# Oncologic Drugs Advisory Committee
# Briefing Document

# NDA # 21-825

# Ferriprox® (deferiprone)

is an iron chelator indicated for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate

Meeting date: **September 14, 2011**

**AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION**

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACE | angiotensin converting enzyme |
| ADR | adverse drug reaction |
| AE | adverse event |
| AFP | α-fetoprotein |
| AHA | anti-histone antibody |
| ALT | alanine aminotransferase |
| ANA | anti-nuclear antibody |
| ANC | absolute neutrophil count |
| ANCOVA | analysis of covariance |
| ANOVA | analysis of variance |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| b.i.d. | bis in die (twice a day) |
| BCS | Biopharmaceutical Classification System |
| BP | blood pressure |
| CBC | complete blood count |
| CEA | carcinogenic embryonic antigen |
| CHF | congestive heart failure |
| CI | confidence interval |
| CK-7 | Cytokeratin 7 |
| CL/F | Clearance/Fraction of drug (apparent clearance) |
| $C_{max}$ | maximum concentration |
| CMR | cardiac magnetic resonance |
| COPD | chronic obstructive pulmonary disease |
| CRF | case report form |
| CRL | Complete Response Letter |
| CRP | C-reactive protein |
| CT | computed tomography |
| CV | coefficient of variation |
| CYP450 | cytochrome P450 |
| DEXA | dual energy x-ray absorptiometry |
| DFO | deferoxamine |
| DFP | deferiprone |
| DFX | deferasirox |
| DHCPL | Dear Health Care Professional Letter |
| DNA | deoxyribonucleic acid |
| dsDNA | double stranded deoxyribonucleic acid |
| dw | dry weight |
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| $ED_{50}$ | effective dose 50 |
| EF | ejection fraction |
| EMA | European Medicines Agency, formerly EMEA |
| EU | European Union |
| F | bioavailability factor |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| G-CSF | granulocyte colony-stimulating factor |
| GGT | gamma glutamyltransferase |
| GI | gastrointestinal |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| Hb | hemoglobin |
| HCP | healthcare provider |
| HCT | hematocrit |
| HCV | hepatitis C virus |
| HDPE | High Density Polyethylene |
| hERG | Human Ether A-Go-Go Related Gene |
| HIV | Human Immunodeficiency Virus |
| HPA | Hypothalamic-Pituitary-Adrenal |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| i.p. | intraperitoneal |
| i.v. | Intravenous |

| | |
|---|---|
| Kel | elimination rate constant |
| LIC | liver iron concentration |
| LOCF | last observation carried forward |
| LVEF | left ventricular ejection fraction |
| LVSF | left ventricular shortening fraction |
| MDS | Myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MRT | mean residence time |
| N/A | Not applicable |
| NAP | Not applicable |
| NDA | New Drug Application |
| NYHA | New York Heart Association |
| ODAC | Oncologic Drugs Advisory Committee |
| PA | pulmonary artery |
| PK | pharmacokinetic |
| PLT | platelet |
| PP | per protocol |
| PT | preferred term |
| RBC | red blood cell |
| RCT | randomized controlled trial |
| RES | reticuloendothelial system |
| RF | rheumatoid factor |
| RM | risk management |
| RMP | Risk Management Plan |
| RR | ribonucleotide reductase |
| SADR | serious adverse drug reaction |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| s.c. | subcutaneous |
| SCD | sickle cell disease |
| SD | standard deviation |
| SF | shortening fraction |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |
| SNP | single nucleotide polymorphism |
| SOC | System Organ Class |
| SQUID | superconducting quantum interference device |
| TEAE | treatment emergent adverse event |
| t.i.d. | ter in die (three times a day) |
| TM | thalassemia major |
| UK | United Kingdom |
| ULN | upper limit of normal |
| $V_d$ | volume of distribution |
| vs. | versus |
| WBC | white blood cell |
| Wt | weight |

# 1. Executive Summary

In the United States, approximately 500 to 1,000 patients with thalassemia major and 5,000 to 10,000 patients with sickle cell disease (SCD), along with smaller numbers of certain other congenital anemias are transfusion-dependent at any given time. Chronic transfusion therapy reduces disease-related morbidity and mortality in these patients, but introduces a progressive iron overload that damages, particularly, the heart, liver, and endocrine organs. In the absence of adequate iron chelation therapy, premature death due to iron overload usually occurs in the second or third decade after transfusions begin, with iron-induced cardiac disease as the primary cause. Although some patients with myelodysplastic syndrome (MDS) are also transfusion-dependent, there is less evidence that most of these patients would realize much clinical benefit from iron chelation.

Only two iron chelators, Desferal® (deferoxamine, DFO) and Exjade® (deferasirox, DFX), are available in the US for the treatment of iron overload. Long-term, compliant use of deferoxamine stabilizes or improves all three clinically utilized measures of iron load: serum ferritin, liver iron concentration and cardiac MRI T2*, reducing iron-induced morbidity and prolonging survival of patients with transfusion-dependent thalassemia. Deferasirox is non-inferior to deferoxamine in controlling serum ferritin and liver iron concentrations. No data are yet available on the relative efficacy of deferasirox to deferoxamine in controlling cardiac iron or in decreasing iron-induced morbidity and mortality.

Despite the ability of these two chelators to promote net iron excretion in treated populations, both are recognized as exerting inadequate control of iron overload in some patients, ranging from 25% when using serum ferritin as the index (Cappellini MD *et al.* 2010) to >30% when using cardiac MRI T2* as the index (Anderson LJ *et al.* 2002; Wood JC *et al.* 2008). Long-term failure to reduce iron levels in these individuals results in an unacceptable level of morbidity and rate of early deaths, primarily from cardiac disease. Some patients cannot tolerate the 8-12 hour nightly infusions of deferoxamine and others cannot cope with the gastrointestinal distress accompanying oral deferasirox. Both have dose-limiting toxicity and the evolving safety profile of deferasirox has revealed serious adverse events including renal and hepatic failure, and gastrointestinal hemorrhage, including fatalities. There remains an unmet medical need for another effective and tolerable iron chelator for those patients in whom existing chelators are inadequate due either to failure to control iron levels or intolerable adverse effects.

ApoPharma is seeking FDA approval of the oral iron chelator deferiprone for the following indication:

> *the treatment of patients with transfusional iron overload when current chelation therapy is inadequate*

Inadequate chelation here is defined as increasing iron load or maintenance of a clinically undesirable iron load, or intolerance to a chelator's use.

Deferiprone is an orally absorbed iron chelator that, like deferoxamine and deferasirox, promotes iron excretion in a dose-dependent manner. At a total daily dose of 75 mg/kg, deferiprone stabilizes or decreases the iron burden in the majority of transfusion-dependent patients, despite continued transfusional iron input. Deferiprone is distinct from the other two chelators mainly in

terms of physicochemical properties that support rapid access to intracellular labile iron stores; this has been demonstrated in isolated cells, including cardiomyocytes, and may underlie deferiprone's clinical effectiveness in reducing cardiac iron loading.

Deferiprone was first approved for the treatment of iron overload in 1999 by the European Medicines Agency (EMA) and it is currently approved in 61 countries. In most, deferiprone is indicated for the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contraindicated or inadequate. In part, because of its commitment to the EMA following European approval, ApoPharma continued to sponsor clinical studies on deferiprone to obtain a more complete understanding of its safety and efficacy. These studies indicate that deferiprone has comparable efficacy to deferoxamine in controlling serum ferritin and liver iron concentrations, and that it is superior to deferoxamine in reducing cardiac iron content in transfusion-dependent patients. The results of natural history studies conducted by or analyzed in depth by ApoPharma are consistent with results from other published studies that patients with transfusion-dependent thalassemia treated long term with deferiprone have a lower incidence of iron-induced cardiac disease than patients treated long term with deferoxamine.

ApoPharma's initial New Drug Application to the FDA in 2009 proposed deferiprone as a first line treatment of transfusional siderosis, but following discussion with the Agency on the clinical studies available, the company accepted advice to reposition the application for second line therapy in the treatment of transfusional iron overload in patients for whom previous chelation therapy had been inadequate. ApoPharma also agreed to submit an analysis of data from all of the company's clinical studies of deferiprone as the central assessment of its efficacy in patients with transfusional iron overload who had previously failed therapy with other iron chelators. The design of the analysis, coded LA36-0310 ('LA36') accommodates the statistical constraints imposed by analysis of pre-existing data collected from clinical trials with diverse objectives, diverse inclusion/exclusion criteria, and diverse treatment regimens and durations. In LA36, inadequate response of patients to previous chelation therapy was defined as compliance with any of the following three conditions:

1. baseline serum ferritin >2,500 µg/L; or
2. baseline liver iron concentration >7 mg/g dry weight, or
3. baseline cardiac MRI T2* <20 ms.

These 3 indices of iron overload appear to characterize iron loading in different pools and have been reported to be independent thresholds for higher risk of iron-induced cardiac toxicity and premature death (Borgna-Pignatti C *et al.* 2004; Kirk P *et al.* 2009; Olivieri NF *et al.* 1994; Telfer PT *et al.* 2000). The purpose of the LA36 analysis was to establish whether the existing data in studies included in the deferiprone NDA provided sufficient evidence to support the use of deferiprone in patients who had failed previous chelation therapy. The primary analysis was for a positive response to deferiprone therapy, defined as at least a 20% reduction in serum ferritin in a treatment period of up to 12 months. Secondary analyses defined a positive response to therapy as at least a 20% reduction in liver or cardiac iron at 12 months. LA36 would be considered positive if no less than 20% of the patients who had failed previous chelation therapy experienced a 20% or greater decline in serum ferritin within up to one year of deferiprone therapy. For added assurance, deferiprone would be considered successful only if the lower limit of the 95% confidence interval for the success rate on serum ferritin was greater than the pre-

defined criterion of 20% treatment success. The same criteria were applied to liver iron concentration and cardiac MRI T2*. Table 1-1 summarizes the results of these analyses.

**Table 1-1: LA36: Analysis of Success Rate (Proportion of Patients with >20% improvement) based on Serum Ferritin, Liver Iron Concentration and Cardiac MRI T2* after up to 1 year of deferiprone therapy**

| Measure | Number of patients meeting criteria for failure of previous therapy | Success rate % (N) | 95% C.I. |
|---|---|---|---|
| Serum Ferritin | 264 | 52% (136) | 45%, 58% |
| Liver Iron Concentration | 117 | 42% (49) | 32%, 51% |
| Cardiac MRI T2* | 39 | 62% (24) | 45%, 77% |

In order to test the impact of the heterogeneity of the data sources for LA36, subgroup analyses were conducted in which the influence of patient demographics factors and the number of serum ferritin measurements available at baseline were examined. Success rates for serum ferritin in pediatric and adult patients were similar (46% vs. 54%, p=0.234), as were those in males and females (53% vs. 50%, p=0.711), and those in 228 patients with thalassemia major and 36 with other transfusion-dependent anemias (50% vs. 58%, p=0.473). The lower limit of the 95% confidence interval for the success rate was greater than 20% for all of the subgroup analyses. In conclusion, the results of study LA36 show that:

- results complied with the primary and secondary criteria agreed with the FDA;
- deferiprone is an effective treatment in patients with iron overload who failed previous therapy;
- based on subgroup analyses, deferiprone is effective in pediatric and adult patients, in males and females, and in thalassemia major and non-thalassemia major patients;

Notwithstanding the inherent limitations of analysis of pre-existing data, LA36 provides broad evidence of the effect of deferiprone in patients enrolled in the ApoPharma clinical trials and who had failed previous chelation therapy. Each study that contributed data to LA36 itself evaluated the efficacy of deferiprone in controlling body iron burden in transfused patients, using one or more of the three nominated indices of iron overload. These source studies are consistent in showing that deferiprone is effective in controlling the iron burden, as assessed by serum ferritin, liver iron concentration or cardiac MRI T2* in transfusion-dependent patients, despite continued transfusional iron input (LA-01, LA-02/06, LA-03, LA-04/06B, LA08, LA-11, LA15, LA16, LA28, LA30, Borgna-Pignatti et al). In addition, deferiprone was superior to deferoxamine in reducing cardiac iron load in a randomized controlled study (LA16). Both conclusions are supported by published literature.

Both deferoxamine and deferasirox are approved for transfusional iron overload, including patients with thalassemia, other congenital anemias and MDS. ApoPharma has provided some data on the use of deferiprone in non-thalassemia populations based upon its compassionate use program and based upon the safety and efficacy of deferiprone as published in the literature, but no formal studies have been conducted in these populations. It is evident both from the

compassionate use program and the literature, that there is a need for an alternative iron chelator in a segment of this transfusion-dependent population who are inadequately treated with previous chelation, and it is widely held that the mechanism of iron removal is not disease specific. Thus to meet the current need, ApoPharma proposes that the data submitted be sufficient for establishing reasonable evidence of the efficacy and safety of deferiprone in transfusion-dependent patients, including those with other than thalassemia, on the understanding that ApoPharma commits to a confirmatory post-approval safety study in patients with sickle cell disease, to be initiated within 9 months of FDA approval. A draft synopsis of the proposed study is provided for comment and for future discussion with the FDA.

The safety profile of deferiprone has been characterized by 23 years of clinical experience, including 11 years' post-marketing outside the US.

*Clinical trials:* The clinical development program of deferiprone did not include a randomized trial designed to compare its safety with that of deferoxamine, as deferiprone's known association with agranulocytosis caused it to be developed initially for the treatment of patients for whom deferoxamine was inadequate. No placebo-controlled studies were conducted because of the life-threatening nature of iron overload. While assessment of efficacy in this document focuses on patients who had failed previous chelation therapy, evaluation of safety considers adverse events (AEs) in all 642 patients, aged 1 to 77 years old, treated with deferiprone in the ApoPharma studies at doses of from 50 to 100 mg/kg/day. The only studies not included in the pooled safety database were single dose pharmacokinetic, bioequivalence or bioavailability studies, and studies in which no safety data were collected.

The most serious adverse event (AE) associated with deferiprone use is agranulocytosis, defined as a confirmed absolute neutrophil count less than $0.5 \times 10^9$/L. Agranulocytosis, irrespective of causality, occurred in 11 (1.7%) of the 642 deferiprone-treated patients in clinical trials, and in none of the 118 deferoxamine-treated patients enrolled in ApoPharma's comparative trials. All 11 episodes resolved upon interruption of deferiprone. Median time for resolution was 10 days (range 3 - 85 days). Less severe episodes of neutropenia (absolute neutrophil count less than $1.5 \times 10^9$/L but not less than $0.5 \times 10^9$/L) occurred in 6.7% of the deferiprone-treated patients and in 4.2% of deferoxamine-treated patients.

Gastrointestinal upset, arthropathies, and increased ALT were common AEs and were considered to be of particular interest mainly because of their temporal relationship to administration of deferiprone and/or a greater incidence than in deferoxamine-treated patients. In general, the gastrointestinal AEs occurred at initiation of deferiprone therapy, were most frequently mild to moderate in severity, and resolved within a week of onset without discontinuation of therapy. Ten (1.6%) patients in clinical trials discontinued therapy due to gastrointestinal AEs. Arthropathies, which ranged from mild pain in one or more joints to severe pain and significant disability, were most frequent in the first year of therapy and usually resolved without discontinuation of therapy. Twelve (1.9%) patients in clinical trials discontinued therapy due to arthropathies. Serum ALT values above the upper limit of normal were observed most frequently during the first 3 months of therapy, were generally mild to moderate in severity, asymptomatic and transient, and returned to baseline without discontinuation or decreasing the dose of deferiprone. Four (0.6%) patients in clinical trials discontinued therapy due to increased serum ALT levels. No consistent pattern or dose relationship were detected among those

episodes of discontinuations due to increased serum ALT levels. One additional patient was withdrawn for increased serum hepatic enzyme (ALT, AST and GGT) levels. Another patient was discontinued for hepatitis, characterized by increased serum ALT and GGT, and jaundice; careful evaluation determined that these findings were most likely related to hepatitis C infection rather than to drug toxicity. There were no episodes of liver impairment/failure. Long-term therapy was not associated with an increase in the nature, frequency or severity of AEs.

*Post-marketing:* Deferiprone benefits from a decade of post-marketing experience exceeding the total number of eligible patients for the proposed indication in the US. In this experience, the most common serious adverse events associated with deferiprone use were neutropenia and agranulocytosis. Ninety four cases of agranulocytosis have been reported since 1999, of which thirteen were fatal. Most or all of these fatal cases were associated with failure to comply with one or more elements of the guidance to management of agranulocytosis provided in the prescribing information, which includes regular routine monitoring of the neutrophil count, and interruption of therapy and close monitoring of the neutrophil count at signs of infection. To improve management of cases, ApoPharma initiated a targeted program in Europe emphasizing to health care providers and to patients the importance of monitoring blood cell counts and of early discontinuation of deferiprone at the first sign of neutropenia. Subsequent surveys of health care professionals by ApoPharma indicate awareness of those measures by the majority of respondents. While the rate of reported cases of agranulocytosis essentially remained constant through the period preceding and following implementation of the program, reported fatalities declined from 0.07 to 0.01 episodes/100 patient-years. The last case of agranulocytosis with fatal outcome reported to ApoPharma was in 2008. No new serious safety concerns have been identified with the use of deferiprone since its first marketing authorization in 1999.

To minimize the risks associated with agranulocytosis, a risk management plan will be discussed with the Agency that controls the dispensing of all prescriptions through a central pharmacy, highly experienced in the distribution of orphan and ultra orphan medicines. It will require the registration of prescribing medical specialists and patients who will sign off on their commitment to an educational and adherence program designed to minimize risk. This program will include monitoring of neutrophil counts on a weekly basis and the interruption of therapy at the earliest sign of neutropenia or at signs of infection. Each time a prescription is issued, a written reminder will be provided to the patient about the risk of agranulocytosis, and the need for monitoring the neutrophil count and of interruption of therapy at signs of infection. Similar to the program in the EU, patients will be issued a wallet-sized card, reminding them of the risk of agranulocytosis, the importance of monitoring their neutrophil count and the need to immediately contact their physician on experiencing signs of infection.

In summary, LA36 demonstrated that deferiprone is an effective treatment in patients with iron overload for whom previous chelation therapy had been inadequate. The individual studies from which LA36 data were drawn uniformly provide evidence of deferiprone's ability to reduce or control the iron burden in transfusionally iron overloaded patients, as measured by serum ferritin or liver iron concentrations, or by cardiac MRI T2*. In addition, the contributory study LA16 demonstrates that deferiprone is superior to deferoxamine in reducing cardiac iron load. Both conclusions are supported consistently by independent publications. Consideration of deferiprone's safety profile, based on data from clinical trials and the learnings of post-marketing experience, show that the benefits of deferiprone for patients who have failed previous chelation

therapy outweigh its potential risks.

The information submitted to the FDA support a decision to make deferiprone available to fulfill the unmet medical need for an iron chelator for the treatment of transfusional siderosis in patients in whom previous chelation therapy has been inadequate.

# 2. Iron Overload and Current Unmet Medical Need

Patients with severe anemia, such as those with thalassemia major, require repeated blood transfusions to maintain life. Other anemias, such as sickle cell disease (SCD), require chronic transfusions to prevent the occurrence of complications that arise as a result of the disease, or episodic transfusions to ameliorate complications when they do arise (NIH guidelines). There are also other rare, congenital anemias, such as Diamond Blackfan anemia, that require patients to receive chronic transfusions for the duration of their lives. Such programs of treatment cause severe iron overload as there is no natural means to remove the excess iron introduced through the transfusion of red blood cells.

Without intervention to remove this excess iron, death frequently occurs in the second or third decade after transfusions begin, mainly due to organ toxicity and iron-induced cardiac disease. Regardless of the underlying primary disease leading to the need for transfusions, these patients require treatment with iron chelators to prevent the morbidity and mortality induced by the iron overload.

## 2.1. Assessment of iron overload and of iron toxicity

Three primary parameters are used to assess the degree of iron overload: serum ferritin, liver iron concentration and cardiac MRI T2*. Each of these three parameters provides information on different aspects of iron loading and each of them are considered independent indicators for higher risk of iron-induced cardiac toxicity and premature death (Borgna-Pignatti C *et al.* 2004; Kirk P *et al.* 2009; Olivieri NF *et al.* 1994; Telfer PT *et al.* 2000).

### *2.1.1.* ***Serum Ferritin***

The most commonly used method for the assessment of body iron burden is the measurement of serum ferritin concentration (Borgna-Pignatti C & Castriota-Scanderbeg. 1991; Brittenham GM *et al.* 1981; Brittenham GM *et al.* 1993; Finch C. 1994; Finch CA *et al.* 1986; Lipschitz DA *et al.* 1974; Worwood M *et al.* 1980). Ferritin is the major storage protein for iron. It is present in small concentrations in the plasma and is a reflection of total body iron. Due to the continuous transfusional iron input and the lack of a natural excretory pathway for the excess iron, a progressive increase in serum ferritin concentration occurs in transfusion-dependent patients, in the absence of effective iron chelation therapy (see Figure 1) (Kattamis C. 1987).

