severity of iron load, and ranged from 75 to 99 mg/kg per day. Patients visited the site quarterly for assessments of safety and efficacy. In addition, those in the

Name of Sponsor: ApoPharma Inc. **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Methodology (cont'd):

DFP-DFP group, who had already been on deferiprone for 12 months, had blood counts monitored monthly, while those in the DFO-DFP group, who were naïve to deferiprone at the start of the extension study, were monitored weekly for the first 6 months, biweekly for the next 6 months, and monthly thereafter.

It had been planned for the initial study to enroll 300 patients, 200 in the DFP arm and 100 in the DFO arm, and for all patients who completed that study to have the option of enrolling in and completing the extension study. However, despite intensive efforts involving reaching out to hundreds of potential sites over 5 years, recruitment in LA38-0411 proceeded very slowly, for reasons that included a lack of prospective patients, screen failures, and unwillingness to take part by otherwise eligible patients. After the findings of an interim analysis indicated that the number of patients already randomized in LA38-0411 would be sufficient to meet that study's primary endpoint, the decision was made to halt further enrollment in that study immediately, and to terminate it as soon as most of the ongoing patients had reached the 12-month time point. Enrollment into the extension study continued in the meantime; however, the data safety monitoring board (DSMB) that was overseeing both studies recommended that this study be terminated as well since existing methods of surveillance for the safety of deferiprone were equally as or more informative than what was being obtained from the trial. Accordingly, the decision was made on 30 April 2019 to terminate both LA38-0411 and LA38-EXT, and patients who were still ongoing in either trial on that date were considered to have been withdrawn.

Number of patients:

	DFP-DFP	**DFO-DFP**	**Total**
Planned	Up to 200	Up to 100	Up to 300
Enrolled	89	45	134
Completed	50	26	76
Withdrawn [1]	39	19	58

[1] Includes 31 patients who were ongoing on the date of study termination, 20 in the DFP-DFP group and 11 in the DFO-DFP group

Diagnosis and main criteria for inclusion:

- Diagnosis of sickle cell disease or other condition with iron overload from repeated blood transfusions
- Completed study LA38-0411

Name of Sponsor: ApoPharma Inc. **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Investigational product:	Product: Ferriprox® (deferiprone) 500 mg tablets or deferiprone 80 mg/mL oral solution Dose: 25–33 mg/kg t.i.d. Mode of administration: Oral [redacted]
Duration of participation:	The duration of participation by each patient was up to 2 years.
Criteria for evaluation:	**Safety:** • 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 **Efficacy:** The time points for the efficacy assessments of deferiprone are defined below. Baseline was defined as the start of deferiprone treatment, so it differed for the two group, as follows: • **DFP-DFP group:** For patients who had received deferiprone in LA38-0411, the start of that study was baseline, the start of the extension study was Year 1 (i.e., the completion of one year of deferiprone treatment), Month 12 of the extension study was Year 2, and Month 24 of the extension study was Year 3. • **DFO-DFP group:** For patients who had received deferoxamine in LA38-0411, the start of the extension study was baseline, Month 12 of the extension study was Year 1, and Month 24 of the extension study was Year 2. There was no Year 3. Endpoints were as follows: • The change from baseline to Year 1 (both groups), from baseline to Year 2 (both groups), and from baseline to Year 3 (DFP-DFP group only) in liver iron concentration (LIC), as measured by magnetic resonance imaging (MRI) • The change from baseline to Year 1 (both groups), from baseline to Year 2 (both groups), and from baseline to Year 3 (DFP-DFP group only) in cardiac MRI T2*