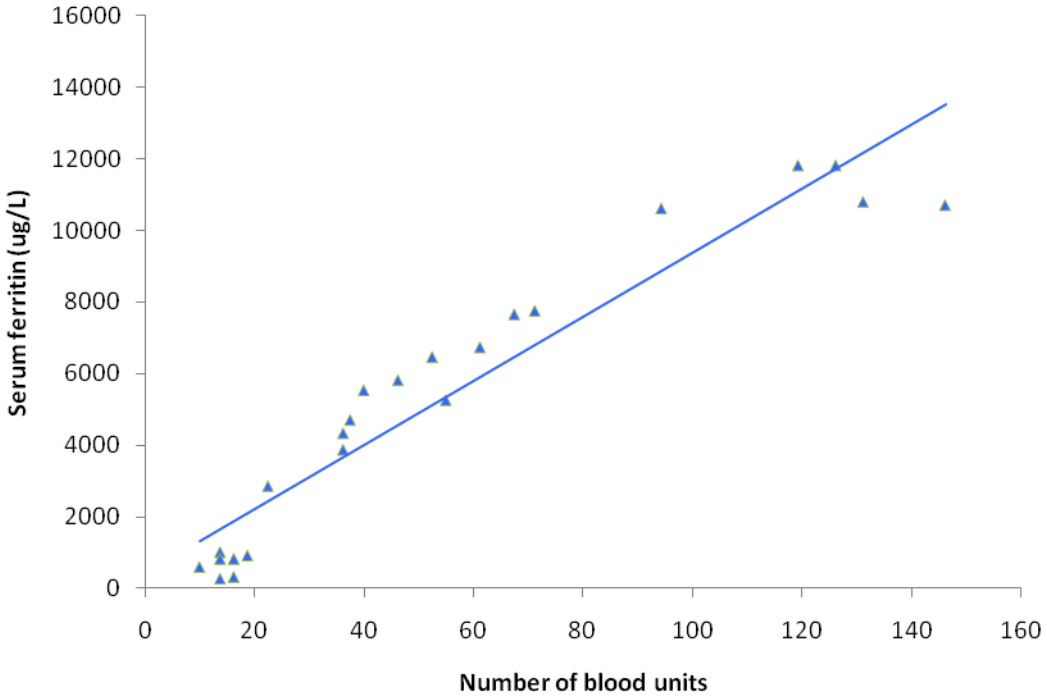


**Figure 1: Serum Ferritin in Patients with Thalassemia who are Regularly Transfused and not Chelated**

*(adapted from Kattamis, 1987)*

Ferritin is also an acute phase reactant, i.e., its plasma levels may increase during inflammatory events. Adult patients who have been transfused from childhood, have a high prevalence of hepatitis C, due to contamination prior to the use of adequate screening tests. These patients will have high, fluctuating levels of ferritin, which may confound the intrepretation of ferritin values during an inflammatory episode (Crosby WH. 1976; Lee MH & Means, Jr. 1995; Olive A & Junca. 1996; Olivieri NF & Brittenham. 1997). Nonetheless, sequential measures of serum ferritin concentration remain the most common method for assessment of body iron burden, and in clinical practice it is the standard for identifying trends in iron status within individuals and across populations. Serum Ferritin, even with its limitations, is a useful index within an individual with respect to changes in iron status, and serum ferritin levels above 2,500 µg/L have been considered an important indicator of the relative risk of cardiac toxiticy and death for decades (Hoffbrand AV *et al.* 2003; Olivieri NF *et al.* 1994; Telfer PT *et al.* 2000).

### *2.1.2. Liver Iron Concentration (LIC)*

The liver contains 70% or more of total body iron (Angelucci E *et al.* 2000), justifying the use of liver iron concentration as a measure of body iron load (Brittenham GM *et al.* 2001; Olivieri NF & Brittenham. 1997; Overmoyer BA *et al.* 1987; St Pierre TG *et al.* 2005). In the absence of effective iron chelation therapy, transfusion-dependent patients experience a progressive increase

in LIC (Cazzola M *et al.* 1983). Although liver iron concentrations may differ from the concentrations of iron in other organs, it has been reported that patients with LIC greater than 7 mg iron/g liver (dry weight; dw) are at increased risk of iron-induced toxicity such as cardiac disease, hepatic fibrosis, diabetes mellitus and death (Hoffbrand AV *et al.* 2003; Olivieri NF & Brittenham. 1997; Telfer PT *et al.* 2000). The current goal for chelation therapy in transfusion-dependent patients is to maintain an "optimal" body iron burden corresponding to hepatic storage concentrations of less than 7 mg/g dw (Olivieri NF & Brittenham. 1997).

### *2.1.3.* ***Cardiac Iron Concentration (Cardiac MRI T2*)***

Although iron-induced cardiac disease is the most common cause of premature death as a result of transfusional iron overload (Borgna-Pignatti C *et al.* 2004; Li CK *et al.* 2002; Telfer P *et al.* 2006), practical and reproducible measures of cardiac iron concentration were not available prior to the development of the cardiac magnetic resonance imaging MRI T2* technique (Anderson LJ *et al.* 2001). It is now known that myocardial MRI T2* can be used to monitor the myocardial iron load resulting from chronic transfusions, with low T2* levels reflecting a high cardiac iron concentrations and high T2* values reflecting low cardiac iron. This technique has been calibrated with cardiac iron concentration in post mortem hearts (Carpenter JP *et al.* 2011). Studies in non iron overloaded subjects reveal that none have a cardiac T2* <20 ms, a value that is now widely used clinically as the threshold for cardiac iron overload (Wood JC. 2007). The ability of cardiac MRI T2* to identify patients at risk of iron-induced cardiac disease and premature death has been reported (Storey P *et al.* 2007), and its predictive value has been prospectively evaluated in 652 transfusion-dependent thalassemia patients from 21 UK centers, who had cardiac MRI T2* assessment and who had their cardiac status followed over time (Kirk P *et al.* 2009). The results of this study demonstrate that the lower the cardiac MRI T2* value, i.e., the higher the cardiac iron load, the higher is the risk of developing iron-induced cardiac failure within the subsequent 12 months.

Most studies reveal that the 3 measures of iron overload do not correlate well with each other, and that should not be surprising as LIC is explicitly measuring iron in the liver and cardiac MRI T2* is explicitly measuring iron in the heart, but all three parameters are widely used as measures of iron overload in clinical practice today, either alone or combined, to assess the adequacy of a patient's chelation treatment. Employed judiciously by a physician experienced in the management of iron overload, each is capable of conveying useful, and complimentary, information.

## 2.2. Current Treatment of Iron Overload in the US

In the US, two iron chelators, Desferal® (deferoxamine, DFO) and Exjade® (deferasirox, DFX), both marketed by Novartis®, are currently available for the treatment of iron overload.

The first commercially available iron chelator was deferoxamine (DFO), which was approved in 1968. To be effective, DFO must be delivered as a constant infusion, usually subcutaneously, for 8 to 12 hours a night, at least five days per week. Long-term use of deferoxamine is associated with stabilization or decline in all three measures of iron load and with decreased iron-induced morbidity and with improved survival of transfusion-dependent thalassemia patients (Borgna-Pignatti C *et al.* 2004; Kwiatkowski JL. 2008). However, there are some

important adverse reactions to deferoxamine. These include local skin reactions which are almost universal, and auditory and visual disturbances. There is a susceptibility to certain gram-negative infections, in particular *Yersinia enterocolitica*, in patients who receive deferoxamine. However, the biggest issue, from a practical point of view, is the lack of compliance with this very demanding, and somewhat painful, drug infusion regimen (Noetzli LJ *et al.* 2008). The use of deferoxamine fewer than 5 days per week is associated with a greater than 50% mortality at 30 years of age (Gabutti V & Piga. 1996). Additionally, accumulation of excess cardiac iron can occur even in patients compliant with deferoxamine chelation therapy that is assessed as adequate by serum ferritin and liver iron concentrations. Measurements of cardiac MRI T2* demonstrate that excess myocardial iron is present in approximately 60% of transfusion-dependent thalassemia patients treated with DFO (Anderson LJ *et al.* 2002; Wood JC *et al.* 2008).

The other therapy currently available in the U.S. is deferasirox, or Exjade. Approved in 2005, deferasirox was the first orally-available iron chelator to be approved in the United States. It is administered once daily. At doses of 20-40 mg/kg/day, deferasirox is non-inferior to deferoxamine in stabilizing or decreasing serum ferritin and liver iron concentrations. While deferasirox can reduce elevated cardiac iron, no randomized clinical studies have evaluated its efficacy in cardiac iron removal relative to that of deferoxamine. No data are available on the ability of deferasirox in reducing iron-induced morbidity and mortality. Deferasirox-induced adverse reactions include gastrointestinal disturbances and increases in serum creatinine and transaminase levels that require monthly monitoring. A MedWatch publication in 2010 reported 1,320 deaths as SAEs in deferasirox-treated patients, most, but not all of which were in MDS patients (ISMP (2010)). In thalassemia, there is a growing concern of deferasirox-induced Fanconi Syndrome (Grange S *et al.* 2010; Rafat C *et al.* 2009). The safety profile of deferasirox is still evolving and a warning about the risk of kidney failure, liver failure, and gastrointestinal hemorrhage, sometimes fatal, has been added to its label. In addition, deferasirox therapy, even at the highest recommended dose, is associated with insufficient efficacy in a substantial number of patients (Cappellini MD *et al.* 2006; Pennell DJ *et al.* 2010). In its pivotal trial for marketing authorization (Cappellini MD *et al.* 2006), low doses of deferasirox fail to achieve non-inferiority to deferoxamine, whereas a segment of patients in the highest dose cohort (30 mg/kg), exhibited net liver iron increase during the one year study period. In another trial, 25% of subjects within the highest dose cohort (mean dose 37 mg/kg/day) showed no decrease or a rise in serum ferritin values (Cappellini MD *et al.* 2010).

In the US, it is evident that there is a body of patients for whom deferoxamine or deferasirox remain inadequate. In records kept by the Cooley's Anemia Foundation (thalassemia patient advocacy group), more than 10% of their registered patients have died over the past decade, predominantly from iron-induced heart disease, and nearly all were relatively young adults. Since the approval of deferasirox at the end of 2005, 52 requests for individual investigator's treatment INDs with deferiprone have been submitted to the FDA for patients who have failed chelation therapy with deferasirox or deferoxamine. In many of those patients, deferiprone has been used as salvage therapy for iron-induced end-stage organ damage as a temporary gap measure to address this unmet need. Unfortunately, waiting until patients are in medical distress to use deferiprone reduces the likelihood of success, and access to deferiprone for a worsening condition, induced by long term transfusions and inadequate chelator efficacy needs to be

available to the clinician as soon as a deterioration is detected.

### 2.3. Background Conclusions

Increased risk of iron-induced cardiac disease and death have been associated with increased serum ferritin, liver iron, or cardiac iron levels. Although deferoxamine and deferasirox are available in the US, some patients continue to exhibit high levels of each of these 3 indices that are employed in clinical practice as predictors of morbidity and early mortality. Drug-induced adverse reactions, sometimes life-threatening, also prevent utilization of the 2 currently available chelators in the US. There remains an unmet medical need for another iron chelator for the treatment of transfusional iron overload for patients with an undesirable or increasing iron load or for patients who cannot tolerate the use of either currently approved chelator.

## 3. Overview of Deferiprone

### 3.1. Chemical Structure and Pharmaceutical Form

Deferiprone (MW 139.15) is a 3-hydroxypyrid-4-one with a high affinity for ferric iron, binding it in a 3:1 molar ratio. The structural formula of deferiprone is shown in Figure 2.

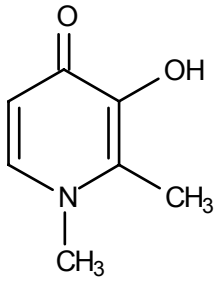


**Figure 2: Chemical structure of deferiprone**

Ferriprox tablets, the ApoPharma formulation of deferiprone, are white to off-white, capsule-shaped, film-coated tablets containing 500 mg of deferiprone. The non-medicinal ingredients are microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide, all commonly used in pharmaceutical dosage forms. The tablets are scored and breakable in half. They are provided in HDPE bottles of 100 tablets with child resistant closures.

### 3.2. Non-Clinical Pharmacology and Toxicology

#### *3.2.1. Non-Clinical Overview*

Deferiprone had been the subject of several non-clinical investigations prior to ApoPharma's involvement in its development, most of which have been published in the scientific literature. Therefore, the following summary is based on data assembled from independent studies in the public domain and from GLP-compliant *in vitro* and *in vivo* studies sponsored or conducted by ApoPharma in order to address deficiencies in the former database.

### *3.2.2.* ***Pharmacodynamics***

Deferiprone is an iron(III)-selective chelator ($pFe^{+3}$ = 19.4) that forms a 3:1 (ligand:iron) complex and preferentially binds trivalent over divalent cations (Liu ZD *et al.* 1999a). Its small molecular size, lack of charge at physiological pH (Liu ZD *et al.* 1999a), and octanol:water partition coefficient (Kontoghiorghes GJ *et al.* 1988) favor both its water solubility and its diffusion through lipid membranes, and hence its rapid absorption from the gut and its cell permeability. Deferiprone rapidly accesses intracellular labile iron; fluorescence microscopy shows that it reaches major intracellular sites of iron accumulation (mitochondria, endosomes, and lysosomes), and facilitates the transfer of iron from the intracellular to extracellular space (Sohn YS *et al.* 2008).

Deferiprone prevents uptake and mobilizes iron from primary cultures of cells derived from the organs most affected clinically by iron overload, including cardiomyocytes (Glickstein H *et al.* 2005; Hershko C *et al.* 1991), and hepatocytes (Glickstein H *et al.* 2005; Mostert LJ *et al.* 1987; Porter JB *et al.* 1988). Iron chelation reduces free radical iron-mediated damage, and protects against iron-induced loss of enzyme activities at concentrations consistent with those achieved therapeutically (Chenoufi N *et al.* 1995; Link G *et al.* 1994; Link G *et al.* 1999).

Deferiprone reduces body iron levels in multiple species, including the mouse (Eybl V *et al.* 2002; Kontoghiorghes GJ. 1986a; Kontoghiorghes GJ. 1986b; Porter JB *et al.* 1991), rat (Bergeron RJ *et al.* 1992; Kontoghiorghes GJ *et al.* 1987; Liu ZD *et al.* 1999b) (Data on file with FDA), gerbil (Hershko C *et al.* 2002), guinea pig (Wong A *et al.* 1997) and monkey (Bergeron RJ *et al.* 1992; Sergejew T *et al.* 2000). In rodent species the majority of iron excretion is biliary (Bergeron RJ *et al.* 1992; Kontoghiorghes GJ *et al.* 1987; Liu ZD *et al.* 1999b) (Data on file with FDA) and there is a clear relationship between dose and total iron excretion (Link G *et al.* 2001) (Data on file with FDA).

Deferiprone significantly reduces iron levels in the kidney, pancreas and liver of iron-loaded mice (Gale GR *et al.* 1991) and eliminates significant amounts of hepatic iron in rodents (Bergeron RJ *et al.* 1992; Kontoghiorghes GJ *et al.* 1987; Liu ZD *et al.* 1999b) at doses of 30 mg/kg/day and higher (Florence A *et al.* 1992). Excess cardiac iron was lowered in some studies (Eybl V *et al.* 2002; Hershko C *et al.* 2002; Wood JC *et al.* 2006) and unaffected in others (Florence A *et al.* 1992; Porter JB *et al.* 1991), possibly reflecting the characteristics of the iron-loading models, and difficulty in quantifying small absolute amounts of cardiac iron. In iron-loaded Mongolian gerbils oral administration of 200 mg/kg/day deferiprone for 20 weeks, or 375 mg/kg/day for 12 weeks, significantly decreased both hepatic and cardiac iron burden (Hershko C *et al.* 2002; Wood JC *et al.* 2006).

Secondary pharmacodynamic findings include the *in vitro* inhibition of soybean lipoxygenase (as an experimental substitute for human 5-lipoxygenase) by approximately 70% after 24 hours' incubation at the supratherapeutic concentration of 330 µM (Kayyali R *et al.* 2001). Another non-heme iron-containing metalloenzyme, ribonucleotide reductase (RR), was inhibited approximately 22% by 33 µM deferiprone and about 40% by 330 µM deferiprone after a 1-hour incubation of K562 erythroleukemia cells (Kayyali R *et al.* 2001). Inhibition of RR, and hence of DNA synthesis, is believed to be responsible for the atrophy of fast proliferating tissues in animals and for the clastogenic activity noted in various *in vitro* and *in vivo* models exposed to

high doses of deferiprone (see section 3.2.4). Deferiprone has also been reported to inhibit catechol-*O*-methyl transferase (COMT; $ED_{50}$ *ca.* 10 mg/kg ip), tyrosine hydroxylase and tryptophan hydroxylase ($ED_{50}$ for both enzymes *ca.* 20-30 mg/kg ip) in the brain of non-iron-loaded rats (Waldmeier PC *et al.* 1993). However, no clinical signs consistent with inhibition of COMT or of tryptophan or tyrosine hydroxylase were evident in non-iron-loaded or iron-loaded rats that received 37.5 to 100 mg/kg b.i.d. of deferiprone for 12 months (internal report).

Oral doses of deferiprone (30 and 300 mg/kg) were shown to increase (≥2-fold) plasma corticosterone and aldosterone in non-iron-loaded rats (Hausler A *et al.* 1993). The stimulatory effect of deferiprone on HPA function may explain adrenal enlargement noted in rats treated with deferiprone (see section 3.2.4).

Safety pharmacology studies indicated no significant effects of deferiprone on the cardiovascular, immune and central nervous systems at therapeutically relevant doses. No significant inhibition of hERG-mediated potassium currents were reported in human cells at concentrations of deferiprone of up to 3,000 µM (24- to 32-fold the reported maximum serum levels in patients given a therapeutically relevant dose of 25 mg/kg deferiprone) (internal report). In non-iron-loaded and iron-loaded cynomolgus monkeys administered deferiprone at doses of from 37.5 to 125 mg/kg twice daily for 12 months there were no effects on heart rate and cardiac conduction, as indicated by absence of significant changes in the duration of the PR interval, QRS wave and uncorrected QT interval (internal report). No treatment-related effects on cardiac rhythm or waveform, or on systolic, diastolic and mean arterial blood pressure were noted.

### *3.2.3.* ***Pharmacokinetics and metabolism***

Deferiprone is absorbed from the gut after oral administration ($t_{max}$ = 0.5-1 h) and is metabolized in the liver to, principally, a pharmacologically inactive 3-*O*-glucuronide (Singh S *et al.* 1992). Bioavailability has been reported to be approximately 60% in rats (Fredenburg AM *et al.* 1996) and 72% in rabbits (Fredenburg AM *et al.* 1993). Distribution of deferiprone into tissues is rapid, and it is cleared quickly from most (Hileti D *et al.* 1993; Singh S *et al.* 1992) (Data on file with FDA). The serum half-life of deferiprone is similar in rats and humans (*ca.* 2-3 h) but shorter in monkeys (*ca.* 0.5-1.5 h). In naïve animals, it is eliminated within approximately 7 days (Singh S *et al.* 1992) predominantly via the urine as the glucuronide, whereas in iron-loaded animals the degree of fecal excretion varies with species, iron status, method of iron loading and chemical form of iron administered.

The potential for pharmacokinetic drug interactions is low, given deferiprone's low plasma protein binding in animal species and humans (<20%) (Yokel RA *et al.* 1995), and its lack of inhibition of human CYP450 isoforms.

### *3.2.4.* ***Toxicology***

#### *3.2.4.1. Single Dose Toxicity*

Deferiprone is of low acute toxicity (median lethal single oral or i.p. dose 500-2,000 mg/kg) in naïve and iron-loaded animals (Kontoghiorghes GJ et al. 1993; Kontoghiorghes GJ & Sheppard. 1987). Convulsions preceded death in mice.

### *3.2.4.2. Repeated Dose Toxicity*

Repeated daily dosing in non-iron-loaded animals induced dose-related effects at ≥ 100 mg/kg/day. Mortality occurred in dogs at 600 mg/kg/day (Data on file with FDA), in rats at 200 mg/kg/day (internal report), in guinea pigs at 300 mg/kg/day (Wong A et al. 1997), and in monkeys given initially 250 mg/kg/day (lowered to 150 mg/kg/day because of excessive toxicity) (Data on file with FDA). In iron-loaded animals, deferiprone showed effects only at doses ≥ 200 mg/kg/day. Treatment-related deaths occurred in rats at 200 mg/kg/day (administered as 100 mg/kg twice daily) (internal report), but not in mice at 300 mg/kg/day or in monkeys at 125 mg/kg twice daily (Kontoghiorghes GJ. 1986a) (internal report). Decreases in body weight gain were seen only in rats, and were less severe than in non-iron-loaded rats (internal report).

In all of these studies in animals, decreases in circulating white blood cell, red blood cell, and platelet counts were associated with bone marrow hypocellularity. Minor bone marrow effects were reported in monkeys receiving 40 or 100 mg/kg orally, once daily (Data on file with FDA). In studies where differential leukocyte counts were reported there was no evidence of a selective loss of any one cell type.

Long-term GLP-compliant studies were sponsored by ApoPharma in rats and monkeys.

Rats

Non-iron-loaded and iron-loaded rats received, respectively, 75 mg/kg and 37.5 to 100 mg/kg of deferiprone by oral gavage twice daily (b.i.d.) for 12 months. Six of 50 non-iron-loaded rats given 75 mg/kg b.i.d. and 3 of 50 iron-loaded rats given 100 mg/kg b.i.d. died or were killed moribund as a result of severe debilitation; the cause of death was concluded on the basis of clinical signs or hematology (hemoglobin levels 10-15% of control levels) to be marked anemia. These animals had reticulocytosis and RBC macrocytosis, non-selective depression of all white cell subpopulations, and marked bone marrow hypocellularity. In a few animals, additional effects included elevated levels of total bilirubin, ALT and/or AST that correlated with minimal to slight hepatic centrilobular and/or midzonal fat vacuolation and slight to moderate centrilobular degeneration and necrosis. Neither bridging necrosis nor fibrosis was present.

In rats that survived to scheduled termination there were no treatment-related clinical signs, and hematological effects were milder. Reduced body weight gain (by 17-47%) in non-iron-loaded animals during treatment generally improved during a 4-week recovery period. Food consumption was not significantly affected. Changes in serum chemistry parameter values and differences from control in hepatic morphology were attributable to gross iron loading rather than to deferiprone. Relative thyroid weights were significantly increased (by 25-52%) in non-iron-loaded and iron-loaded rats, and were associated with diffuse basophilia of follicular colloid in both sexes, and with minimal or slight diffuse hypertrophy of the follicular epithelium principally in females. These effects only partially regressed during the recovery period. Pituitary and adrenal weights were also increased, in a dose-dependent manner, irrespective of iron loading, but without accompanying changes in tissue morphology. A slightly increased incidence and severity of mammary gland hyperplasia in females was not evident after 4 weeks without administration of deferiprone. Decreases in bone marrow cellularity were accompanied

by extramedullary hematopoiesis in the spleen of both sexes and were still apparent at the end of the recovery period in non-iron-loaded, but not in iron-loaded animals. No evidence of liver fibrosis was present in animals sacrificed prematurely or following 12 months of daily dosing.

Monkeys

In non-iron-loaded monkeys dosed orally with 75 mg/kg deferiprone b.i.d. for 12 months (internal report), there were no treatment-related clinical signs, and no significant changes in body weight and food consumption, ophthalmological and cardiovascular parameters (conduction, blood pressure, heart rate), or hematology, serum chemistry and urinalysis. Iron-loaded monkeys that received 37.5, 75 or 100 mg/kg (125 mg/kg after 3 months) b.i.d. showed minimal effects. Modest increases in serum ALT activity in all iron-loaded groups, including controls, were slightly exacerbated by deferiprone, but without a consistent pattern or dose relationship. No treatment-related tissue changes were observed microscopically.

Reproductive and Embryo-Fetal Toxicity

Deferiprone had no significant effects on the reproductive performance of male and female rats dosed orally at up to 150 mg/kg/day (75 mg/kg twice daily) prior to and through mating (males) or through early gestation (females) in an ApoPharma-sponsored, GLP-compliant study. The only finding was prolonged diestrus in females. Low oral doses (≤10 mg/kg/day) of deferiprone were reported to be teratogenic in non-iron-loaded rats and rabbits treated throughout organogenesis (Data on file with FDA).

Genotoxicity and Carcinogenesis

Deferiprone was not mutagenic in a bacterial reverse mutation assay using S. typhimurium tester strains TA98, TA100, TA1535 and TA1537 and E. coli tester strain WP2 uvrA, in the presence and absence of metabolic activation (internal report). It showed evidence of clastogenicity in an in vitro L5178Y/TK+/- mouse lymphoma mutagenesis assay at all concentrations tested (15 to 5,000 μg/mL) in the absence of an exogenous metabolizing system, but no unequivocally positive response was detected at less than 250 μg/mL in the presence of such a system (internal report). In in vivo mouse micronucleus assays, significant increases in micronucleated polychromatic erythrocytes were noted in the bone marrow of non-iron-loaded and nominally iron-loaded animals 48 hours after a single oral dose of 250 or 500 mg/kg deferiprone. No significant changes were noted at 125 mg/kg (internal report). A program of studies to evaluate the oncogenic potential of deferiprone in iron-supplemented rodents is in progress.

## 3.3. Clinical Pharmacology

The following is an overview of deferiprone's pharmacokinetics in healthy volunteers (Studies LA20 and LA21) and in iron-overloaded patients (Studies LA-01 and LA14, and literature).

Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract, appearing in the blood within five to 10 minutes after its oral administration (Kontoghiorghes GJ *et al.* 1990; Matsui D *et al.* 1991). The pharmacokinetics of deferiprone and the effect of food on its bioavailability were evaluated in study LA20. In healthy volunteers, peak serum concentrations

occurred approximately 1 hour after a single oral dose of 3×500 mg of deferiprone immediate-release tablets (Table 3-1). When deferiprone was taken after a high fat meal, $AUC_{0-t}$ and $AUC_{inf}$ were not significantly affected (Table 3-2), but peak concentration decreased by 38% and time to reach peak concentration was extended to 2 hours.

**Table 3-1: Serum pharmacokinetic parameter values for deferiprone administered as a tablet under fasted and fed conditions (LA20)**

| | Mean (CV%) | |
|---|---|---|
| | Fasted (n = 15) | Fed (n = 14) |
| $AUC_{0-t}$ (µg·h/mL)* | 49.2 (34.2) | 43.9 (36.3) |
| $AUC_{inf}$ (µg·h/mL)* | 50.4 (33.9) | 44.6 (36.7) |
| $C_{max}$ (µg/mL)* | 18.8 (37.8) | 11.7 (35.2) |
| $t_{max}$(h) | 1.06 (64.0) | 1.99 (97.1) |
| MRTpo (h) | 3.21 (15.0) | 3.76 (17.4) |
| CL/F (L/h) | 31.3 (34.6) | 35.7 (38.2) |
| kel (1/h) | 0.370 (11.8) | 0.363 (14.7) |
| Half-life (h) | 1.90 (12.5) | 1.95 (15.8) |

n: number of observations
*Geometric means

**Table 3-2: Effect of food on pharmacokinetics of deferiprone tablets (LA20)**

| Parameter | Deferiprone Fed vs. Fasted [Ratio of Least-Squares Geometric Means % (90% Confidence Interval)] |
|---|---|
| $AUC_{0-t}$ | 88.6% (83.5% – 94.0%) |
| $AUC_{inf}$ | 90.2% (85.1% – 95.7%) |
| $C_{max}$ | 62.0% (51.1% – 75.3%) |

Similarly, in patients with thalassemia, a single oral dose of 25 mg/kg of an independently prepared, non-commercial, immediate-release capsule formulation of deferiprone showed a

lower peak serum concentration in the fed state (mean of 13.2 μg/mL) than in the fasting state (mean of 17.5 μg/mL), whereas a measure of overall exposure (AUC) was not significantly affected in the presence of food (Kontoghiorghes GJ *et al.* 1990; Matsui D *et al.* 1991).

Over the concentration range reached at therapeutic doses in humans (10 to 200 μM), deferiprone exhibits less than 10% binding to plasma proteins (Guo F. 1998). Based on oral data, the volume of distribution of deferiprone was estimated to be 1.6 L/kg in thalassemia patients and about 63% of that value in healthy volunteers (Fassos FF *et al.* 1996; Stobie S *et al.* 1993).

Deferiprone is metabolized predominantly to a 3-*O*-glucuronide conjugate, without evidence of dose-dependent kinetics over the therapeutic dose range. This metabolite lacks iron-binding capability due to inactivation of the 3-hydroxy group of deferiprone. Peak serum concentrations of the glucuronide occur approximately 2 to 3 hours after oral administration of deferiprone.

In humans, deferiprone is eliminated mainly via the kidneys: 75% to 90% of the ingested dose is reported as being recovered in the urine in the first 24 hours in the form of free deferiprone, the glucuronide metabolite and the iron-deferiprone complex (Collins AF *et al.* 1994; Olivieri NF *et al.* 1990). Most of the deferiprone-induced iron excretion is urinary, and the remainder (approximately 20%; range 3-60%) is excreted in feces (Collins AF *et al.* 1994; Grady RW *et al.* 2001). The absolute amount of deferiprone-induced iron excretion is influenced by the dose of deferiprone and the degree of iron overload (Addis A *et al.* 1999; Agarwal MB *et al.* 1992; Al-Refaie FN *et al.* 1992; Al-Refaie FN *et al.* 1995; Grady RW *et al.* 1997; Olivieri NF *et al.* 1995b). The elimination half-life of deferiprone is approximately 2 hours in healthy volunteers, and typically 2 to 3 hours in patients (Kontoghiorghes GJ *et al.* 1990; Matsui D *et al.* 1991).

The pharmacokinetics of deferiprone was also studied in thalassemia patients undergoing chronic treatment with deferiprone for 1 year during study LA01-PK. Deferiprone tablets at a dose of 25 mg/kg were administered after a standard breakfast (low fat). In a similar study (LA14), the pharmacokinetics of deferiprone was studied in thalassemia patients with a histologically confirmed diagnosis of liver cirrhosis. The results of the two studies are summarized in Table 3-3. There were no apparent changes in disposition of deferiprone at steady state in patients with liver cirrhosis. There was also no significant difference in degree of fluctuation of steady-state serum concentrations between the two cohorts of thalassemia patients.

**Table 3-3: Steady-state pharmacokinetic parameter values for deferiprone in thalassemia patients with or without liver cirrhosis**

| | Mean (CV%) | |
|---|---|---|
| | No Cirrhosis (n = 7) | With Cirrhosis (n = 4) |
| $AUC_T$ (µg·h/mL)* | 34.7 (20.7) | 33.0 (30.0) |
| $C_{max}$ (µg/mL)* | 11.8 (26.1) | 10.9 (41.4) |
| $C_{min}$ (µg/mL)* | 0.760 (39.7) | 0.564 (75.7) |
| $t_{max}$(h) | 2.23 (58.5) | 1.75 (82.8) |
| Half-life (h) | 1.82 (11.8) | 1.92 (8.1) |
| Fluctuation (%) | 256 (21.5) | 253 (39.4) |

n: number of observations
*Values were reported in µmol·h/mL in the original study reports.

ApoPharma has developed a 100 mg/mL oral solution formulation of deferiprone. This formulation was intended to be used in patients unable to swallow the tablets. A bioequivalence study (LA21) was conducted to evaluate the relative bioavailability of the tablet and solution formulations in fasted healthy volunteers. Following a single dose of 1,500 mg deferiprone either as 3×500 mg tablets or 15 mL of the 100 mg/mL solution, bioequivalence criteria were met for $C_{max}$, $AUC_{0-t}$ and $AUC_{inf}$, i.e., deferiprone oral solution and tablets are bioequivalent under fasting conditions. The oral solution was the formulation used in study LA30, which assessed the safety and efficacy of deferiprone for the treatment of iron overload in pediatric (<10 years old) patients with transfusion-dependent anemia.

# 4. Overview of Clinical Development Program

## 4.1. Discovery and Early Development

Deferiprone was first synthesized 26 years ago. Due, in part, to the lack of a composition of matter patent, there was little interest in its commercial development, but it was studied by individual hematologists interested in finding an effective oral iron chelator. By 1993, there was evidence from independent studies on the efficacy of deferiprone in controlling the body iron load, as assessed by serum ferritin and liver iron concentrations, in transfusion-dependent patients, but also of infrequent agranulocytosis, which reversed upon interruption of therapy. Based on the available data on its benefits and risks, deferiprone was considered as an iron chelator for the treatment of patients for whom deferoxamine was inadequate. In 1993, ApoPharma (a division of Apotex, Canada) agreed to develop deferiprone, targeting an indication in patients for whom deferoxamine was inadequate. Between 1993 and 1996,

ApoPharma sponsored three studies: 1) a randomized clinical trial (Study LA-01) comparing the efficacy of deferiprone to that of deferoxamine in 71 patients with thalassemia major, 2) a single arm safety trial in 187 patients (Study LA-02) and 3) a compassionate use program (Study LA-03) that provided deferiprone to 25 patients (Appendix A). Study LA-01 was prematurely terminated and subsequently provided only limited data on the efficacy of deferiprone relative to that of deferoxamine.

In 1997, the Italian Ministry of Health created a special program for the controlled distribution of deferiprone to collect data and to evaluate its safety and effectiveness in long-term use. Five hundred and thirty-two thalassemia patients from 86 treatment centers were enrolled in this program. In 1999, the European Medicines Agency (EMA) granted the first marketing authorization for deferiprone. Its original indication was for the treatment of iron overload in patients with thalassemia major for whom deferoxamine therapy was contra-indicated or who presented serious toxicity with deferoxamine therapy. In part because of its commitment to the EMA following EU approval, ApoPharma continued to sponsor studies (Appendix A). Study LA06, a continuation of LA-02, examined the long-term safety (up to 4 years) in patients with thalassemia major, Study LA10 examined the clastogenic potential of deferiprone relative to deferoxamine, Study LA12 assessed the incidence of cardiac disease and deaths in patients administered deferiprone or deferoxamine and Study LA14 evaluated the pharmacokinetic profile of deferiprone in subjects with transfusion-dependent thalassemia major and cirrhosis of the liver. ApoPharma also conducted other studies to compare the efficacy of deferiprone to deferoxamine in removing iron from the heart (Study LA16) and its safety and efficacy profile in young children (Study LA30). Collectively, these studies led to a greater understanding of both the risks and benefits of the use of deferiprone in the treatment of patients with transfusional iron overload. Deferiprone is currently approved in 61 countries. In most of these countries, deferiprone is indicated for the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contraindicated or inadequate.

As deferiprone became more widely available in Europe, independent natural history and epidemiological studies in countries with the highest prevalence of thalassemia patients (Italy, Greece, Cyprus and the UK), reported that deferiprone use was associated with lower incidence of iron-induced cardiac disease than the incidence observed during deferoxamine therapy (Borgna-Pignatti C *et al.* 2006; Ceci A *et al.* 2006; Ladis V *et al.* 2010; Maggio A *et al.* 2009a; Modell B *et al.* 2008; Piga A *et al.* 2003; Telfer P *et al.* 2006; Telfer PT *et al.* 2009). Based on the results of the ApoPharma studies and of the published literature by independent investigations, in 2010 the EMA updated the deferiprone label to include the following information:

> *Data from the published literature are consistent with the results from the Apotex (ApoPharma) studies, demonstrating less heart disease and/or increased survival in deferiprone-treated patients than in those treated with deferoxamine (DFO).*

## 4.2. Filing NDA with the FDA

On 15 May 2006, ApoPharma met with the FDA to discuss the submission of an NDA for deferiprone. In that meeting, ApoPharma summarized the studies it had conducted and the

published literature and expressed the view that the available safety and efficacy data supported a first line indication for deferiprone. The primary evidence in support of efficacy was the randomized controlled trial LA16-0102 (LA16), which had confirmed previous studies that deferiprone was superior to deferoxamine in removing excess cardiac iron. The proposal was to use LA16 as the pivotal study forming the foundation of the application, with Study LA12-9907 (LA12), a natural history study indicating lower incidence of iron-induced cardiac disease in patients treated with deferiprone than in patients treated with deferoxamine, as a supporting study, since it also focused on iron-related heart disease. Other studies provided additional information on the control of overall body iron in transfusion-dependent patients. ApoPharma prepared the NDA in line with its agreement with the FDA and completed its application on January 2009. An ODAC meeting for NDA 21-825, originally scheduled for October 6, 2009, was cancelled to allow the FDA more time to review the NDA. A subsequent Complete Response Letter (CRL) was addressed by the company.

ApoPharma accepted the advice of the FDA to reposition the application from first to second line therapy in the treatment of transfusional iron overload when current chelation therapy is inadequate.

# 5. Clinical Efficacy

Iron balance studies (urine and fecal iron excretion vs. estimated transfusional and dietary iron intake) in thalassemia patients with iron overload demonstrated a dose-response relationship for deferiprone and iron excretion at doses of between 50 and 100 mg/kg/d (Agarwal MB *et al.* 1992; Grady RW *et al.* 2002; Grady RW *et al.* 2001). In clinical studies, deferiprone at doses of 75 mg/kg/day promoted enough iron excretion to at least neutralize the continued iron loading regimen from transfusions in the majority of transfusion-dependent patients, either preventing a further increase or reducing their iron load (al Refaie FN *et al.* 1995). Doses may need to be increased up to 100 mg/kg/day for those patients with greater transfusional iron regimens (Agarwal MB *et al.* 1992; Grady RW *et al.* 2002; Grady RW *et al.* 2001).

In iron balance studies, concurrent administration of deferiprone and deferoxamine results in greater iron excretion compared to either chelator alone, and promotes sufficient iron excretion to neutralize the iron input even in patients with the greatest rate of transfusional iron input (Grady RW *et al.* 2002; Grady RW *et al.* 2001). Various regimens of adjunctive deferiprone-deferoxamine therapy, commonly referred to in the medical literature as “combination therapy”, demonstrate that the use of both chelators also results in a greater reduction of the iron loading indices, LIC and serum ferritin, even if the combination is administered as infrequently as 1 or 2 days per week, using monotherapy on the other days (Appendix B).

ApoPharma clinical studies evaluated patients treated with deferiprone monotherapy at doses of 50, 75 or 100 mg/kg/day, or with “combination therapy”. The results of these studies indicate that the efficacy of deferiprone monotherapy at 75-100 mg/kg/day is comparable to that of deferoxamine at 40-60 mg/kg for controlling total body iron, and better than deferoxamine in reducing cardiac iron overload.

The deferiprone NDA was submitted in January 2009 for first line therapy. Upon assessment of those studies, the FDA concluded that there was no single randomized, controlled study that was large enough based on established surrogate markers to provide substantial evidence of deferiprone's safety and efficacy as a first line treatment for transfusional iron overload. An alternate consideration was to determine if the available data could provide evidence of deferiprone's benefit/risk profile as a second line treatment. The Agency suggested that ApoPharma propose a plan to analyze the efficacy of deferiprone in those patients enrolled in the ApoPharma studies for whom previous chelation therapy had been inadequate. The analysis of the pooled efficacy data from those patients was coded as LA36-0310, which is referred to in this document as LA36.

This section of the briefing document summarizes the results of LA36 and of the individual studies from which the data analyzed were drawn.

## 5.1. LA36-0310

To facilitate analysis of the efficacy of deferiprone for the treatment of transfusional iron overload in patients for whom previous chelation therapy had been inadequate, ApoPharma worked with the Agency to identify acceptable indices of iron load which could be used to assess chelation efficacy and to define adequate and inadequate chelation. The statistical analysis plan was designed to accommodate the constraints of pre-existing data that had been collected from studies with diverse objectives, diverse inclusion/exclusion criteria, and diverse treatment regimens and durations. Table 5-1 lists studies of deferiprone, all of which were carried out by ApoPharma, except for that of Borgna-Pignatti et al., that had patients eligible to be included in the LA36 analysis, identifying for each study key characteristics and the number of patients meeting criteria (*vide infra*) for inclusion in the LA36 analysis. A synopsis of each of these studies is provided in Appendix A.

**Table 5-1: ApoPharma studies included in the LA36 analysis**

| Type of Study | Study ID | Location | Duration | Monotherapy or Combination Therapy, No. of Subjects Exposed by Arm |
|---|---|---|---|---|
| GCP Studies: Randomized Controlled Trials | LA08 | Italy, Greece | 12 Months | DFO, N = 29; DFP + DFO, N = 30 (Alternating therapy) |
| | LA16* | Italy, Greece | 12 Months | DFP, N = 29; DFO, N = 32 |
| GCP Studies: Non-Randomized Controlled Trials | LA12 | Italy | 5 Years | DFP, N = 54; DFO, N = 75 |
| GCP Studies: Non-Randomized Trials | LA-02/06 | Italy, US | 1 Year; 7 years | DFP, N = 187 (monotherapy) |
| | LA30 | Egypt, Malaysia, Indonesia | 24 Weeks | DFP , N = 100 (monotherapy) |
| Non-GCP Studies: Randomized Controlled Trials | LA-01*ǂ | Canada | 2 Years | DFP, N = 35; DFO N = 36 |
| Non-GCP Studies: Non-Randomized Trials | LA-03 ǂ | Canada | 7 Years | DFP, N = 25 (monotherapy) |
| | LA-04/06B ǂ | Canada, Italy, US | 1996-Present | DFP, N = 114 (monotherapy); DFP + DFO, N = 60 (combined therapy) |
| | LA-11 ǂ | Thailand | 2 Years | DFP, N = 24 (monotherapy) |
| | LA15 ǂ | Iran | 3 Months | DFP, N = 29 (monotherapy) |
| | LA28 ǂ | Egypt, Malaysia, Singapore | 3 Years | DFP, N = 83 (monotherapy) |
| | Borgna-Pignatti ǂ | Italy | 8 Years | DFP, N = 157; DFO, N = 359 |

* Studies were inspected by the FDA.

ǂ "Non GCP" is defined as a clinical trial conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and in compliance with the principles of Good Clinical Practice (GCP) outlined in E6, local and international laws and regulations but were characterized as Non-GCP due to either a) early termination due to investigator non-compliance with the study protocol (LA-01 & LA-03); b) CRF or data not monitored against source documents (LA-03, LA-04/6B, LA-11, LA15, LA28, Borgna-Pignatti).

### *5.1.1. Criteria for Adequate or Inadequate Chelation*

In the absence of authoritative guidelines on what constitute clinically meaningful changes in any of the primary parameters used for the assessment of the degree of iron loading, i.e., serum ferritin concentrations, liver iron concentration or cardiac MRI T2*, a review of the published literature was conducted to identify suitable criteria for characterizing both inadequate and adequate chelation therapy, based upon outcomes in patients treated with iron chelators. These criteria, which had been vetted by experts in the field, were used to identify patients from the studies listed in Table 5-1 that would be classified as having had inadequate previous chelation therapy at time of enrollment in those studies. The criteria were:

- baseline serum ferritin >2,500 µg/L, or
- liver iron concentration (LIC) >7mg/g dry weight, or
- excess cardiac iron stores as defined by a cardiac MRI T2* <20 ms.