Name of Sponsor: ApoPharma Inc. **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Criteria for evaluation (cont'd):	• The change from baseline to Year 1 (both groups), from baseline to Year 2 (both groups), and from baseline to Year 3 (DFP-DFP group only) in serum ferritin • Responder analysis, defined as the percentage of patients who showed a ≥20% decline from baseline in LIC or serum ferritin or a ≥20% increase from baseline in cardiac MRI T2* at Year 1 (both groups), at Year 2 (both groups), and at Year 3 (DFP-DFP group only)
Statistical methods:	Safety Analysis The incidences of AEs and SAEs reported from the start of deferiprone therapy for all patients were tabulated. For patients continuing on deferiprone, this time period was from the start of LA38-0411 to the completion of LA38-EXT; while for those switching to deferiprone, it was from the start of LA38-EXT to the completion of LA38-EXT. AEs were summarized by worst severity and by relationship to the study medication. Time to onset and duration of all SAEs, of AEs of special interest such as neutropenia, agranulocytosis, increased ALT, and arthralgia, were analyzed as follows: 1) the mean time to the first onset and the mean time to the last recurrence were calculated, and 2) the mean duration for the first episode and the mean duration for any recurrent episodes, excluding the first episode, were calculated for all SAEs and such AEs. The percentage of discontinuations due to AEs was calculated, and the AEs leading to discontinuation were summarized in a frequency table. Laboratory data (hematology and chemistry) were summarized using descriptive statistics for continuous variables and frequency tables for discrete variables. The incidences of out-of-range data that were seen for two consecutive measurements were tabulated, and the changes from baseline to the end of study were presented in shift tables. Efficacy Analysis Changes in LIC, in cardiac MRI T2*, and in serum ferritin from baseline to Year 1 (both groups; DFP-DFP data are from LA38-0411), from baseline to Year 2 (both groups), and from baseline to Year 3 (DFP-DFP group only) were summarized with descriptive statistics, and were tested against no change using a one-sample t-test. The changes in these 3 efficacy measures from the start of deferiprone therapy to the last visit of LA38-EXT in all patients, irrespective of whether deferiprone therapy was initiated in LA38-0411 or in LA38-EXT, were also tested using a one-sample t-test. In addition, the percentages of responders were tabulated for Year 1 (both groups; DFP-DFP group data were from LA38-0411), for Year 2 (both groups), and for Year 3 (DFP-DFP group only) of deferiprone therapy.

Name of Sponsor: ApoPharma Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Deferiprone		
Name of Active Ingredient: 3-hydroxy-1,2-dimethylpyridin-4-one		

RESULTS

PATIENT POPULATION

Of the 164 participants who completed the randomized study, 134 enrolled in the single-arm extension study: 89 who had received deferiprone and were continuing on it (the DFP-DFP group) and 45 who had received deferoxamine and were being switched to deferiprone (the DFO-DFP group). All 134 patients received at least one dose of deferiprone during the extension study. Slightly over half (56.7%) completed the study, with essentially the same rate of withdrawal in both groups: 39 DFP-DFP patients (43.8%) and 19 (42.2%) DFO-DFP patients. The most common reason for withdrawal was sponsor decision, with 31 ongoing patients (53.4% of the 58 withdrawn patients) being involuntarily withdrawn when the study was terminated. Four patients were withdrawn due to adverse events, although in two cases the event was pregnancy, which mandated withdrawal as per protocol. The other AEs leading to withdrawal were considered to be at least possibly related to deferiprone: one patient with neutropenia and thrombocytopenia, who recovered, and one with generalized edema, who later died of causes that were not determined.

The mean age of participants at the start of the extension study was 16.2 years, with a range from 4 to 47 years. The ratio of females to males was approximately 2 to 3. The majority of participants were white (85.1%) and the remainder black. One was ethnically Hispanic. With respect to diagnosis, 115 (85.8%) participants had some form of sickle cell disease, while the remaining 19 had some other type of transfusion-dependent anemia.

EFFICACY

Efficacy was assessed by examining the changes from baseline for different periods of exposure to deferiprone (one vs. two vs. three years) for each of the measures of iron load:

- For the **DFP-DFP** patients, baseline was the first visit of the main study, Year 1 was completion of the main study, Year 2 was 12 months into the extension study, and Year 3 was completion of the extension study.
- For the **DFO-DFP** patients, baseline was the first visit of the extension study, Year 1 was 12 months into the extension study, Year 2 was completion of the extension study, and Year 3 was not applicable.