Those levels for the 3 primary indices of iron overload have been reported to be independent thresholds for higher risk of iron-induced cardiac toxicity and premature death (Borgna-Pignatti C *et al.* 2004; Kirk P *et al.* 2009; Olivieri NF *et al.* 1994; Telfer PT *et al.* 2000).

A patient complying with any one of the three criteria was eligible for inclusion in LA36.

Definition of adequate (successful) chelation therapy was complicated by the lack of published consensus as to what constitutes clinically meaningful changes in any of the parameters used for the assessment of iron load. As transfusion-dependent patients, not receiving chelation therapy, show an inexorable and progressive increase in iron load due to ongoing blood transfusions (see Figure 1), it is evident that a decrease in iron burden would not be possible without effective chelation therapy. However, to ensure there was a clinically meaningful decline in iron load, while continuing the transfusion regimen, a minimum reduction of 20% in serum ferritin or liver iron concentration, or a minimum increase in cardiac MRI T2* (indicative of a reduction in cardiac iron load) of 20% in up to 12 months' treatment with deferiprone was defined for LA36. Both concept and quantitative criteria were endorsed by expert consultants.

To minimize the risk of including a patient who was inappropriately identified as having had an inadequate response to previous chelation therapy, any patient who had experienced an improvement of 20% or greater in the specified parameter within the year prior to initiation of deferiprone therapy was not categorized as having had previous inadequate therapy and was not included in the analysis.

#### *5.1.1.1. Primary and Secondary Efficacy Endpoints*

The primary efficacy endpoint was based on the change in serum ferritin concentration from baseline to within 1 year of deferiprone therapy.

The change in serum ferritin concentration was based on the baseline value vs. the value closest to the one year anniversary date of deferiprone therapy. To accommodate assessment of patients whose ferritin concentration was not measured on the one-year anniversary, the up-to-one-year window allowed use of data obtained within +3 months of the anniversary date. For patients who participated in studies of less than one year's duration or whose study therapy was stopped

prior to completion of one year (including therapy interruptions and discontinuation of therapy due to adverse events or inadequate response), the value obtained closest to the stopping date, but within 3 months after medication ceased was regarded as the final result.

The secondary efficacy endpoints were the change in LIC or in cardiac MRI T2* from baseline to within 1 year of deferiprone therapy. The change in LIC or in cardiac T2* was based on the baseline values vs. the value closest to the one year anniversary date of deferiprone therapy. To accommodate assessment of patients whose LIC or cardiac T2* was not measured on the one-year anniversary the up-to-one-year window allowed use of data obtained within + 3 months of the anniversary date. For patients who participated in studies of less than one year duration and for patients for whom study therapy was stopped prior to completion of one year (including therapy interruptions and patients who had discontinued therapy during that period due to adverse events or inadequate response), data collected up to 3 months after the medication termination was included and the value obtained at a time closest to the stopping date was used as the final result.

#### *5.1.1.2. Measures of Success*

LA36 would be considered positive if 20% or more of the patients who had failed previous chelation therapy experienced a 20% or greater decline in the primary endpoint measure, i.e., serum ferritin, within the specified time of deferiprone therapy.

For added assurance, it was established that the results would be considered successful only if the lower limit of the 95% confidence interval for the success rate was greater than the pre-defined criterion of 20% treatment success.

Equivalent criteria were applied to the secondary endpoints, i.e., LIC and cardiac MRI T2*.

#### *5.1.1.3. Subgroup Analyses*

Five subgroup analyses of the serum ferritin values were performed to meet a request by the FDA to test the impact of diversity among studies on the outcome of treatment success. The planned subgroups included:

(1) age (pediatric patients vs. adult patients);
(2) sex (male vs. female);
(3) primary disease (thalassemia major vs. non-thalassemia major);
(4) region (European vs. Non-European countries) and
(5) Good Clinical Practice (GCP) studies.

In addition to the subgroup analyses requested by the FDA, the following subgroup analyses were evaluated to further test the impact of the heterogeneity of the pooled data:

(6) deferiprone monotherapy vs. “combination” therapy
(7) patients with two or more serum ferritin values prior to starting deferiprone vs

patients with a single serum ferritin value prior to starting deferiprone[1]

(8) dosage regimen (≤50, 75 and 100 mg/kg/day)

#### *5.1.1.4. Statistical Methodology*

All statistical tests were two sided and a p-value of ≤0.05 was used for the determination of statistical significance. The 95% CI for the success rate by study and overall success rate was calculated based on the Clopper-Pearson exact confidence interval.

Trend analysis over time on the observed data for each of the three efficacy measures at different time points after the start of deferiprone treatment, including those beyond the first year of therapy, was established. The main factor, time variable, was calculated using the unit month of exposure to deferiprone treatment.

#### *5.1.1.5. Patient Selection*

Once the criteria for inadequate and adequate chelation therapy had been defined, and the measures of success and the analysis plan had been established and agreed upon by the Agency, data from all patients enrolled in the ApoPharma studies were sent to an independent committee (Ron Keren MD, MPH, Associate Professor of Pediatrics and Epidemiology, University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia and Xianqun Luan, MS, Technical Director, CHOP Healthcare Analytics Unit) who determined which patients fulfilled the inclusion and exclusion criteria and whose data were to be analyzed in LA36.

Some patients met more than one inclusion criterion and were eligible for inclusion in analysis of more than one efficacy measure. For example, a patient for whom serum ferritin data and LIC data were collected would be included in the analysis of both measures if both data met the corresponding inclusion criterion.

### *5.1.2. **Study Findings***

Serum ferritin, LIC and/or cardiac MRI T2* data in 747 individual patients were analyzed by the Independent Committee for study eligibility. The number of patients who met the inclusion/exclusion criteria, by study, for serum ferritin, LIC and cardiac MRI T2*, is presented in Table 5-2.

[1] The objective was to determine if those patients with multiple baseline serum ferritin values greater than 2,500 µg/L exhibited the same degree of response to deferiprone treatment as did the patients who had only a single baseline ferritin concentration to designate them as having failed previous chelation therapy.

**Table 5-2: LA36 Patient Selection**

| Studies | Serum Ferritin > 2,500 µg/L | LIC > 7 mg/g dw | MRI T2* < 20 ms |
|---|---|---|---|
| LA-01 | 8 | 15 | |
| LA-02/06 | 65 | | |
| LA-03 | 8 | 12 | |
| LA-04 | 56 | 11 | 10 |
| LA08 | 7 | 21 | |
| LA-11 | 12 | 3 | |
| LA12 | 19 | 35 | |
| LA15 | 18 | | |
| LA16 | 5 | 20 | 29 |
| LA28 | 3 | | |
| LA30 | 36 | | |
| Borgna-Pignatti | 27 | | |
| **Total** | **264** | **117** | **39** |

A shaded cell in the table on the right indicates that the efficacy parameter was not measured in the corresponding study.

Thirty patients were eligible according to the criteria of inadequate therapy for both serum ferritin and LIC, 25 patients for both LIC and cardiac T2*, 12 patients for both serum ferritin and cardiac T2*, and 7 patients for all 3 indices.

#### *5.1.2.1. Demographics*

Table 5-3 summarizes the demographics of the cohorts of patients evaluated in the study. The dose of deferiprone ranged from 35 to 100 mg/kg/day.

**Table 5-3: LA36 Demographics**

| Cohorts | Age (Years) | | | Sex (N) | |
|---|---|---|---|---|---|
| | Min | Max | Mean | Male | Female |
| Serum Ferritin | 2 | 76 | 20.1 | 119 | 145 |
| LIC | 6 | 52 | 19.4 | 62 | 55 |
| Cardiac MRI T2* | 12 | 33 | 24.3 | 21 | 18 |

#### *5.1.2.2. Efficacy Results for Primary and Secondary Endpoints*

Table 5-4 shows the mean values for each of the 3 indices in patients in LA36, comparing the mean value at baseline to the last observation within 1 year (up to + 3 months) of treatment with deferiprone. Analysis revealed a significant improvement in the mean values for all 3 indices for these patients who had failed previous chelation therapy.

**Table 5-4: LA36 Descriptive Statistics for Serum Ferritin, LIC, cardiac MRI T2***

| Measure | Number of Patients | Baseline Mean ±SD (Minimum, Maximum) | Last Observation within 1 year (up to + 3 months) Mean ±SD (Minimum, Maximum) | Change Mean ±SD (Minimum, Maximum) | P |
|---|---|---|---|---|---|
| Serum Ferritin (µg/L) | 264 | 4416 ± 2288 (2505, 16550) | 3453 ± 2099 (184, 16139) | -962 ± 1907 (-10385, 10002) | <0.0001 |
| LIC (mg Fe/g dw) | 117 | 16.2 ± 10.3 (7.1, 66.6) | 14.5 ± 9.1 (1.6, 54.2) | -1.7 ± 7.5 (-32.6, 14.5) | 0.0404 |
| Cardiac MRI T2* (ms) | 39 | 11.8 ± 4.9 (4.0, 19.5) | 15.1 ± 7.0 (3.4, 28.0) | 3.3 ± 3.4 (-2.0, 12.7) | <0.0001 |

Note: An increase in MRI T2* represents a decline in iron load

The success rate for each efficacy endpoint was calculated for each of the 12 studies separately. The results are summarized in Tables 5-5 to 5-7. All of the individual success rates were greater than 20%; however, due to a small number of eligible patients in some studies, the lower limit of the 95% CI was not greater than 20% for the efficacy endpoints of serum ferritin and LIC.

**Table 5-5: LA36: Success rate by study for serum ferritin**

| Study | Number of patients | Success rate (N) | 95% C.I. |
|---|---|---|---|
| LA-01 | 8 | 50% (4) | (16%, 84%) |
| LA-02/06 | 65 | 40% (26) | (28%, 53%) |
| LA-03 | 8 | 63% (5) | (24%, 91%) |
| LA-04/06B | 56 | 52% (29) | (38%, 65%) |
| LA08 | 7 | 57% (4) | (18%, 90%) |
| LA-11 | 12 | 83% (10) | (52%, 98%) |
| LA12 | 19 | 26% (5) | (9%, 51%) |
| LA15 | 18 | 100% (18) | (81%, 100%) |
| LA16 | 5 | 80% (4) | (28%, 99%) |
| LA28 | 3 | 67% (2) | (9%, 99%) |
| LA30 | 36 | 47% (17) | (30%, 65%) |
| Borgna-Pignatti | 27 | 44% (12) | (25%, 65%) |
| **Overall success rate** | **264** | **52% (136)** | **(45%, 58%)** |

**Table 5-6: LA36: Success rate by study for LIC**

| Study | Number of patients | Success rate (N) | 95% C.I. |
|---|---|---|---|
| LA-01 | 15 | 33% (5) | (12%, 62%) |
| LA-03 | 12 | 67% (8) | (35%, 90%) |
| LA-04/06B | 11 | 36% (4) | (11%, 69%) |
| LA08 | 21 | 57% (12) | (34%, 78%) |
| LA-11 | 3 | 67% (2) | (9%, 99%) |
| LA12 | 35 | 26% (9) | (12%, 43%) |
| LA16 | 20 | 45% (9) | (23%, 68%) |
| **Overall success rate** | **117** | **42% (49)** | **(33%, 51%)** |

**Table 5-7: LA36: Success rate by study for cardiac MRI T2***

| Study | Number of patients | Success rate (N) | 95% C.I. |
|---|---|---|---|
| LA-04/06B | 10 | 60% (6) | (26%, 88%) |
| LA16 | 29 | 62% (18) | (42%, 79%) |
| **Overall success rate** | **39** | **62% (24)** | **(45%, 77%)** |

*5.1.2.3. Overall Success Rates*

Table 5-8 shows the overall success rate and 95% C.I. for serum ferritin, LIC and cardiac MRI T2*. The lower limit of the 95% C.I. was greater than the analysis success criterion of 20% for all 3 efficacy measures.

**Table 5-8: LA36: Percent of Patients with >20% improvement (Success Rate) in Serum Ferritin, Cardiac MRI T2* and Liver Iron Concentration after up to 1 year of deferiprone therapy**

| Measure and Study | Number of patients | Success rate (N) | 95% C.I. |
|---|---|---|---|
| Serum Ferritin | 264 | 52% (136) | 45%, 58% |
| Liver Iron Concentration | 117 | 42% (49) | 33%, 51% |
| Cardiac MRI T2* | 39 | 62% (24) | 45%, 77% |

From the trend analysis of data including those obtained beyond the first year of deferiprone therapy, mean serum ferritin decreased by 22 μg/L per month, $p<0.0001$; MRI T2* increased (consistent with a reduction in cardiac iron load) by 0.3065 ms per month, $p<0.0001$. For both measures, the number of patients displaying an improving trend was also significantly greater than that displaying a worsening trend. For LIC, there was no significant change detected in the trend analysis (slope = -0.01442 mg Fe/g dw per month, $p=0.6333$).

#### *5.1.2.4. Efficacy Results for Subgroup Analyses*

The results of the subgroup analyses are presented in Table 5-9.

**Table 5-9: LA36: Results of Subgroup Analysis of the primary index (serum ferritin concentration)**

| | Subgroup (N) | Success rate (N, %) | 95% CI | P-value |
|---|---|---|---|---|
| Age | Pediatric Patients (83)<br>Adult Patients (181) | 38 (46%)<br>98 (54%) | (35%, 57%)<br>(47%, 62%) | 0.2335 |
| Sex | Male (119)<br>Female (145) | 63 (53%)<br>73 (50%) | (44%, 62%)<br>(42%, 59%) | 0.7113 |
| Primary Disease | Thalassemia Major (228)<br>Non-Thalassemia Major (36) | 115 (50%)<br>21 (58%) | (44%, 57%)<br>(41%, 74%) | 0.4734 |
| Geographic Region | European Countries (136)<br>Non-European Countries (128) | 54 (40%)<br>82 (64%) | (31%, 48%)<br>(55%, 72%) | 0.0001 |
| GCP Study | LA-0206, LA08, LA12, LA16, LA30 (132) | 56 (42%) | (34%, 51%) | Not Applicable |
| Regimen | Monotherapy (236)<br>“Combination” therapy (28)* | 118 (50%)<br>18 (64%) | (43%, 57%)<br>(44%, 81%) | 0.1668 |
| Number of Serum Ferritin (SF) Values | 2 or More SF (63)<br>A Single SF (156) | 45 (71%)<br>70 (45%) | (59%, 82%)<br>(37%, 53%) | 0.0001 |
| Dosage regimen | ≤50 mg/kg/day (14)<br>75 mg/kg/day (203)<br>100 mg/kg/day (47) | 11 (79%)<br>101 (50%)<br>24 (51%) | (49%, 95%)<br>(43%, 57%)<br>(36%, 66%) | 0.1197 |
| Baseline serum ferritin | 2500 – 5000 µg/L (198)<br>>5000 ug/L (66) | 95 (48%)<br>41 (62%) | (41%, 55%)<br>(49%, 74%) | 0.0482 |

* Combination therapy indicates a chelation regimen where deferiprone is added to a regimen of deferoxamine”

A statistically significant difference in success rate between patients with two or more serum ferritin values of which a majority of the values were greater than 2,500 µg/L prior to starting deferiprone and those with a single serum ferritin value prior to starting deferiprone was observed (71% vs. 45%, p=0.0001). There was a concern that a single serum ferritin value prior to starting deferiprone might not have provided sufficient evidence that the patients were inadequately controlled by previous chelation therapy. The results of this analysis show that the inclusion of these patients was not responsible for the favorable outcome for deferiprone, as the success rate for these patients was lower than that for patients with two or more serum ferritin values prior to starting deferiprone. Therefore, the higher success rate of deferiprone in patients with two or more serum ferritin values supports the inclusion of patients with only one pre-deferiprone serum ferritin value in the analysis.

There was a statistically significant difference in success rate between European countries and non-European countries (40% vs. 64%, p=0.0001). This is likely to have been a function of the less intensive transfusion regimens generally used for patients in the relevant non-European

countries (Thailand and Iran), leading to a lower rate of transfusional iron input, although the premise cannot be verified because no data were collected on the transfusion load in these patients.

There was a marginally significant difference between patients with baseline serum ferritin of 2,500-5,000 µg/L and >5,000 µg/L. The higher success rate for patients with >5,000 µg/L is not unexpected, as a high baseline ferritin generally has been associated with a greater magnitude of response to chelation therapy in published studies (Cohen AR *et al.* 2000).

In all cases where significant differences were found in subgroup analyses, both the mean response and the lower limit of the 95% confidence interval for the success rate were greater than 20% for all of the subsets of patients (Table 5-9). Therefore, none of the factors examined contradicted the conclusion of success for deferiprone in meeting the prespecified criteria.

#### *5.1.2.5. Sensitivity Analyses*

The efficacy criterion of the LA36 analysis was based on the change in serum ferritin from baseline to within one year of deferiprone therapy. For patients who stopped study treatment prior to completion of one year of deferiprone therapy, data collected up to 3 months after the termination of treatment were included, and the value closest to the stopping date was used as the final result. This approach is equivalent to applying the last-observation-carried-forward (LOCF) method to impute the endpoint value used in the assessment of treatment success in these patients. A potential problem with this LOCF imputation approach is that the last observed efficacy value prior to withdrawal of the patients might have exhibited ≥20% improvement from baseline, thereby satisfying the treatment success criterion, even though the underlying trend of treatment response might have been worsening and have been the reason for withdrawal, or an adverse event might have caused termination. This could create a false assignment of treatment success for these patients. To examine the impact of using the LOCF method, the determination of success rate for each efficacy measure was repeated for the Per-Protocol (PP) population, patients who had the efficacy endpoint data available from the respective study in which they were enrolled. Overall success rates for the PP population were very similar to those for the LOCF population, as summarized in Table 5-10, indicating that any theoretical bias inherent in using the LOCF method had no important impact.

**Table 5-10: LA36: Overall success rate – PP and LOCF (ITT) populations**

| Efficacy | Population | Number of patients | Success rate (N, %) | 95% C.I. |
|---|---|---|---|---|
| Serum Ferritin | LOCF<br>PP | 264<br>261 | 136 (52%)<br>134 (51%) | (45%, 58%)<br>(45%, 58%) |
| LIC | LOCF<br>PP | 117<br>116 | 49 (42%)<br>48 (41%) | (33%, 51%)<br>(32%, 51%) |
| Cardiac MRI T2* | LOCF<br>PP | 39<br>37 | 24 (62%)<br>23 (62%) | (45%, 77%)<br>(45%, 78%) |

It is noteworthy that the numbers of patients in the LOCF and PP populations were very similar. Generally, patients who were withdrawn from a study (dropouts) would not be included in the PP

population. However, for this analysis many of the dropouts were included in the PP population because they had efficacy data within the study time window of 12+3 months from baseline. Most of the remaining dropouts were excluded from both populations because they did not meet the inclusion/exclusion criteria of the study.

### *5.1.3. LA36 Conclusion*

LA36 assessed three measures of whole body or specific organ iron load (serum ferritin as the primary index, and LIC and cardiac MRI T2* as secondary indices) in thalassemia major and non-thalassemia major patients receiving deferiprone to control accumulation of transfusional iron input. For each of these measures, criteria that reflected inadequate control of iron burden were based on the medical literature and expert interpretation of clinical practice.

Data from patients included in studies submitted by ApoPharma in the deferiprone NDA and identified as having inadequate response to previous chelation therapy were collected and subjected to a subgroup analysis for their subsequent response to deferiprone, according to predetermined criteria for success. For all 3 measures, deferiprone met the criteria for a successful response. Further subgroup analyses of LA36 data showed that in all cases the lower limit of the 95% CI for the success rate of deferiprone was greater than 20%, indicating that the diversity of the studies involved in the assessment did not affect the validity of the principal analyses. Statistical assessments did not detect bias from using LOCF observations.

The data generated from the LA36 analysis fulfilled the criteria established with the FDA for success and support the use of deferiprone in the treatment of patients with transfusion-dependent iron overload who have failed previous chelation therapy.

## 5.2. Individual Studies

### *5.2.1. Overview*

LA36, the primary analysis on which the application for second line therapy is based, drew patient data from all studies submitted to the NDA that generated measurements amenable to analysis. Some of those studies were designed specifically to explore whether deferiprone might have particular benefit in addressing iron-induced heart disease, a major contributor to early death in patients receiving long term transfusion therapy. A summary of the 3 studies which explored this area is provided to facilitate an understanding of the potential that deferiprone would be expected to have if accepted for second line therapy for transfusion-dependent patients in the US.

One of the most likely consequences of failed chelation therapy in patients with transfusional iron overload is iron-induced cardiac failure and premature death. ApoPharma study LA16 was a controlled randomized trial that was designed to compare the efficacy of deferiprone to that of deferoxamine in controlling cardiac MRI T2*, with serum ferritin and liver iron concentration as secondary endpoints, in patients with transfusion-dependent thalassemia. Two other studies, the natural history studies LA12 and Borgna-Pignatti *et al,* provide evidence of the value of deferiprone in terms of clinical outcomes. Each of these studies are summarized in the following sections, with outcomes based on all the patients for each study, not limited to patients for whom

previous chelation therapy had been inadequate. A summary of all studies is provided in Appendix A.

### *5.2.2. **ApoPharma Randomized, Controlled Clinical Study LA16-0102***

#### *5.2.2.1. Overview of Study Design*

LA16 was a randomized, active controlled, open-label, multicenter clinical trial designed to test the hypothesis that deferiprone is superior to deferoxamine in removing excess myocardial iron in transfusion-dependent thalassemia patients. The study was not blinded due to the different route of administration of the two chelators: parenteral administration of deferoxamine vs. oral administration of deferiprone. The study was conducted to a 12-month efficacy time point.

The primary efficacy measure was cardiac MRI T2* value, as an assessment of the cardiac iron status, taken at baseline and after 6 and 12 months of treatment. The T2* data are presented as the geometric mean (anti-log of the mean of the log data) ± the coefficient of variation (CV) due to the use of post-hoc log-transformation in the analysis; it was known that cardiac iron load is inversely related to T2*, therefore log-transformation of the MRI T2* data was used to linearize the scale, resulting in normalization of the MRI T2* data.

The secondary efficacy measurements were serum ferritin concentrations and liver iron concentrations (LIC). Measurements were taken at baseline and at 3, 6, 9 and 12 months for serum ferritin, or at early withdrawal. The LIC measurements were taken at baseline and 12 months (± 1 month) or at early withdrawal.

The tertiary efficacy measure was cardiac function, which was evaluated by measuring the left ventricular ejection fraction (LVEF) and left ventricular shortening fraction (LVSF) at baseline and after 6 and 12 months using cardiovascular magnetic resonance (CMR) and echocardiogram (ECHO). All CMR measures were made 1 week (7 days ± 3 days) after a transfusion visit to avoid a potential effect of blood transfusions on cardiac function.

Safety was evaluated on a weekly basis by monitoring standard laboratory tests, comprising serum ALT, zinc and creatinine, and blood ANC, Hb, WBC (total and differential) and platelet counts, and vital signs. Adverse events were assessed for frequency, severity and causality.

#### *5.2.2.2. Patients and methods*

Unbiased assessment of the cardiac data was achieved by sending data electronically to a central CMR center (Cardiovascular MRI unit, Royal Brompton Hospital, London, UK) where the data were assessed by 2 cardiologists in consensus who were blinded to the chelation therapy the patients were receiving.

#### *5.2.2.3. Inclusion and exclusion criteria*

The main inclusion criteria included a confirmed diagnosis of β thalassemia major, age between 18 and 36 years, undergoing regular transfusions to maintain pre-transfusion hemoglobin (Hb) of no less than 9 g/dL, ongoing chelation therapy with deferoxamine for at least the past 5 years and no exposure to deferiprone within the last 2 years. Myocardial T2* levels were greater than or

equal to 8 ms to less than 20 ms, indicative of moderate to mild cardiac siderosis. The rationale for exclusion of patients with severe cardiac iron overload was the high risk of cardiac failure in those patients and to allow them to receive best clinical management. The main exclusion criteria were abnormal cardiac function as assessed by a CMR-derived LVEF of less than 56% and/or CMR-derived LVSF of <30%, and serum liver enzymes >3 times the upper limit of normal.

#### *5.2.2.4. Randomization and stratification*

Patients were stratified into two groups, moderate or mild cardiac iron overload, according to their baseline cardiac MRI T2* assessment: ≥8 ms to <14 ms or ≥14 ms to <20 ms. Stratified patients were randomized in blocks of 4 to either of two treatment groups. Patients randomized to deferiprone were prescribed an oral dose of 33.3 mg/kg, t.i.d. for a total daily dose of 100 mg/kg. Therapy was initiated at 25 mg/kg t.i.d. followed by an ascending titration over 8 weeks to 33.3 mg/kg t.i.d. and remained at that level until completion of the study. Patients randomized to deferoxamine were prescribed 50 mg/kg of the chelator, to be delivered by subcutaneous infusion on 5-7 days per week for the duration of the 12 months.

#### *5.2.2.5. Statistical Methods*

The sample size calculation for the determination of deferiprone superiority over deferoxamine for the removal of myocardial iron (as defined by MRI T2*) was based on 80% power and a one-sided $\alpha$=0.025. The T2* data were presented as the geometric mean (anti-log of the mean of the log data) ± the coefficient of variation (CV) due to the use of log-transformation in the analysis; it was known that cardiac iron load is inversely related to T2*, therefore log-transformation of the MRI T2* data was used to linearize the scale, resulting in normalization of the MRI T2* data. Statistical significance was established using the two-sample t-test. The LVEF and LVSF data, serum ferritin, and LIC data are presented as the mean ± standard deviation (SD) change from baseline to 12 months. The last-observation-carried-forward (LOCF) was used where data were missing. A p-value of 0.05 was used to determine statistical significance. Analysis was conducted on the intent-to-treat population (ITT) in which each patient received at least one dose and had a post-baseline efficacy measurement. The per protocol (PP) group included all randomized patients that had completed the study. The LOCF method was used to fill in missing data for the 5 withdrawn patients in the efficacy analysis of the ITT population.

#### *5.2.2.6. Patient Disposition*

Twenty nine patients were randomized to deferiprone and 32 patients were randomized to continue deferoxamine.

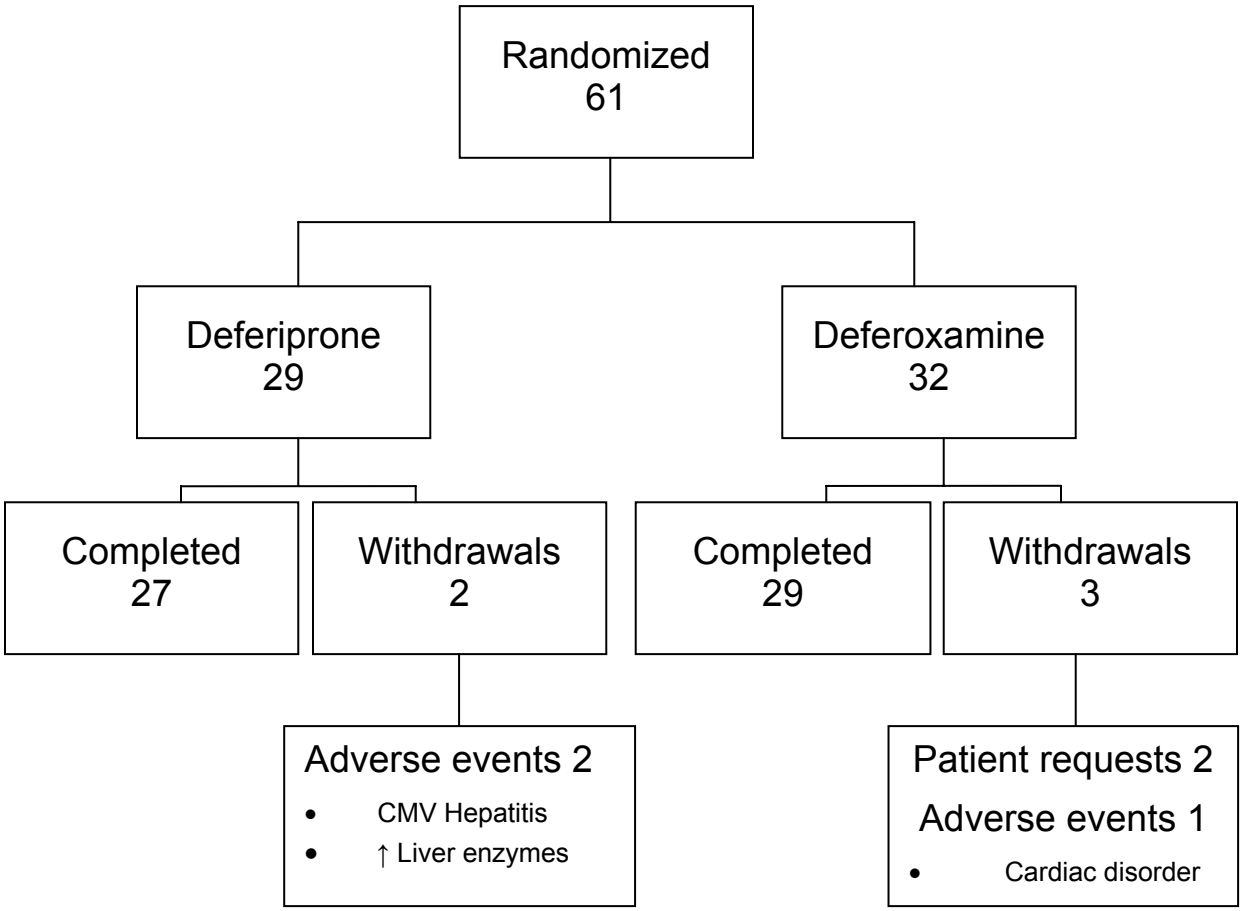


**Figure 3: LA16 Patient Disposition**

*5.2.2.7. Demographics*

The demographics for the 61 randomized patients are summarized in Table 5-11. The deferoxamine- and deferiprone-treated groups were well matched for the primary endpoint of myocardial siderosis. Matching was good for most other measures including liver iron and transfusional iron input, but a significant difference was present for serum ferritin, with deferoxamine-treated patients having values higher than deferiprone-treated patients. The inability to match patients for all 3 measurements of iron overload should not be unexpected given the lack of a significant correlation among the 3 parameters (Anderson LJ *et al.* 2001).

**Table 5-11: LA16: Summary of randomized patient characteristics at baseline**

| | Deferiprone (n= 29) | Deferoxamine (DFO) (n= 32) |
|---|---|---|
| Age, Years Mean ±SD | 25.1 ± 3.8 | 26.2 ± 4.7 |
| Sex Male:Female (n%) | 15:14 (52:48) | 16:16 (50:50) |
| Cardiac MRI T2* (ms) Mean ± SD | 13.6 ± 3.9 | 13.9 ± 3.8 |
| Serum Ferritin (µg/L) Mean ±SD | 1790.6 ± 1028.9 | 2795.1 ± 2441.2 |
| LIC (mg Fe/g dry weight) Mean ±SD | 6.16 ± 6.02 | 6.32 ± 5.77 |

The mean study dose of DFO was 43 mg/kg for 5.7 days/week. The mean study dose of deferiprone was 92 mg/kg/day. The overall compliance was similar between the deferiprone and the DFO treatment groups (93.7 ± 5.3% versus 93.2 ± 9.7%; p=0.81) indicating that any differences in efficacy were not due to a difference in treatment compliance.

#### *5.2.2.8. Efficacy Results*

Analysis of MRI T2*

The results of MRI T2* measurements for patients in both study arms are presented in Table 5-12. Deferiprone-treated patients had a significantly greater improvement in MRI T2*, indicative of a decrease in myocardial iron concentration, than DFO-treated patients. The geometric mean resulting from deferiprone treatment was an MRI T2* of 16.5 ms compared to 15.0 ms for the DFO-treated patients at 12 months. The difference in relative change from baseline between the two treatment arms was significant (p = 0.0228).

**Table 5-12: LA16: Log (MRI T2*) of the deferiprone and deferoxamine (DFO) Treatment Groups for the ITT Population**

| MRI T2* | Randomized Treatment Groups | | | | | |
|---|---|---|---|---|---|---|
| | Baseline | | 6 Months | | 12 Months | |
| | Deferiprone [n=29] | DFO [n=32] | Deferiprone [n=29] | DFO [n=31†] | Deferiprone [n=29] | DFO [n=31†] |
| Geometric Mean (milliseconds)* | 13.03 | 13.32 | 15.37 | 14.43 | 16.51 | 15.01 |
| Coefficient of Variation (%)‡ | 32 | 30 | 38 | 37 | 38 | 39 |
| Percentage of Baseline | | | 118 | 109 | 127 | 113 |
| Ratio of Means (%)§ | 98 | | 109 | | 112 | |
| p-value‖ | 0.7731 | | 0.0404 | | 0.0228 | |

* Geometric mean is defined as antilog of the mean of the log data

† Subject C1-40 had baseline MRI T2* level value only and was not eligible to be included in the ITT population.

‡ Coefficient of variation is defined as 100% × $\sqrt{[e^{variance-1}]}$, where variance is the variance of the mean in log scale.

§ The ratio is defined as deferiprone mean/DFO mean. At 6 and 12 months, the ratio is corrected for the difference in baseline mean between the two treatment groups by dividing it by 0.98.

‖ The Log (MRI T2*) values of the deferiprone and DFO treatment groups were compared by the two-sample t-test.

Analysis of Body Iron Load

As a secondary objective, this study also evaluated the relative efficacy of deferiprone and DFO as assessed by serum ferritin concentration and liver iron concentration (LIC). No significant difference (p= 0.1598) in mean change of serum ferritin from baseline to 12 months between the two treatment groups was detected (Table 5-13). However, as the baseline serum ferritin values were significantly different between the DFO and deferiprone groups of patients (2,795 µg/L vs. 1,791 µg/L, respectively), the statistical non-significance of the difference in mean change at 12 months between the 2 treatment groups should be interpreted with caution.

The difference in mean decrease in LIC at 12 months (0.61 mg/g dw) between the 2 groups was both clinically and statistically non-significant (p = 0.3961) (Table 5-14).

**Table 5-13: LA16 serum ferritin concentrations of the deferiprone and deferoxamine (DFO) Treatment Groups within the ITT population**

| Serum Ferritin Concentration (µg/L) | Randomized Treatment Groups | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | Change from Baseline to 3 Months | | Change from Baseline to 6 Months | | Change from Baseline to 9 Months | | Change from Baseline to 12 Months | |
| | DFP [n=29] | DFO [n=32] | DFP [n=29] | DFO [n=32] | DFP [n=29] | DFO [n=32] | DFP [n=29] | DFO [n=32] | DFP [n=29] | DFO [n=32] |
| Mean ± SD | 1790.6 ± 1028.9 | 2795.1± 2441.2 | 354.8 ± 743.3 | -169.1 ± 814.4 | 150.9 ± 713.4 | -314.3 ± 921.0 | -72.3 ± 658.3 | -548.4 ± 868.2 | -181.0 ± 825.5 | -466.1 ± 738.9 |
| Min, Max | 289, 5345 | 280, 9300 | -394, 3610 | -2222, 3041 | -816, 1782 | -3979, 1812 | -1833, 1606 | -2894, 306 | -2179, 1990 | -2208, 606 |
| p-value* | 0.0391 | | 0.0113 | | 0.0326 | | 0.0199 | | 0.1598 | |

SD = standard deviation
* Mean changes of serum ferritin concentrations from baseline to 3, 6, 9, and 12 months were compared between the treatment groups by using the two sample t-test.

**Table 5-14: LA16: Liver Iron Concentration (LIC) in deferiprone and deferoxamine (DFO) Treatment Groups**

| LIC (mg Fe/g dry weight liver) | Randomized Treatment Groups | | | |
|---|---|---|---|---|
| | Baseline | | Change from Baseline to 12 Months | |
| | Deferiprone [n=28†] | DFO [n=32] | Deferiprone [n=27‡] | DFO [n=30‡] |
| Mean ± SD | 6.16 ± 6.02 | 6.32 ± 5.77 | -0.93 ± 2.93 | -1.54 ± 2.49 |
| Min, Max | 1.5, 33.3 | 0.7, 26.4 | -8.7, 5.2 | -8.8, 1.6 |
| p-value* | 0.9161 | | 0.3961 | |

Fe = iron; ITT = intent-to-treat; LIC = liver iron concentration; SD = Standard Deviation.
* Mean changes from baseline to 12 months were compared between the two treatment groups by using the two-sample t test.
† Subject C1-44 did not have a baseline LIC value and was not eligible to be included in the ITT population.
‡ Subjects A1-20, C1-40, C1-44 and C1-52 did not have LIC values at 12 months and were not eligible to be included in the ITT population.

Analysis of LVEF and LVSF

The mean changes in CMR LVEF from baseline to 6 and 12 months of therapy were compared between the two treatment groups. As shown in Table 5-15, the deferiprone treatment group showed significantly greater improvement in the LVEF compared to patients treated with deferoxamine (p=0.0034) at 12 months. These data are consistent with previous studies showing significantly superior EF in deferiprone-treated patients than in DFO-treated patients (Anderson LJ *et al.* 2002; Peng CT *et al.* 2003; Perifanis V *et al.* 2007).

**Table 5-15: LA16 CMR LVEF of the Deferiprone (DFP) and Deferoxamine (DFO) Treatment Groups for the ITT population**

| CMR LVEF (%) | Randomized Treatment Groups | | | | | |
|---|---|---|---|---|---|---|
| | Baseline | | Change from Baseline to 6 Months | | Change from Baseline to 12 Months | |
| | DFP [n=29] | DFO [n=32] | DFP [n=29] | DFO [n=31†] | DFP [n=29] | DFO [n=31†] |
| Mean ± SD | 69.66 ± 5.44 | 68.38 ± 4.92 | 2.00 ± 2.73 | 0.52 ± 3.52 | 3.07 ± 3.58 | 0.32 ± 3.38 |
| Min, Max | 58, 80 | 60, 79 | -3, 9 | -9, 9 | -3, 11 | -8, 5 |
| p-value* | 0.3382 | | 0.0744 | | 0.0034 | |

CMR = cardiovascular magnetic resonance; ITT = intent-to-treat; LVEF = left ventricular ejection fraction; max = maximum; min = minimum.

* Changes in CMR LVEF from baseline to 6 months and 12 months were compared between the two treatment groups by using the two-sample t-test.

† Subject C1-40 had a baseline CMR LVEF level value only and was not eligible to be included in the ITT population.

An ECHO was performed at baseline and at 12 months to measure LVEF and provided similar results as CMR, both approaches showing significantly better response to deferiprone.

The efficacy of deferiprone and deferoxamine in improving cardiac function was further compared by determining the change in the mean value of LVSF relative to baseline. An ECHO was performed at baseline and at 12 months to measure LVSF. The comparative analysis of the two treatment groups used the two sample t-test. The change from baseline to 12 months in the two treatment groups is presented in Table 5-16.

**Table 5-16: LA16 ECHO LVSF of the Deferiprone (DFP) and Deferoxamine (DFO) Treatment Groups for the ITT population**

| ECHO LVSF (%) | Randomized Treatment Groups | | | |
|---|---|---|---|---|
| | Baseline | | Change from Baseline to 12 Months | |
| | Deferiprone [n=29] | DFO [n=32] | Deferiprone [n=28†] | DFO [n=31†] |
| Mean ± SD | 36.32 ± 4.39 | 36.38 ± 4.25 | 2.62 ± 7.41 | -1.08 ± 3.82 |
| Min, Max | 31.2, 47.0 | 30.0, 44.0 | -8.0, 12.0 | -8.8, 8.0 |
| p-value* | 0.9540 | | 0.0175 | |

ECHO = echocardiogram; ITT = intent-to-treat; LVSF= left ventricular shortening fraction; SD = Standard deviation.

* Mean changes from baseline to 12 months were compared between the two treatment groups by using the two-sample t-test.

† Subjects A1-47 and C1-40 did not have ECHO LVSF values at 12 months and were not eligible to be included in the ITT population.

#### *5.2.2.9. Conclusion*

The study objective, as defined by the primary end point, was met, i.e., the data demonstrated superiority of deferiprone over DFO in removing myocardial iron. The change in geometric mean MRI T2* from baseline to 12 months generated by deferiprone was significantly (p=0.0228; two sample t-test) better than that associated with deferoxamine. While more patients would be needed to confirm the similarity in efficacy on the secondary endpoints, the results of the study show that changes in serum ferritin and liver iron concentration were not different after 12 months therapy with the two chelators. Changes in CMR LVEF measurement significantly (p= 0.0034) favored deferiprone, as did changes in ECHO measures of LVEF and LVSF. Overall, the effect of deferiprone on cardiac iron reduction and improvement in cardiac function was better in patients randomized to the deferiprone treatment arm than in patients randomized to deferoxamine, while the ability of deferiprone to control general measures of iron overload (LIC and serum ferritin) was similar to that of deferiprone in this study.

### *5.2.3. **ApoPharma Clinical Study LA12-9907***

#### *5.2.3.1. Overview of LA12 Study Design*

Study LA12 was a single center, retrospective study of a registry of patients with transfusion-dependent thalassemia. It was conducted at the request of the European Medicines Agency (EMA) as a post-marketing approval study to compare the long-term (>4 years) efficacy of deferiprone to that of DFO on the clinical outcomes of cardiac disease and death in those patients. After EMA approval of the protocol, data were collected from medical records of eligible subjects at the thalassemia center of the University of Turin, Italy, which has conducted a prospective assessment on survival and major clinical complications of iron overload for those subjects since 1981 (Gabutti V & Piga. 1996; Piga A *et al.* 2003).

Primary Endpoint and Secondary Endpoint

The primary endpoint was the incidence of cardiac disease and survival in patients treated with deferiprone compared with those patients treated with deferoxamine, over the same period of time. The secondary endpoint was the progression of cardiac disease in patients treated with either deferiprone or deferoxamine.

#### *5.2.3.2. Patient Inclusion and Exclusion Criteria*

All transfusion-dependent thalassemia patients who were followed at the thalassemia center of the University of Turin were treated with DFO until January 1995. Starting in 1995 a substantial proportion of those patients were switched to deferiprone due to their enrollment in clinical trials such as studies LA-02/06 and LA08 or the Italian Ministry of Health active drug surveillance program (LA17). The remaining patients maintained therapy with DFO. Due to the retrospective nature of the study, no formal randomization was performed and all of the available data were collected from patients with thalassemia major on either deferiprone or DFO therapy between January 1995 and March 2001. Patients with transfusion-dependent anemias other than thalassemia, who were younger than 5 years of age, HIV antibody positive, or who had a history of malignancy or required radiation or chemotherapy, were not included in the study.