Liver Iron Concentration

Change from baseline: Liver iron concentration decreased consistently over time, with the mean value dropping from 14.93 mg/g dw at baseline to 12.30 mg/g dw after one year of treatment, to 11.19 mg/g dw after two years of treatment, to 10.45 mg/g dw after three years of treatment. The change from baseline was significant at each time point.

Responder analysis: Responders were defined as individuals who had at least a 20% decline in LIC since the start of deferiprone treatment. There was a consistent increase in the percentage of responders at each time point, going from fewer than half the patients after one year to two-thirds after three years.

Name of Sponsor: ApoPharma Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Deferiprone		
Name of Active Ingredient: 3-hydroxy-1,2-dimethylpyridin-4-one		

Subgroup analyses: The analyses described above were additionally carried out on the subpopulations of patients with SCD and those with other anemias. For both groups, the change from baseline was significant at each time point. For the responder data, the percentages of responders in the SCD subpopulation were similar to those in the overall population, increasing from 42.7% of patients after one year of deferiprone treatment, to 54.2% after two years, to 66.0% after three years. For the patients with other anemias, the rate of responders increased from 68.4% after one year to 75.0% after two years, but then dropped to 66.7% after 3 years.

Cardiac MRI T2*

Change from baseline: Mean cardiac MRI T2* values did not change over time, ranging only from 32.04 ms to 32.90 ms, and the geometric mean MRI T2* at each year was almost identical to that at baseline (i.e., ratio close to 1.00, p-value>0.05).

Responder analysis: Responders were defined as individuals who had at least a 20% increase in cardiac MRI T2* since the start of deferiprone treatment. The percentage of responders was similar after one, after two, and after three years of treatment.

Subgroup analyses: The analyses described above were additionally carried out on the subpopulations of patients with SCD and those with other anemias. For the SCD patients, the ratios of geometric mean cardiac MRI T2* at Years 1, 2, and 3 were 1.02, 1.00, and 0.99, respectively, while for the patients with other anemias, they were 0.98, 0.99, and 0.89, respectively. None of the geometric means were significantly different from that of baseline (all p-values >0.05). For the responder data, as in the overall population, the percentages of responders in the SCD subpopulation varied little over 3 years (18.9% to 21.9%). For the patients with other anemias, the rate of responders was similar to the overall population at Years 1 and 2, but then dropped to 11.1% at Year 3.

Serum Ferritin

Change from baseline: The mean value did not change significantly over the first year, and decreased thereafter. There was effectively no change from baseline at Year 1, while significant decreases were seen at Year 2 and Year 3.

Responder analysis: Responders were defined as individuals who had at least a 20% decline in serum ferritin since the start of deferiprone treatment. There was a consistent increase in the percentage of responders at each time point, doubling from 35.2% after one year to 70.9% after three years.

Subgroup analyses: The analyses described above were additionally carried out on the subpopulations of patients with SCD and those with other anemias. For SCD patients, the results were similar to those of the overall population: serum ferritin increased at Year 1 by 130 ± 2086 µg/L (p=0.5222), was significantly decreased from baseline at Year 2 by -711 ± 2310 µg/L (p=0.0070), and was decreased at Year 3 (-918 ± 3926 µg/L) although here the change from baseline was not significant (p=0.1198), likely because the number of patients at this time point was too small (N=46) and the variability was higher. For the patients with other anemias, significant decreases from baseline were seen at Year 1 (-733 ± 1066 µg/L; p=0.0078), Year 2 (-1095 ± 1175 µg/L; p=0.00280), and Year 3 (-1517 ± 1120 µg/L;

Name of Sponsor: ApoPharma Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Deferiprone		
Name of Active Ingredient: 3-hydroxy-1,2-dimethylpyridin-4-one		

p=0.0036). For the responder data, the percentage in the SCD subpopulation who had at least a 20% decline in serum ferritin since the start of deferiprone treatment increased from 28.3% of patients after one year of deferiprone treatment, to 51.9% after two years, to 69.6% after three years. For the patients with other anemias, the rate remained the same: 73.7% at Year 1, 73.3% at Year 2, and 77.8% at Year 3.