#### *5.2.3.3. Statistical Methodology*

A single cardiologist assessed the cardiac status of each of the patients at each year of therapy during the review period. The assessment was based on review of existing cardiac records of those patients. The cardiologist was not provided information on the chelation therapy the patients had received during the review period. No other blinding was applied in this study. Endpoints for censoring were based on death or occurrence of *de novo* cardiac dysfunction. Change in cardiac status was determined by the New York Heart Association (NYHA[2]) classification (The Criteria Committee of the New York Heart Association. 1994), left ventricular shortening fraction and left ventricular ejection fraction in echocardiogram, and electrocardiogram. The NYHA classification was not applicable (NAP) to subjects who were cardiac disease-free.

A two sample t-test or Chi-square test, as appropriate, was used to compare the subject characteristics and chelation status of the two treatment groups at the beginning and at the end of the study period. The frequency (%) of patients with cardiac dysfunction at the first cardiac assessment was evaluated. The first cardiac assessment was considered as the baseline value for each patient. The Kaplan-Meier analysis of heart disease-free survival for patients who were disease-free (NYHA class not applicable = 0) at the first assessment was performed by using the procedure LIFETEST from SAS (SAS Institute, Cary, North Carolina). The primary comparison of the two groups was based on the log rank test. As not all patients had a cardiac assessment at the beginning of the review period (year 0 for each individual patient), the time for development of heart disease was calculated as the time difference between the first available NYHA class of NAP and the first occurrence of NYHA class of I or greater. Change in cardiac status was evaluated by the Chi-square test.

#### *5.2.3.4. Results*

<u>Demographics</u>

One hundred and twenty nine of the 168 transfusion-dependent thalassemia patients followed at the thalassemia center had been treated with deferiprone or DFO for four or more years and complied with the inclusion/exclusion criteria. Sixteen patients were excluded from the analysis because they had less than 4 years of chelation with either deferiprone or DFO during the review period (one of those patients was lost to follow up, none of the other 15 patients died or experienced a cardiac event during the study period), 10 patients were excluded due to lack of data on the cardiac assessments made while on the chelation regimen, 6 patients had a single

[2] Functional Capacity

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.

Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

cardiac assessment, 6 patients were younger than 5 years, and one patient was excluded due to sero-positivity for HIV. None of the excluded patients died or manifested cardiac disease during the review period.

All 129 patients had been treated with DFO prior to the initiation of the study period. Table 5-17 summarizes the results of the assessments in each study group at the start of the review period.

**Table 5-17: LA12: Comparison of deferiprone- and DFO-treated patient groups at the start of the study**

| | Deferiprone (N = 54) | DFO (N = 75) | p |
|---|---|---|---|
| Mean age ± S.D. (years) | 17.1 ± 4.1 | 19.4 ± 6.9 | 0.0184 |
| Mean age in years ± S.D. at start of chelation therapy with deferoxamine (No. of patients available) | 4.5 ± 2.7 (54) | 6.8 ± 4.7 (72) | 0.0010 |
| Mean serum ferritin μg/L ± S.D. (No. of patients available) | 2033 ± 919 (51) | 1809 ± 1464 (60) | 0.3277 |
| Percentage of patients with more than 50% of their serum ferritin results >2,500 μg/L | 24% (12/51) | 15% (9/60) | 0.2529 |
| Percentage of patients with cardiac dysfunction at first assessment (No. of patients available)* | 13% (7/54) | 16% (12/75) | 0.6311 |

* The cardiac abnormalities were evaluated as NYHA Class I in 13 patients (six in the deferiprone group and seven in the DFO group), Class II in 3 patients (all in the DFO group), Class III in two patients (one in each therapy group) and Class IV in one DFO-treated patient.

Efficacy Results

Worsening of pre-existing cardiac status was observed in 4 (33%) of the 12 patients with abnormal cardiac function at the first study assessment in the DFO group. None of the seven deferiprone-treated patients who had cardiac dysfunction at the first assessment had worsening of their cardiac status during the study period (p = 0.245). Improvement of cardiac status was observed in 3 (43%) of the 7 deferiprone-treated patients and in 3 (25%) of the 12 DFO-treated patients with cardiac dysfunction at the first assessment (p = 0.617).

*De novo* cardiac dysfunction occurred in 13 (20.6%) of the 63 DFO-treated patients and in 2 (4.3%) of the 47 deferiprone-treated patients (p = 0.0133). All but two of the 15 subjects were classified as NYHA class I. Of the two, one subject was classified as NYHA class II, while the other patient was classified as NYHA class I and later, class III; both patients were treated with DFO. In two of the 13 DFO subjects the cardiac dysfunction was considered resolved at the end of the study period. These subjects were not included in the analysis of worsening of cardiac function at the last assessment.

Overall, whether patients were cardiac dysfunction free or not at the first assessment, a worsening of the cardiac function in the last assessment was diagnosed in two (3.7%) deferiprone-treated patients (two *de novo* cardiac dysfunction) and in 15 (20.0%) DFO-treated patients (p = 0.0069). Subjects in the deferiprone group had longer cardiac disease-free survival

compared with subjects in the DFO group. Kaplan-Meier analysis of cardiac disease-free survival over a 5-year period was significantly more favorable in the deferiprone group ($p = 0.0033$).

Mean compliance with chelation therapy during the study period was 89 ± 7% (N = 53) with deferiprone, and 85 ± 11% (N = 73) with DFO, indicating that the less favorable clinical outcomes in the DFO-treated group were not due to lack of compliance.

Four subjects, all treated with DFO, died during the study period; in three, death was attributed to irreversible progression of cardiac dysfunction that was present at first assessment. The fourth subject died within a few hours of being admitted to a provincial hospital for acute abdominal pain. No cause of death for this subject was provided to the study center.

#### *5.2.3.5. Conclusion*

Although this study was requested by the EMA and the analysis plan approved by them, this study has the limitation of being a retrospective cohort study and being a single center study. The results of this retrospective analysis suggest that in patients with thalassemia major, long term deferiprone treatment is associated with a lower incidence of iron-induced cardiac disease than long-term treatment with deferoxamine.

### *5.2.4. **Natural History Study; Borgna-Pignatti et al. 2006***

#### *5.2.4.1. Overview of Study Design*

The largest and most comprehensive natural history studies of morbidity and mortality in patients with thalassemia have been conducted by a group that collects data from seven of the thalassemia treatment centers in Italy and has been following all their patients since 1983 with periodic reports on status at varying intervals (Borgna-Pignatti C et al. 1989; Borgna-Pignatti C et al. 1998; Borgna-Pignatti C et al. 2004; Zurlo MG et al. 1989). Those studies have documented the significant reduction in morbidity and mortality that was associated with the introduction of chelation with DFO in the 1970s (Borgna-Pignatti C et al. 1989; Borgna-Pignatti C et al. 1998; Borgna-Pignatti C et al. 2004; Zurlo MG et al. 1989). However, they also documented that iron-induced cardiac disease had persisted and remained the most common cause of premature death in these patients (Borgna-Pignatti C et al. 1998; Borgna-Pignatti C et al. 2004). As of 31 December 1999, 35 (5%) of the 720 patients born after 1970 had died due to iron-induced cardiac disease (Borgna-Pignatti C et al. 2004).

In 2006, the data from the patients followed in those seven treatment centers were analyzed for cardiac disease and survival based on the chelation therapy they had received (Borgna-Pignatti C *et al.* 2006). The study database, the statistical analysis plan and the statistical analysis have been provided to the FDA as part of the current deferiprone NDA. Although ApoPharma did not sponsor this study, the database was provided to the company by the investigators once the results had been published.

#### *5.2.4.2. Primary Endpoint and Secondary Endpoint*

The primary endpoint of this study was the incidence of cardiac events.

The secondary endpoint was the rate of deaths from all causes.

#### *5.2.4.3. Inclusion and Exclusion Criteria*

The analyses conducted for this study included all patients with transfusion-dependent thalassemia followed in those seven centers, born between 1970 and 1993 and who on January 31, 1995 were alive, had not had a cardiac event, defined as cardiac failure or arrhythmias requiring use of inotropic or antiarrhythmic drugs, and on follow-up had not undergone bone marrow transplantation. The 1970 to 1993 time period was chosen because regular chelation therapy with DFO was initiated around 1975 and little deferiprone was being used in Italy prior to 1995. The last follow-up date was December 31, 2003.

#### *5.2.4.4. Statistical Methodology*

The primary approach to analyzing the data was a time-to-event analysis, where an event was a cardiac complication, defined as cardiac failure or arrhythmias requiring use of inotropic or antiarrhythmic drugs. Time zero, or study entry, was defined as January 31, 1995, for all patients, as a common baseline for treatment outcome comparisons. An observation was considered censored if the patient was cardiac event–free on December 31, 2003, or at last follow-up, or at bone marrow transplantation (N=9), or at switch to deferasirox (DFX) (N=46). If a death occurred that was clearly not cardiac related, the observation was also considered censored at time of death for the time to cardiac events analysis. Any cardiac event was defined as a failure event, and observation of the patient was terminated for the purpose of this study.

The incidence of cardiac events was calculated by treatment group for each calendar year. The definition of "group" for each year was based on the treatment that the patient was receiving on January 1 of the given year. It was possible to therefore be classified on one treatment on January 1, switch treatments during the year, and have a cardiac event at a later date in the year. In this case, the event would be attributed to the January 1 treatment. This interval definition was used in order to apply a consistent definition throughout the data. However, no scenario occurred where a patient was on DFO on January 1, then changed to deferiprone and had a cardiac event attributed to DFO. The incidence rates and exact 95% binomial confidence intervals (CIs) were calculated for all incidence estimates. For each year of the study period, a $2 \times 2$ table was constructed. The factors were: having a cardiac event vs. not having an event, and treatment group (deferiprone or DFO). All the annual tables were combined and subsequently tested for whether the combined odds ratio was 1.0. For descriptive purposes only, two treatment groups were defined, including either the patients who received DFO only or the patients who received deferiprone at some point in time during the review period. The two treatment groups were compared for baseline characteristics to explore whether there was some disposition to provide deferiprone to a particular subset of patients.

Because it was unknown at study entry how many and which patients would receive deferiprone and which would not, it would not have been correct to use the descriptive 2 treatment groups

and compare them using a proportional hazards model and a log-rank test. Moreover, because all those patients who received deferiprone also received DFO during part of the study (either only before or before and after deferiprone), they were not defined as patients receiving deferiprone for the duration of the study. Therefore, a time-varying treatment variable was defined. For each patient, treatment at time "t" was defined as 0 if the treatment was DFO and 1 if the treatment was deferiprone. All patients had, therefore, a starting value of 0. The patients who switched to deferiprone had their time-varying treatment variable switched to deferiprone at the time when they changed treatment. Some patients on deferiprone at some point switched back to DFO treatment. Their time-varying treatment variable was changed back to 0 at the time that they switched back to DFO. A Cox regression model with this time-varying treatment variable was used to test the efficacy of deferiprone. Additional Cox regression models were fit to test for the effect of sex, of birth cohort, and of ferritin level at baseline (using 2,500 µg/L as a cutoff value). An additional analysis compared the rates of events using a person-years method. In this approach, the rate of events was compared by calculating the number of events relative to the number of person-years of exposure to either DFO or deferiprone, as appropriate. It was assumed that the cardiac events were generated by a Poisson distribution and tested for equality between a Poisson process underlying cardiac events generated while on DFO and a Poisson process underlying cardiac events generated while on deferiprone.

As a secondary endpoint, the study compared the rate of deaths from all causes using the same Cox regression model approach with treatment as a time-varying covariate. In this approach, a failure event was death due to any cause, and censoring occurred if a patient was alive at the end of the follow-up period, or received bone marrow transplantation, or switched to DFX.

#### *5.2.4.5. Results*

Patient Disposition and Demographics

Five hundred and sixteen patients met the inclusion/exclusion study criteria defined above: 359 (70%) received only DFO throughout the study period, while 157 (30%) patients were treated with deferiprone at some point during the study. There were relatively more patients with ferritin levels greater than 2,500 µg/L among the patients switched to deferiprone (31%) than in the group that remained on DFO (21%; p = 0.003). All other baseline characteristics were similar. The total study duration was nearly 9 years. All the patients were followed for the entire study duration, except two (both on DFO) who were lost to follow-up. The median duration of deferiprone treatment was 4.3 years (range, 0.02-8.9 years), for a total of 750 patient-years. The median duration of DFO treatment was 7 years.

Study Results

In this group of patients, without any clinical evidence of pre-existing cardiac disease, there were 52 cardiac events during the observation period in the 516 transfused patients. All 52 cardiac events occurred in patients treated with DFO.

The annual incidence of cardiac events (cardiac failure or arrhythmias requiring use of inotropic or antiarrhythmic drugs) while on DFO ranged from 0.6 to 3.4 (Table 5-18). This table shows the number of patients at risk in each therapy, by calendar year. In each year of the study newly

developed cardiac disease occurred during therapy with DFO. During the nine-year period of this study, no subject treated with deferiprone developed cardiac disease. The confidence intervals for events on DFO were narrow, approximately 2% to 4% wide. The (1-sided) confidence intervals for deferiprone were between 4% and 6% wide, depending on the number of subjects at risk. No patient was on DFO on January 1, changed to deferiprone, had a cardiac event, and had the event attributed to DFO. The odds ratio of a cardiac event on DFO versus deferiprone is estimated at infinity, since there were no events on deferiprone, with a lower 95% confidence bound of 2.75.

**Table 5-18: Borgna-Pignatti, 2006: Number of patients at risk and number of patients with cardiac events (cardiac failure or arrhythmias requiring use of inotropic or antiarrhythmic drugs), while taking either DFO or deferiprone therapy during 1995-2003**

| Year* | DFO | | | Deferiprone | | |
|---|---|---|---|---|---|---|
| | Subjects at Risk | Cardiac Events | Percentage (95% CI) | Subjects at Risk | Cardiac Events | Percentage (95% CI)† |
| 1995 | 516 | 3 | 0.58 (0.12, 1.69) | 0 | 0 | NA |
| 1996 | 444 | 11 | 2.48 (1.24, 4.39) | 63 | 0 | 0 (0, 5.69) |
| 1997 | 420 | 4 | 0.95 (0.26, 2.42) | 75 | 0 | 0 (0, 4.80) |
| 1998 | 398 | 5 | 1.26 (0.41, 2.91) | 93 | 0 | 0 (0, 3.85) |
| 1999 | 396 | 3 | 0.76 (0.16, 2.20) | 89 | 0 | 0 (0, 4.06) |
| 2000 | 393 | 4 | 1.02 (0.28, 2.59) | 87 | 0 | 0 (0, 4.15) |
| 2001 | 387 | 6 | 1.55 (0.57, 3.34) | 89 | 0 | 0 (0, 4.06) |
| 2002 | 374 | 4 | 1.07 (0.29, 2.72) | 88 | 0 | 0 (0, 4.30) |
| 2003 | 358 | 12 | 3.35 (1.74, 5.78) | 92 | 0 | 0 (0, 3.93) |

CI = confidence interval; DFO = deferoxamine; NA = not applicable.
* Each subject is included once in each year, based on the treatment received on 01 Jan of that year.
† One-sided 97.5% CI.

Because all events in this study occurred while on DFO, a coefficient for a treatment effect in the Cox regression with treatment as a time-varying covariate could not be estimated. The hazard of a cardiac event on deferiprone is estimated at 0, and on DFO as more than 0; therefore, the hazard ratio between the 2 treatments is 0, and DFO is a significant risk factor for a cardiac event. In order to estimate the statistical significance, one artificial cardiac event on deferiprone was created. In this analysis, the hazard ratio on deferiprone compared with DFO was 0.09 (CI 0.012, 0.66; P = 0.017).

An additional analysis conservatively assumed that a lack of protection of deferiprone from cardiac events may extend up to 2 years beyond the end of therapy with deferiprone. This is modeled by keeping the group assignment of deferiprone for an additional 2 years of exposure for all patients who received deferiprone. Under this assumption, one of the 6 cardiac events that occurred after deferiprone treatment (20 months after treatment ended) would be attributed to deferiprone. In this analysis, the hazard ratio on deferiprone compared with DFO was 0.08 (CI 0.011, 0.57; p =0.012). When the known risk factors of sex, age, and ferritin level at baseline were included in the model in addition to deferiprone, the hazard ratio on deferiprone

compared with DFO was 0.075 (CI 0.010, 0.55; p = 0.011), and all the risk factors were significant (p<0.005). Thus, consistent with the person-years analysis, the hazard of a cardiac event on deferiprone is estimated to be less than a tenth of the hazard of a cardiac event on DFO (Table 5-19). The lower prevalence of cardiac events on deferiprone occurred in spite of a heavier starting iron overload in deferiprone-treated patients than in patients on DFO, based on serum ferritin values [median 1,870 µg/L vs. 1,461 µg/L; p<0.001].

**Table 5-19: Hazard Ratios: Deferiprone vs. Deferoxamine, Borgna-Pignatti, 2006**

| | Hazard Ratio for DFO vs. DFP | Hazard Ratio After Additional 2 Years of Exposure * | Hazard Ratio for DFO vs. DFP With Risk Factors Included º | Baseline Serum Ferritin Concentrations | | |
|---|---|---|---|---|---|---|
| | | | | Treatment | DFO | DFP |
| Hazard Ratio | 0.07 | 0.08 | 0.075 | Median (Range) µg/L | 1461 (160 – 9458) | 1870 (532 – 10632) |
| CI | 0.012, 0.66 | 0.011, 0.57 | 0.010, 0.55 | n/a | | |
| p Value | 0.017 | 0.012 | 0.011 † | p Value | <0.001 | |

* Under this assumption, 16.7% (1 out of 6) cardiac events occurred 20 months after end of DFP treatment

º Known risk factors of sex, age, and ferritin level at baseline included in this model

† All the risk factors were significant (p<0.005)

Fifteen of the 52 patients who experienced a cardiac event died of cardiac disease. All deaths occurred while patients were on DFO.

Six of the 52 cardiac events occurred in patients who had previously received deferiprone but were on DFO at the time of the event. The time interval between stopping deferiprone treatment and the occurrence of the cardiac event ranged from 1 year and 8 months to 5 years and 4 months. Eight patients were switched to deferiprone after development of a cardiac event while on DFO, but none developed a further event on deferiprone.

Twenty-six (5%) patients died during the study period, 24 (6.7%) in the DFO group and 2 (1.3%) in the deferiprone-switched group. Of the 24 deaths on DFO, 15 were cardiac related. Neither death on deferiprone was cardiac related. One patient died in a car crash; the other, of bacterial endocarditis that originated from an indwelling catheter inserted for DFO administration and that was still in place. Neutropenia was not present either before or during the event.

#### *5.2.4.6. Conclusion*

The results of this natural history study demonstrate that patients with transfusion-dependent thalassemia who switched from deferoxamine to deferiprone therapy had a lower prevalence of cardiac disease than patients chelated with deferoxamine.

### *5.2.5. **Other studies***

A summary of each individual study that contributed patients to the LA36 analysis is provided in

Appendix A. In each of those studies, serum ferritin concentrations were assessed as an efficacy endpoint. Figure 4 illustrates the mean change from baseline to the end of the study or up to one year of deferiprone therapy, when the study extended beyond one year, in patients participating in the individual studies that contributed patients to LA36 (Table 5-1). The results of those studies, based on the response in all patients and not only on patients for whom previous chelation therapy had been inadequate, support the efficacy of deferiprone in controlling the iron load, as assessed by serum ferritin measurements, despite the continued transfusional iron accumulation.

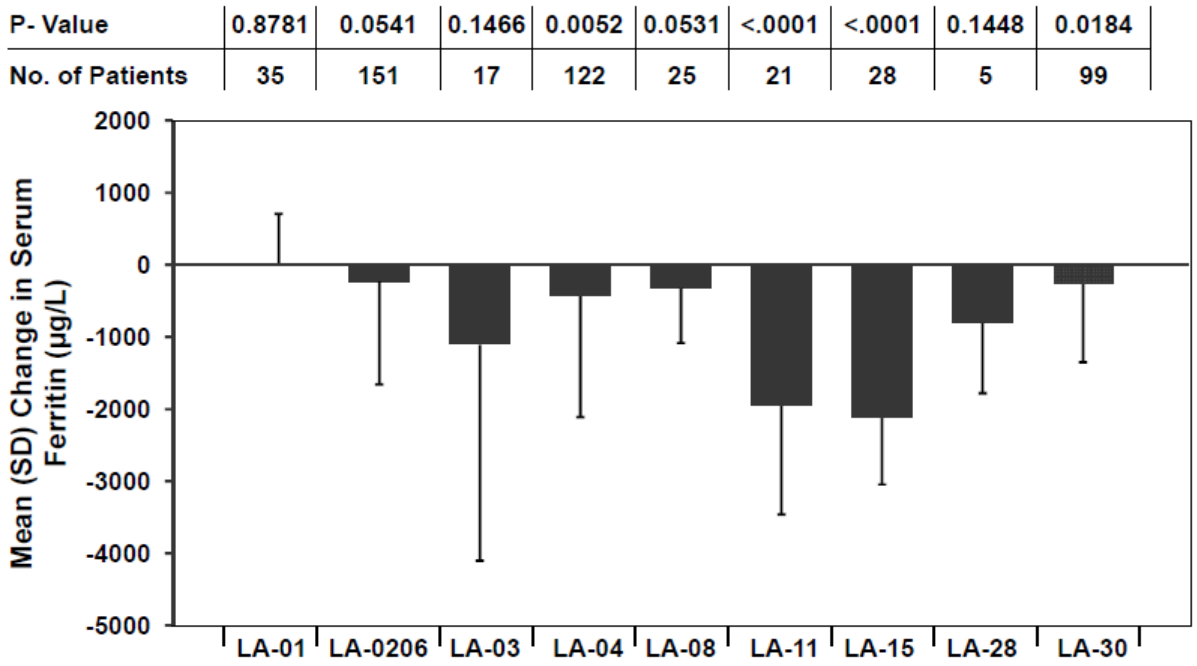


**Figure 4: Mean change from baseline to the end of study (or up to one year of deferiprone therapy when the study extended beyond one year) in patients participating in each study contributing to LA36**

## 5.3. Results of published studies by independent investigators

Data from studies published in the literature and not sponsored by ApoPharma also support the ability of deferiprone to reduce body iron load as reflected in serum ferritin concentration. The mean initial and final serum ferritin values during therapy with deferiprone reported in the medical literature is presented in Appendix C.1 (controlled studies) and Appendix C.2 (uncontrolled studies). The results of the Italian Ministry of Health special program, created in 1997 for the controlled distribution of deferiprone to collect data and to evaluate deferiprone's safety and effectiveness in long-term use prior to its market authorization are presented in Appendix A, section 13 under "Study LA17". Five hundred and thirty-two patients with thalassemia from 86 treatment centers were enrolled in this program and treated with deferiprone at a fixed dose of 75 mg/kg/day.

The results from studies LA12 and Borgna-Pignatti et al are consistent with results from other published studies looking at the relative effect of deferiprone to that of deferoxamine in preventing iron-induced cardiac disease (Borgna-Pignatti C *et al.* 2006; Ceci A *et al.* 2006; Ladis V *et al.* 2010; Maggio A *et al.* 2009a; Modell B *et al.* 2008; Piga A *et al.* 2003; Telfer P *et al.* 2006; Telfer PT *et al.* 2009). Figure 5 illustrates the relative effect ratio of deferiprone vs deferoxamine in preventing iron-induced cardiac disease. A short summary of those studies is provided in Appendix D.

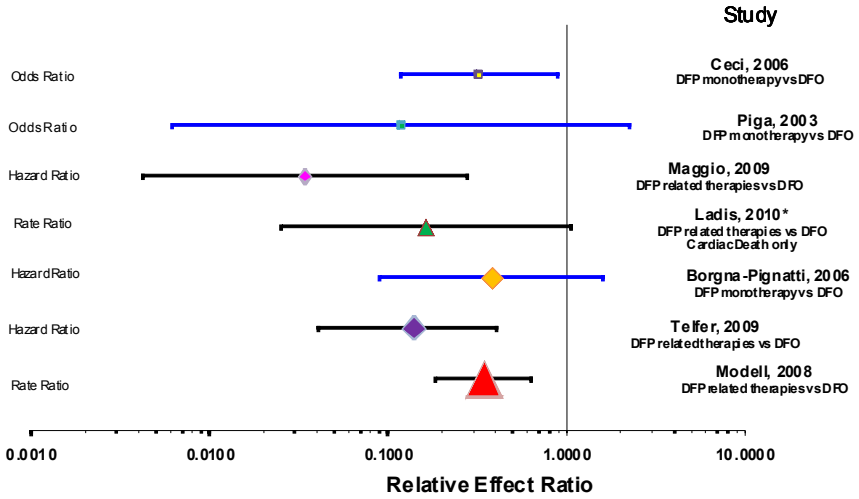


**Figure 5: Forest plot of the relative effect ratio of deferiprone to deferoxamine in preventing iron-induced cardiac disease**

These published studies individually do not provide Level 1 or Level 2 evidence, nor do they meet the standards of randomized controlled trials. They vary in design and have potentially important limitations. Nevertheless, they are consistent in showing a difference in iron-induced cardiac disease during therapy with deferiprone or deferoxamine.

## 5.4. Transfusion-Dependent Patients with underlying conditions other than Thalassemia

Both deferoxamine and deferasirox are approved for use in transfusional iron overload, including in patients with thalassemia, other congenital anemias and MDS. ApoPharma has provided some safety and efficacy data on the use of deferiprone in non-thalassemia patients treated in its compassionate use program and extracted from the literature, but no formal studies have been conducted in non-thalassemia populations.

The published literature on the use of deferiprone in patients with sickle cell disease is limited to small studies, although each suggests favorable results of deferiprone in treating transfusional iron overload in this patient population (Kersten MJ *et al.* 1996; Nzouakou R *et al.* 2009; Olivieri NF *et al.* 1993; Tsironi M *et al.* 2005; Voskaridou E *et al.* 2005). All of these studies were conducted by clinicians in the field who held the view that deferiprone was needed as a potential treatment for transfusional iron load in patients with sickle cell disease, and none were designed

for the purpose of regulatory review.

It is evident both from the compassionate use program and the literature, that there is a need for an alternative iron chelator in a segment of this transfusion-dependent population in whom previous chelation is inadequate. Thus to meet the current need, ApoPharma proposes that the data submitted and the supporting literature be sufficient for establishing reasonable evidence of the efficacy of deferiprone in transfusion-dependent patients other than thalassemia, and commits to initiate a post-approval study in patients with sickle cell disease within 9 months of FDA approval. A draft synopsis of the proposed study is provided in Appendix E for comment and for future discussion with the FDA.

### 5.5. Efficacy conclusion

In summary, the LA36 analysis met the requirements for a successful analysis and the results suggest that deferiprone is effective in the treatment of iron overload in patients whose previous chelation therapy did not produce adequate control of iron burden using any of the 3 measures of iron overload widely employed in transfusion-dependent patients: serum ferritin concentrations, liver iron concentrations and cardiac MRI T2*. Results of the contributor study LA16 demonstrated that deferiprone is superior to deferoxamine in reducing cardiac iron load. The individual studies including LA16, and the natural history studies LA12 and Borgna-Pignatti et al, as well as the other ApoPharma studies and the published literature, provide additional evidence of the efficacy of deferiprone for the treatment of patients with transfusional iron overload.

## 6. Overview of Clinical Safety

### 6.1. Safety in ApoPharma-Sponsored Clinical Trials

#### *6.1.1.* ***Overview of Pooled Safety Data***

The safety data evaluated are from all patients in all studies referred to in Table 5.1, with the addition of study LA10 (comparison of the clastogenicity of deferiprone and deferoxamine in peripheral lymphocytes), and omission of the natural history studies LA-12 and Borgna-Pignatti et al, in which safety data were not collected. The pooled safety data also excludes observations from bioequivalence or bioavailability studies in healthy volunteers (studies LA20, LA21), a single dose pharmacokinetic study in 6 patients (study LA14), and the Active Drug Surveillance Program (LA17) instituted by the Italian Ministry of Health for which the safety database was not provided to ApoPharma. No significant adverse events were reported in the single dose trials or in the publication of the results of the Italian Active Drug Surveillance Program (Ceci A *et al.* 2002). Nothing in this publication suggests that safety findings were inconsistent with the ApoPharma pooled safety database.

During the development of deferiprone for its first regulatory approval in 1999, ApoPharma did not conduct a large randomized trial to directly compare the safety of deferiprone to that of deferoxamine (DFO), because deferiprone was not intended to be an alternative to deferoxamine, at the time. It was perceived as a therapy for patients for whom deferoxamine was inadequate, due to the already recognized risk of agranulocytosis associated with its use, and the lack of any

evidence, at the time, for improved removal of cardiac iron. The life-threatening consequences of iron overload precluded a placebo-controlled study.

### *6.1.2. Demographics and baseline characteristics*

The pooled safety data presented in this section (Table 6-1) were collected from 642 patients exposed to deferiprone at any dose. The 642 patients took doses of 50 mg/kg/day (N = 25; 3.9%), 75 mg/kg/day (N= 407; 63.4%), or 100 mg/kg/day (N= 108; 16.8%), or were exposed to chelation regimens in which deferiprone was used as adjunctive therapy to deferoxamine or deferasirox (N= 89; 13.9%), which is referred to in this document as "alternate/combination therapy". Of the eighty-nine alternate/combination therapy patients, 29 of them were administered deferiprone orally 5 days per week alternating with deferoxamine infusions on the other 2 days per week. In the 58 other combination therapy patients, deferiprone was administered concurrently with deferoxamine and in 2 patients, deferiprone was administered concurrently with deferasirox. Thirteen additional patients were treated with deferiprone at doses other than 50, 75 or 100 mg/kg/day but not exceeding 100 mg/kg/day. These 13 patients are included in the <All doses> category. Thirty-five percent of the 642 deferiprone-treated patients were children, of whom 61 were 1 to 5 years old. The oldest patient treated with deferiprone was 77 years at initiation of therapy.

The pooled safety data includes data from 118 patients treated with deferoxamine, which was the control therapy in some of the deferiprone clinical trials. Safety data from those 118 patients are provided alongside the deferiprone safety data for comparison only.

**Table 6-1: Pooled Safety Data: Demographic Profile**

| | **Deferiprone 50 mg/kg/d n=25 (%)** | **Deferiprone 75 mg/kg/d n=407 (%)** | **Deferiprone 100 mg/kg/d n=108 (%)** | **Deferiprone (all doses) mg/kg/d n=642 (%)** | **Deferoxamine 50 mg/kg/d n=118 (%)** | **Alternate/Combination Therapy with Deferiprone n=89 (%)** |
|---|---|---|---|---|---|---|
| N | 25 | 407 | 108 | 642 | 118 | 89 |
| Mean | 33.2 | 20.7 | 14.7 | 20.7 | 20.4 | 24.3 |
| SD | 12.1 | 13.2 | 12.7 | 13.3 | 6.8 | 9.5 |
| Median | 32.0 | 18.0 | 8.5 | 19.0 | 20.0 | 23.0 |
| Min, Max | 5, 62 | 1, 77 | 1, 70 | 1, 77 | 6, 35 | 10, 54 |
| | | | | Age [n(%)] | | |
| 1 - 5 Years | 1 ( 4.0) | 25 ( 6.1) | 33 (30.6) | 61 ( 9.5) | 0 ( 0.0) | 0 ( 0.0) |
| 6 - 11 Years | 0 ( 0.0) | 40 ( 9.8) | 31 (28.7) | 81 ( 12.6) | 15 ( 12.7) | 6 ( 6.7) |
| 12 - 15 Years | 0 ( 0.0) | 72 (17.7) | 0 ( 0.0) | 80 ( 12.5) | 16 ( 13.6) | 7 ( 7.9) |
| 16 - 17 Years | 2 ( 8.0) | 44 ( 10.8) | 0 ( 0.0) | 51 ( 7.9) | 10 ( 8.5) | 4 ( 4.5) |
| >= 18 Years | 22 ( 88.0) | 226 (55.5) | 44 (40.7) | 369 ( 57.5) | 77 ( 65.3) | 72 ( 80.9) |

| | Deferiprone 50 mg/kg/d n=25 (%) | Deferiprone 75 mg/kg/d n=407 (%) | Deferiprone 100 mg/kg/d n=108 (%) | Deferiprone (all doses) mg/kg/d n=642 (%) | Deferoxamine 50 mg/kg/d n=118 (%) | Alternate/Combination Therapy with Deferiprone n=89 (%) |
|---|---|---|---|---|---|---|
| | | | Sex [n(%)] | | | |
| Male | 17 ( 68.0) | 197 (48.4) | 57 (52.8) | 320 ( 49.8) | 56 ( 47.5) | 44 ( 49.4) |
| Female | 8 ( 32.0) | 210 (51.6) | 51 (47.2) | 322 ( 50.2) | 62 ( 52.5) | 45 ( 50.6) |
| | | | Race [n(%)] | | | |
| White | 1 ( 4.0) | 333 (81.8) | 71 (65.7) | 457 ( 71.2) | 103 ( 87.3) | 50 ( 56.2) |
| Black | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 4 ( 0.6) | 1 ( 0.8) | 1 ( 1.1) |
| Asian | 24 ( 96.0) | 34 ( 8.4) | 33 (30.6) | 114 ( 17.8) | 14 ( 11.9) | 14 ( 15.7) |
| Unknown | 0 ( 0.0) | 36 ( 8.8) | 2 ( 1.9) | 59 ( 9.2) | 0 ( 0.0) | 20 ( 22.5) |
| Multi-Racial | 0 ( 0.0) | 1 ( 0.2) | 2 (1.9) | 8 ( 1.2) | 0 ( 0.0) | 4 ( 4.5) |
| | | | Primary Disease (Sponsor Defined) [n (%)] | | | |
| Thalassemia Major | 1 ( 4.0) | 375 ( 92.1) | 97 ( 89.8) | 560 ( 87.2) | 118 ( 100.0) | 78 ( 87.6) |
| Non Thalassemia Major | 24 ( 96.0) | 32 ( 7.9) | 11 ( 10.2) | 82 ( 12.8) | 0 ( 0.0) | 11 ( 12.3) |

1) Percentage is calculated based on the number of patients exposed in each dosing group.
2) Age is based on when patients were first exposed to deferiprone.
3) Non Thalassemia Major primary diagnosis consists of hemoglobin E-β thalassemia disease (n=42), myelodysplasia (n=15), sickle cell disease (n=5), thalassemia intermedia (n=5), myelofibrosis (n=4), congenital anemia (n=2), refractory anemia (n=2), and in 1 patient each with pure red cell aplasia, aplastic anemia, Blackfan-Diamond anemia, chronic lymphocytic leukemia, hereditary haemochromatosis, severe hemolytic anemia, transfusion-dependent aase syndrome

### *6.1.3. Patient exposure and dose distribution*

Similar to the current available chelators deferoxamine and deferasirox, deferiprone reduces total body iron in a dose-dependent manner. The dose of deferiprone most frequently used is 75 mg/kg/day, which can promote enough iron excretion to neutralize the mean transfusion iron input in the majority of transfusion-dependent patients. A dose of 50 mg/kg/day was used for patients who were less frequently transfused, mainly patients with hemoglobin E-β thalassemia disease, who received fewer than 8 blood transfusions per year. A dose of 100 mg/kg/day is recommended for patients with high transfusional iron input or for whom a rapid decline in iron load is required. The targeted dose for deferoxamine treated patients was 50 mg/kg/day.

Table 6-2 summarizes the overall exposure to deferiprone in clinical trials for all patients, by dose and by primary disease. For comparison purposes, all 118 DFO-treated patients in the ApoPharma controlled studies had thalassemia major as the primary disease and were exposed to DFO for a mean duration of 1.10 ± 0.74 years (range: 0.06-2.67 years), for an overall total exposure of 129.3 patient-years.

**Table 6-2: Pooled Safety Data: Exposure to deferiprone, by primary disease, and dose**

| | Thalassemia Major | Non Thalassemia Major | Total |
|---|---|---|---|
| Duration of exposure, Years mean ± SD (minimum, maximum)* | 2.2 ± 2.14 (0.00, 14.89) | 1.3 ± 1.88 (0.03, 14.28) | 2.09 ± 2.13 (0.00,14.89) |
| **Total exposure Years (N patients exposed)** | | | |
| All Doses mg/kg/d | 1231.9 (560) | 106.9 (82) | 1338.8 (642) |
| 50 mg/kg/d | 0.02 (1) | 25.9 (24) | 25.9 (25) |
| 75 mg/kg/d | 935.25 (375) | 51.87 (32) | 987.1 (407) |
| 100 mg/kg/d | 139.1 (97) | 9.4 (11) | 148.5 (108) |
| There are 13 patients, whose maximum dose of DFP was other than 50, 75 or 100 mg/kg/day, but did not exceed 100 mg/kg/day. | | | |

### *6.1.4. Adverse Events (AEs)*

Eighty-four percent of the 642 deferiprone-treated patients and 85% of the 118 DFO-treated patients experienced at least one treatment-emergent adverse event (AE). The total number of AEs for deferiprone–treated patients was 7091, which corresponded to 529.7 AEs per 100 patient-years' exposure to deferiprone. The total number of AEs for DFO–treated patients was 1152, which corresponded to 891.2 AEs per 100 patient-years exposure to DFO. A summary of the AEs experienced by >5% of the patients in the deferiprone group, and more common in the deferiprone group than in the DFO group by at least 0.5%, is provided in Table 6-3. Adverse events that were more commonly observed in deferiprone-treated patients than in DFO-treated patients, irrespective of their relationship to the study drug, included gastrointestinal upset such as abdominal pain, nausea, vomiting and diarrhea; respiratory infections such as influenza, pharyngitis, tonsillitis and bronchitis (listed in Table 6-3 under Infections and Infestations); neutropenia, decreased neutrophil count, fever, liver biopsy, increased alanine aminotransferase (ALT), ear infection, toothache, chromaturia (deferiprone bound to iron and excreted in the urine imparts a reddish color, which in some patients was captured as an AE for complete reporting) and arthralgia. A summary of all AEs, irrespective of causality, occurring in at least one deferiprone treated-patient is in Appendix F.

## Table 6-3: Pooled Safety Data: Summary of AEs irrespective of relationship to deferiprone occurring in >5% patients in the deferiprone group and more common in the deferiprone group than in the deferoxamine group by at least 0.5%

| | Deferiprone N patients exposed=642 Total Exposure=1338.8 pt.-years | | Deferoxamine N patients exposed=118 Total Exposure = 129.3 pt.-years | |
|---|---|---|---|---|
| **Body System Preferred Term** | **N patients (%)** | **Events (Rate per 100 Patient Years)** | **N patients (%)** | **Events (Rate per 100 Patient Years)** |
| **Blood and lymphatic system disorders** | **43 ( 6.7)** | **49 ( 3.66)** | **5 ( 4.2)** | **6 ( 4.64)** |
| Neutropenia | 43 ( 6.7) | 49 ( 3.66) | 5 ( 4.2) | 6 ( 4.64) |
| **Gastrointestinal disorders** | **272 ( 42.4)** | **887 ( 66.25)** | **36 ( 30.5)** | **68 ( 52.60)** |
| Nausea | 117 ( 18.2) | 182 ( 13.59) | 3 ( 2.5) | 3 ( 2.32) |
| Vomiting | 108 ( 16.8) | 187 ( 13.97) | 14 ( 11.9) | 18 ( 13.92) |
| Abdominal pain upper | 79 ( 12.3) | 166 ( 12.40) | 10 ( 8.5) | 12 ( 9.28) |
| Abdominal pain | 76 ( 11.8) | 123 ( 9.19) | 11 ( 9.3) | 14 ( 10.83) |
| Diarrhoea | 73 ( 11.4) | 122 ( 9.11) | 5 ( 4.2) | 8 ( 6.19) |
| Toothache | 53 ( 8.3) | 107 ( 7.99) | 9 ( 7.6) | 13 ( 10.06) |
| **General disorders and administration site conditions** | **181 ( 28.2)** | **477 ( 35.63)** | **15 ( 12.7)** | **24 ( 18.57)** |
| Pyrexia | 181 ( 28.2) | 477 ( 35.63) | 15 ( 12.7) | 24 ( 18.57) |
| **Infections and infestations** | **298 ( 46.4)** | **1115 ( 83.28)** | **64 ( 54.2)** | **150 ( 116.04)** |
| Pharyngitis | 149 ( 23.2) | 264 ( 19.72) | 23 ( 19.5) | 30 ( 23.21) |
| Influenza | 127 ( 19.8) | 266 ( 19.87) | 15 ( 12.7) | 23 ( 17.79) |
| Tonsillitis | 40 ( 6.2) | 56 ( 4.18) | 2 ( 1.7) | 2 ( 1.55) |
| Bronchitis | 36 ( 5.6) | 54 ( 4.03) | 3 ( 2.5) | 4 ( 3.09) |
| Ear infection | 33 ( 5.1) | 46 ( 3.44) | 1 ( 0.8) | 1 ( 0.77) |
| **Investigations** | **161 ( 25.1)** | **234 ( 17.48)** | **10 ( 8.5)** | **14 ( 10.83)** |
| Biopsy liver | 70 ( 10.9) | 74 ( 5.53) | 1 ( 0.8) | 1 ( 0.77) |
| Neutrophil count decreased | 57 ( 8.9) | 75 ( 5.60) | 4 ( 3.4) | 7 ( 5.42) |
| Alanine aminotransferase increased | 56 ( 8.7) | 85 ( 6.35) | 5 ( 4.2) | 6 ( 4.64) |
| **Musculoskeletal and connective tissue disorders** | **152 ( 23.7)** | **404 ( 30.18)** | **32 ( 27.1)** | **66 ( 51.06)** |
| Arthralgia | 101 ( 15.7) | 216 ( 16.13) | 9 ( 7.6) | 13 ( 10.06) |
| **Renal and urinary disorders** | **94 ( 14.6)** | **475 ( 35.48)** | **0 ( 0.0)** | **0 ( 0.00)** |
| Chromaturia | 94 ( 14.6) | 475 ( 35.48) | 0 ( 0.0) | 0 ( 0.00) |

Gastrointestinal adverse events, arthropathies (including arthralgia, arthritis and arthropathy), increased ALT and neutropenia were common adverse events that were considered to be of particular interest mainly because of their temporal relationship to administration of deferiprone and/or a greater incidence than in deferoxamine-treated patients. An overview of those adverse

events is presented in section 6.2.2 of this document.