SAFETY

The examination of safety focused on the events that occurred during the extension study in all patients (N=134), with supplementary summaries produced of the events experienced by just the subset of patients with sickle cell disease (N=115). In addition, summaries were produced of all safety events that occurred during deferiprone therapy: i.e., the total of the events reported for the DFP-DFP patients (N=89) during both the main and extension studies plus those reported for the DFO-DFP patients (N=45) during the extension study only. Those findings are provided in an appendix.

About three-quarters of patients experienced at least one AE of any type; about a quarter experienced at least one serious adverse event (SAE); about a third experienced an AE that was considered at least possibly related to study product; and about 10% experienced an SAE that was considered at least possibly related to study product. Nineteen patients (14.2%) had AEs of severe intensity, and 4 (3.0%) had AEs that led to withdrawal from the study, although in 2 of these cases the event was pregnancy, which was defined as an AE in the CRF. The percentages for each category for the subset of patients with sickle cell disease were similar to those in the overall population.

Adverse Events

Overall, 104 (77.6%) patients reported a total of 836 AEs. The most commonly reported events were pyrexia and bone pain in 35 (26.1%) patients each, abdominal pain in 26 (19.4%), and sickle cell crisis in 25 (18.7%). Fourteen other types of AEs were seen in from between 7 (5.2%) to 18 (13.4%) patients, and the remainder were each seen in less than 5%. The highest numbers of events were seen for bone pain (97), sickle cell crisis (81), pyrexia (56), back pain (51), abdominal pain (44), pain in extremity (33), decreased neutrophil count (29), nasopharyngitis and oropharyngeal pain (28 each), and headache (23). For all other types of AEs, fewer than 20 events were reported.

For the subset of the study population with sickle cell disease (N=115), 90 (78.3%) patients reported a total of 774 AEs. The frequencies of rates of each type of AE were comparable to those seen in the overall study population.

Severity of Adverse Events

The severity (intensity) of adverse events was rated as mild, moderate, or severe. Severe cases of sickle cell crisis were reported in 11 patients (8.2%), severe cases of pyrexia in 3 (2.2%), and severe cases of agranulocytosis, cholecystectomy, pneumonia, and decreased neutrophil count in 2 each (1.5%). No other type of severe event was seen in more than one patient. For moderate intensity, the most frequent event was bone pain, reported in 10 patients (7.5%), followed by sickle cell crisis and back pain in 8 each (6.0%), pain in extremity in 7 (5.2%), and neutropenia in 5 (3.7%). No other event of moderate intensity was seen in more than 4 patients (3.0%).

Name of Sponsor: ApoPharma Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Deferiprone		
Name of Active Ingredient: 3-hydroxy-1,2-dimethylpyridin-4-one		

Of the 836 AEs reported in the study, 567 (67.8%) were rated as mild, 213 (25.5%) as moderate, and 56 (6.7%) as severe. Those rated as severe included 15 cases of sickle cell crisis, 3 each of pyrexia and dyspnoea, and 2 each of agranulocytosis, osteomyelitis, pneumonia, decreased neutrophil count, and cholecystectomy. All other types of severe AEs occurred only once. Of the events rated as moderate, there were 48 cases of sickle cell crisis, 23 of bone pain, 16 of back pain, 9 of nausea, 8 of pain in extremity, 6 each of neutropenia and pyrexia, and 5 each of anemia, vomiting, and arthralgia. No other type of moderate AEs was seen more than 4 times.

In the subset of the study population with sickle cell disease, the percentages of patients experiencing events of severe and moderate intensity were comparable to what was seen in the overall study population.

Drug Relationship of Adverse Events

Adverse events that were considered to be at least possibly related to study product were identified as adverse drug ***reactions*** (ADRs). Of the 836 AEs that were reported in the extension study, 109 (13.0%) events in 41 (30.6%) patients were defined as ADRs. Neutropenia and decreased neutrophil count were each reported in in 12 (9.0%) patients, and abdominal pain was reported in 10 (7.5%). Eight other ADRs were reported in between 2 and 5 patients, and the remainder in only 1 patient each. Two patients experienced agranulocytosis, which is the most serious adverse event associated with deferiprone use. Both of these patients recovered.

With respect to the number of occurrences of each type of ADR, there were 22 related events of decreased neutrophil count, 15 of neutropenia, 14 of abdominal pain, 6 of increased ALT, 5 each of headache and chromaturia, and 4 each of vomiting, pyrexia, and increased AST. No other ADR occurred more than 3 times.

Of the 115 patients in the SCD group, 37 (32.2%) experienced at least one ADR. The most commonly reported events were neutropenia and abdominal pain, both seen in 10 patients (8.7%), followed by decreased neutrophil count in 9 (7.8%). No other ADR was seen in more than 5 (4.3%) patients.

Serious Adverse Events

Overall, 35 patients (26.1%) experienced a total of 106 serious adverse events during the extension study. The most frequent SAEs were sickle cell crisis in 19 patients (14.2%) and neutropenia in 12 (9.0%). No other type of SAE was seen in more than 5 patients, and the majority were seen in only one. With respect to the number of SAEs, there were 42 events of sickle cell crisis, 15 of neutropenia, 6 of pyrexia, and 3 each of dyspnoea and cholecystectomy. No other SAE had more than 3 occurrences. Thirteen (9.7%) patients experienced SAEs that were deemed to be at least possibly related to deferiprone. These events were neutropenia, seen in 12 (9.0%) patients, agranulocytosis in 2 (1.5%), and thrombocytopenia and generalized edema in 1 each (0.7%). The number of cases of agranulocytosis, which is the deferiprone side effect of greatest concern, is comparable to the rate seen in thalassemia patients. All patients recovered with the exception of the patient with edema, described below.

There was one death: a subject who was hospitalized with generalized edema about 3 months into the extension study and died about 4 weeks after the onset of the event. Medical history included hepatitis C infection, mild mesangial glomerulonephritis, and iron overload as well as elevated bilirubin and AST

Name of Sponsor: ApoPharma Inc. **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

prior to the start of deferiprone therapy. The cause of death was not clarified, although hepatic encephalopathy was clinically suspected by the investigator. The investigator considered the generalized edema to be possibly related to deferiprone, and the event is reported as such in the database. The company considered a causal relationship to deferiprone to be unlikely, reasoning that deferiprone has not previously been associated with liver failure, that the patient's medical history included significant risk factors for the events reported, and that possible inadequate management could have contributed to the fatal outcome.

Other Significant Adverse Events

Four withdrawals from the study were attributed to adverse events, although in two cases the event was pregnancy, which mandated withdrawal as per protocol. (Pregnancies were reported in the CRF as AEs.) One patient experienced events of thrombocytopenia and neutropenia which were considered serious, severe, and assessed by the investigator as definitely related to deferiprone. Both these events resolved. The fourth withdrawal attributed to an adverse event was the patient who died due to reasons that were not clarified. This case is described briefly above.

CONCLUSIONS

- The long-term safety profile of deferiprone in patients with sickle cell disease and other transfusion-dependent anemias was acceptable, there were no new safety concerns, and the long-term safety profile is consistent with that seen in other populations.
- Deferiprone continued to show efficacy in controlling body iron load beyond 12 months of treatment in patients with sickle cell disease and other transfusion-dependent anemias.

Date of the report: 26 MAY 2020