Table 6-4 summarizes by age the number of deferiprone-treated patients who experienced AEs, showing AEs in >5% of patients in either the pediatric (patients <16 years) or adult (≥16 years) groups. These data indicate that more pediatric than adult deferiprone-treated patients experienced episodes of neutropenia, abdominal pain, respiratory infections such as pharyngitis, nasopharyngitis and influenza, ear infections, increased serum ALT levels and decreased neutrophil counts (a single drop in neutrophil count below 1.5 x $10^9$/L which was not confirmed as neutropenia). This greater proportion of children experiencing episodes of neutropenia and decreased neutrophil count is consistent with the observed greater rate of neutropenia in healthy children than in healthy adults (Hsieh MM *et al.* 2007). While increased serum ALT was more frequently reported as an AE in pediatric patients 10.4% vs 7.9%, when the ALT values were examined, the proportion of pediatric patients with normal ALT at baseline experiencing ALT elevation of >2×, 3× or 5× ULN (32.9%, 16.4% and 6.2%) was lower than those experienced by adults (35.3% , 19% and 7.6%).

**Table 6-4: Pooled Safety Data: Summary of AEs, irrespective of relationship to deferiprone, occurring in >5% pediatric or adult patients**

| | **Total Exposure: 1338.8 yrs<br>Total N of unique patients exposed=642** | |
|---|---|---|
| | **PEDIATRIC<br>N patients exposed=222<br>Total Exposure (yrs) = 483.7** | **ADULT<br>N patients exposed=420<br>Total Exposure (yrs)=855.1** |
| **Body system<br>preferred term** | **N patients (%)** | **N patients (%)** |
| **Blood and lymphatic system disorders** | **18 ( 8.1)** | **25 ( 6.0)** |
| Neutropenia | 18 ( 8.1) | 25 ( 6.0) |
| **Eye disorders** | **7 ( 3.2)** | **24 ( 5.7)** |
| Conjunctivitis | 7 ( 3.2) | 24 ( 5.7) |
| **Gastrointestinal disorders** | **77 ( 34.7)** | **201 ( 47.9)** |
| Nausea | 15 ( 6.8) | 102 ( 24.3) |
| Vomiting | 34 ( 15.3) | 74 ( 17.6) |
| Diarrhoea | 12 ( 5.4) | 61 ( 14.5) |
| Abdominal pain upper | 21 ( 9.5) | 58 ( 13.8) |
| Toothache | 7 ( 3.2) | 46 ( 11.0) |
| Abdominal pain | 31 ( 14.0) | 45 ( 10.7) |
| Dyspepsia | 3 ( 1.4) | 22 ( 5.2) |
| **General disorders and administration site conditions** | **61 ( 27.5)** | **135 ( 32.1)** |
| Pyrexia | 60 ( 27.0) | 121 ( 28.8) |
| Fatigue | 5 ( 2.3) | 26 ( 6.2) |

| | Total Exposure: 1338.8 yrs<br>Total N of unique patients exposed=642 | |
|---|---|---|
| | **PEDIATRIC**<br>**N patients exposed=222**<br>**Total Exposure (yrs) = 483.7** | **ADULT**<br>**N patients exposed=420**<br>**Total Exposure (yrs)=855.1** |
| **Body system preferred term** | **N patients (%)** | **N patients (%)** |
| **Infections and infestations** | **106 ( 47.7)** | **199 ( 47.4)** |
| Nasopharyngitis | 69 ( 31.1) | 113 ( 26.9) |
| Pharyngitis | 62 ( 27.9) | 87 ( 20.7) |
| Influenza | 50 ( 22.5) | 77 ( 18.3) |
| Bronchitis | 6 ( 2.7) | 30 ( 7.1) |
| Tonsillitis | 13 ( 5.9) | 27 ( 6.4) |
| Upper respiratory tract infection | 10 ( 4.5) | 25 ( 6.0) |
| Rhinitis | 6 ( 2.7) | 24 ( 5.7) |
| Ear infection | 15 ( 6.8) | 18 ( 4.3) |
| **Investigations** | **68 ( 30.6)** | **93 ( 22.1)** |
| Biopsy liver | 22 ( 9.9) | 48 ( 11.4) |
| Alanine aminotransferase increased | 23 ( 10.4) | 33 ( 7.9) |
| Neutrophil count decreased | 32 ( 14.4) | 25 ( 6.0) |
| **Metabolism and nutrition disorders** | **13 ( 5.9)** | **19 ( 4.5)** |
| Increased appetite | 13 ( 5.9) | 19 ( 4.5) |
| **Musculoskeletal and connective tissue disorders** | **39 ( 17.6)** | **118 ( 28.1)** |
| Arthralgia | 26 ( 11.7) | 75 ( 17.9) |
| Back pain | 18 ( 8.1) | 72 ( 17.1) |
| Pain in extremity | 5 ( 2.3) | 24 ( 5.7) |
| **Nervous system disorders** | **45 ( 20.3)** | **111 ( 26.4)** |
| Headache | 45 ( 20.3) | 111 ( 26.4) |
| **Renal and urinary disorders** | **32 ( 14.4)** | **62 ( 14.8)** |
| Chromaturia | 32 ( 14.4) | 62 ( 14.8) |
| **Respiratory, thoracic and mediastinal disorders** | **51 ( 23.0)** | **113 ( 26.9)** |
| Cough | 44 ( 19.8) | 85 ( 20.2) |
| Oropharyngeal pain | 28 ( 12.6) | 61 ( 14.5) |

Table 6-5 presents a summary of common AEs occurring in deferiprone-treated patients by primary diagnosis: thalassemia major vs. non-thalassemia major patients, showing AEs >5% in either group. The data suggest that other than neutropenia and respiratory infections, patients with conditions other than thalassemia major are not more frequently affected by adverse events than do thalassemia major patients, during deferiprone therapy.

## Table 6-5: Pooled Study Data: Summary of AEs irrespective of relationship to deferiprone occurring in >5% patients, stratified by primary diagnosis

| | Total Exposure: 1338.8 yrs N patients exposed=642 | |
|---|---|---|
| | **Thalassemia Major** | **Non Thalassemia Major*** |
| | **N patients exposed=560 Total Exposure (yrs)=1231.9** | **N patients exposed=82 Total Exposure (yrs)=106.9** |
| **Body System Preferred Term** | **N patients (%)*** | **N patients (%)*** |
| **Blood and lymphatic system disorders** | **34 ( 6.1)** | **9 ( 11.0)** |
| Neutropenia | 34 ( 6.1) | 9 ( 11.0) |
| **Eye disorders** | **30 ( 5.4)** | **1 ( 1.2)** |
| Conjunctivitis | 30 ( 5.4) | 1 ( 1.2) |
| **Gastrointestinal disorders** | **245 ( 43.8)** | **27 ( 32.9)** |
| Nausea | 102 ( 18.2) | 15 ( 18.3) |
| Vomiting | 102 ( 18.2) | 6 ( 7.3) |
| Abdominal pain upper | 76 ( 13.6) | 3 ( 3.7) |
| Abdominal pain | 75 ( 13.4) | 1 ( 1.2) |
| Diarrhoea | 63 ( 11.3) | 10 ( 12.2) |
| Toothache | 53 ( 9.5) | 0 ( 0.0) |
| **General disorders and administration site conditions** | **186 ( 33.2)** | **10 ( 12.2)** |
| Pyrexia | 173 ( 30.9) | 8 ( 9.8) |
| Fatigue | 29 ( 5.2) | 2 ( 2.4) |
| **Infections and infestations** | **285 ( 50.9)** | **20 ( 24.4)** |
| Nasopharyngitis | 174 ( 31.1) | 8 ( 9.8) |
| Pharyngitis | 142 ( 25.4) | 7 ( 8.5) |
| Influenza | 127 ( 22.7) | 0 ( 0.0) |
| Tonsillitis | 39 ( 7.0) | 1 ( 1.2) |
| Bronchitis | 34 ( 6.1) | 2 ( 2.4) |
| Ear infection | 32 ( 5.7) | 1 ( 1.2) |
| Rhinitis | 29 ( 5.2) | 1 ( 1.2) |
| Upper respiratory tract infection | 24 ( 4.3) | 11 ( 13.4) |
| **Investigations** | **151 ( 27.0)** | **10 ( 12.2)** |
| Biopsy liver | 70 ( 12.5) | 0 ( 0.0) |
| Alanine aminotransferase increased | 52 ( 9.3) | 4 ( 4.9) |
| Neutrophil count decreased | 50 ( 8.9) | 7 ( 8.5) |

| | Total Exposure: 1338.8 yrs<br>N patients exposed=642 | |
|---|---|---|
| | **Thalassemia Major**<br><br>**N patients exposed=560**<br>**Total Exposure (yrs)=1231.9** | **Non Thalassemia Major***<br><br>**N patients exposed=82**<br>**Total Exposure (yrs)=106.9** |
| **Body System**<br>**Preferred Term** | **N patients (%)*** | **N patients (%)*** |
| **Metabolism and nutrition disorders** | **30 ( 5.4)** | **2 ( 2.4)** |
| Increased appetite | 30 ( 5.4) | 2 ( 2.4) |
| **Musculoskeletal and connective tissue disorders** | **141 ( 25.2)** | **11 ( 13.4)** |
| Arthralgia | 95 ( 17.0) | 6 ( 7.3) |
| Back pain | 85 ( 15.2) | 5 ( 6.1) |
| **Nervous system disorders** | **154 ( 27.5)** | **2 ( 2.4)** |
| Headache | 154 ( 27.5) | 2 ( 2.4) |
| **Renal and urinary disorders** | **93 ( 16.6)** | **1 ( 1.2)** |
| Chromaturia | 93 ( 16.6) | 1 ( 1.2) |
| **Respiratory, thoracic and mediastinal disorders** | **159 ( 28.4)** | **5 ( 6.1)** |
| Cough | 127 ( 22.7) | 2 ( 2.4) |
| Oropharyngeal pain | 86 ( 15.4) | 3 ( 3.7) |

*Non Thalassemia Major primary diagnosis consists of hemoglobin E-β thalassemia disease (n=42), myelodysplasia (n=15), sickle cell disease (n=5), thalassemia intermedia (n=5), myelofibrosis (n=4), congenital anemia (n=2), refractory anemia (n=2), and in 1 patient each with pure red cell aplasia, aplastic anemia, Blackfan-Diamond anemia, chronic lymphocytic leukemia, hereditary haemochromatosis, severe hemolytic anemia, transfusion-dependent aase syndrome

Pooled safety data were also examined to compare safety profile of deferiprone monotherapy (N=553) versus alternate/combination therapy (N=89). Table 6-6 shows a summary of AEs, irrespective of relationship to deferiprone, occurring in >5% patients, by deferiprone monotherapy or in combination with deferoxamine or deferasirox. This comparison indicates that more patients on alternate/combination therapy experienced congestive cardiac failure than patients on deferiprone therapy. When looking at all cardiac disorders between the monotherapy and alternate/combination therapy groups, 30 (5.4%) subjects versus 14 (15.7%) subjects experienced cardiac AEs, respectively. This difference is likely due to the use of combination therapy in patients who are at greatest risk of iron-induced toxicity, mainly to the heart. In fact, in 12 of the 14 patients with cardiac disorders on combination therapy, deferiprone had been requested due to pre-existing cardiac disease. In 5 of those patients, deferiprone was provided under emergency drug release conditions due to the severity of the cardiac condition.

## Table 6-6: Pooled Study Data: Summary of AEs irrespective of relationship to deferiprone occurring in >5% patients, by deferiprone monotherapy or in combination with deferoxamine or deferasirox

| | Total Exposure: 1338.8 yrs<br>Total # of patients exposed=642 | |
|---|---|---|
| | DFP Monotherapy (all doses)<br>n patients exposed=553<br>Total Exposure (yrs)=1204.1 | Alternate/Combination Therapy<br>n patients exposed=89<br>Total Exposure (yrs)=134.6 |
| **Body System<br>Preferred Term** | **N patients (%)** | **N patients (%)** |
| **Blood and lymphatic system disorders** | **38 ( 6.9)** | **5 ( 5.6)** |
| Neutropenia | 38 ( 6.9) | 5 ( 5.6) |
| **Cardiac disorders** | **5 ( 0.9)** | **6 ( 6.7)** |
| Cardiac failure congestive | 5 ( 0.9) | 6 ( 6.7) |
| **Eye disorders** | **28 ( 5.1)** | **3 ( 3.4)** |
| Conjunctivitis | 28 ( 5.1) | 3 ( 3.4) |
| **Gastrointestinal disorders** | **251 ( 45.4)** | **21 ( 23.6)** |
| Nausea | 110 ( 19.9) | 7 ( 7.9) |
| Vomiting | 96 ( 17.4) | 12 ( 13.5) |
| Abdominal pain upper | 77 ( 13.9) | 2 ( 2.2) |
| Abdominal pain | 74 ( 13.4) | 2 ( 2.2) |
| Diarrhoea | 63 ( 11.4) | 10 ( 11.2) |
| Toothache | 50 ( 9.0) | 3 ( 3.4) |
| **General disorders and administration site conditions** | **180 ( 32.5)** | **16 ( 18.0)** |
| Pyrexia | 166 ( 30.0) | 15 ( 16.9) |
| Fatigue | 29 ( 5.2) | 2 ( 2.2) |
| **Infections and infestations** | **278 ( 50.3)** | **27 ( 30.3)** |
| Nasopharyngitis | 171 ( 30.9) | 11 ( 12.4) |
| Pharyngitis | 139 ( 25.1) | 10 ( 11.2) |
| Influenza | 121 ( 21.9) | 6 ( 6.7) |
| Tonsillitis | 37 ( 6.7) | 3 ( 3.4) |
| Bronchitis | 35 ( 6.3) | 1 ( 1.1) |
| Ear infection | 32 ( 5.8) | 1 ( 1.1) |
| Upper respiratory tract infection | 29 ( 5.2) | 6 ( 6.7) |
| Rhinitis | 28 ( 5.1) | 2 ( 2.2) |
| **Investigations** | **149 ( 26.9)** | **12 ( 13.5)** |
| Biopsy liver | 68 ( 12.3) | 2 ( 2.2) |

| | Total Exposure: 1338.8 yrs<br>Total # of patients exposed=642 | |
|---|---|---|
| | **DFP Monotherapy (all doses)<br>n patients exposed=553<br>Total Exposure (yrs)=1204.1** | **Alternate/Combination Therapy<br>n patients exposed=89<br>Total Exposure (yrs)=134.6** |
| **Body System<br>Preferred Term** | **N patients (%)** | **N patients (%)** |
| Alanine aminotransferase increased | 52 ( 9.4) | 4 ( 4.5) |
| Neutrophil count decreased | 50 ( 9.0) | 7 ( 7.9) |
| **Metabolism and nutrition disorders** | **32 ( 5.8)** | **0 ( 0.0)** |
| Increased appetite | 32 ( 5.8) | 0 ( 0.0) |
| **Musculoskeletal and connective tissue disorders** | **138 ( 25.0)** | **14 ( 15.7)** |
| Arthralgia | 94 ( 17.0) | 7 ( 7.9) |
| Back pain | 81 ( 14.6) | 9 ( 10.1) |
| **Nervous system disorders** | **147 ( 26.6)** | **9 ( 10.1)** |
| Headache | 147 ( 26.6) | 9 ( 10.1) |
| **Renal and urinary disorders** | **94 ( 17.0)** | **0 ( 0.0)** |
| Chromaturia | 94 ( 17.0) | 0 ( 0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **157 ( 28.4)** | **7 ( 7.9)** |
| Cough | 123 ( 22.2) | 6 ( 6.7) |
| Oropharyngeal pain | 87 ( 15.7) | 2 ( 2.2) |

### *6.1.5. Deaths*

Three deferiprone-treated patients enrolled in the ApoPharma clinical studies died between 1993 and 31 Aug 2010 (Table 6-7). None of those deaths were attributed to deferiprone use.
One patient with thalassemia major was withdrawn from study LA-01 due to worsening of pre-existing cardiac disease and died one month after discontinuation of deferiprone during surgery for a heart transplant. One patient with thalassemia major enrolled in study LA-02/06 died of injuries sustained in a car accident. The death of the third patient, a 33-year old man with diagnosis of hemoglobin E-β thalassemia, enrolled in study LA-11, in Thailand, was attributed by the treating physician to acute diarrhea. The patient was hospitalized for fever and severe acute diarrhea, and treatment with deferiprone was discontinued. There was no neutropenia. On the day of admission to the hospital, the patient's neutrophil count was $4.5 \times 10^9$/L. The patient's death on the following day was ascribed to acute severe diarrhea.

Fourteen additional patients treated with deferiprone as compassionate therapy (LA-04) died during the same period of observation (Table 6-7). Seven of the 14 deaths were due to cardiac failure. Six of those patients (Patients 38; 109; 172; 220; 240, and 277) had pre-existing cardiac conditions and in four of them (Patients 172; 220; 240, and 277) deferiprone was provided as emergency drug release as salvage therapy for cardiac failure. The time on deferiprone therapy in these patients ranged from 2 days to 5 months. The seventh death due to cardiac failure

occurred in Patient 114, whose cardiac disease was considered related to the end stage of myelofibrosis. One of the 7 deaths (cardiogenic shock in Patient 277) was judged by an investigator to be possibly related to deferiprone use. The remaining 7 deaths were due to other causes: multi-organ failure (Patient 39), lung neoplasm (Patient 127), acute myeloid leukemia (Patient 207), post procedural complication (Patient 49), pleural effusion (Patient 224), adenocarcinoma (Patient 98) and intestinal obstruction (Patient 222) (Table 6-8). Narratives of the fatal cases are presented in Appendix G.

## Table 6-7: Listing of Reported Deaths in the Pooled Safety Database

| Study ID | Patient ID | Treatment Group | Sponsor Defined Primary Diagnosis | Age at the time of Death (years) | Sex | Total Days on Study (before Death) | Days while Exposed | Days after end of Exposure (before Death) | Relationship to Study Drug | Primary Cause of Death (Preferred Term)* |
|---|---|---|---|---|---|---|---|---|---|---|
| **Clinical trials** | | | | | | | | | | |
| LA_01 | 61 | DFP 75 mg/kg/day | Thalassemia major | 27 | M | 200 | 170 | 30 | Doubtful | Cardiac failure |
| LA_0206 | 604 | DFP 75 mg/kg/day | Thalassemia major | 22 | M | 1726 | 1706 | 20 | Not related | Internal injury |
| LA_11 | 107 | DFP 50 mg/kg/day | Hemoglobin e-thalassemia disease | 33 | M | 148 | 146 | 2 | Doubtful | Diarrhoea |
| **Compassionate therapy** | | | | | | | | | | |
| LA_04 | 38 | DFP 75 mg/kg/day | Thalassemia major | 23 | F | 53 | 46 | 7 | Doubtful | Cardiac failure |
| LA_04 | 39 | DFP 75 mg/kg/day | Myelofibrosis | 68 | M | 209 | 180 | 29 | Not related | Multi-organ failure |
| LA_04 | 49 | DFP 75 mg/kg/day | Thalassemia major | 45 | M | 2704 | 2681 | 23 | Not related | Post procedural complication |
| LA_04 | 98 | DFP 91.2 mg/kg/day | Thalassemia major | 53 | F | 2626 | 2606 | 20 | Not related | Adenocarcinoma |
| LA_04 | 109 | DFP 75 mg/kg/day and DFO | Thalassemia major | 39 | M | 157 | 157 | 0 | Not related | Cardiomyopathy |
| LA_04 | 114 | DFP 75 mg/kg/day | Myelofibrosis | 45 | F | 242 | 242 | 0 | Not related | Cardiac failure |
| LA_04 | 127 | DFP 75 mg/kg/day | Myelodysplasia | 65 | F | 410 | 302 | 108 | Not related | Lung neoplasm malignant |
| LA_04 | 172 | DFP 75 mg/kg/day and DFO | Transfusion dependent aase syndrome | 20 | M | 27 | 26 | 1 | Not related | Cardiac failure* |
| LA_04 | 207 | DFP 75 mg/kg/day | Myelodysplasia | 74 | M | 260 | 257 | 3 | Not related | Acute myeloid leukaemia |
| LA_04 | 220 | DFP 75 mg/kg/day and DFO | Thalassemia major | 18 | M | 30 | 29 | 1 | Not related | Cardiac failure * |
| LA_04 | 222 | DFP 75 mg/kg/day | Hereditary haemochromatosis | 53 | F | 343 | 343 | 0 | Not related | Intestinal obstruction |
| LA_04 | 224 | DFP 100 mg/kg/day | Myelodysplasia | 72 | M | 753 | 713 | 40 | Not related | Pleural effusion |
| LA_04 | 240 | DFP 96 mg/kg/day AND DFO | Thalassemia major | 31 | M | 2 | 2 | 0 | Not related | Arrhythmia and cardiac failure* |
| LA_04 | 277 | DFP 75 mg/kg/day and DFO | Thalassemia major | 32 | F | 6 | 5 | 1 | Possible | Cardiogenic shock* |

*Deferiprone was provided as salvage therapy under emergency drug release protocol

## 6.2. Serious Adverse Events

Table 6-8 lists serious adverse events (SAEs), irrespective of a relationship to the study drug, that were observed in 2 or more deferiprone-treated patients enrolled in clinical trials or who received deferiprone as compassionate therapy. Table 6-8 does not include the deaths reported in the previous section of this document. A summary of all non fatal SAEs, irrespective of causality, occurring in at least one deferiprone treated-patient is in Appendix H.

The most common SAEs observed during deferiprone therapy were neutropenia and agranulocytosis. Those events are described in detail in Section 6.2.2 (Adverse Events of Special Interest). Other more common SAEs were classified as "Infections and Infestations" or as "Surgical and Medical Procedures" based on the MedDRA System Organ Classification version 13.0. Most SAEs required no action to be taken or required temporary discontinuation of study drug. Discontinuations of deferiprone due to adverse events are presented in Section 6.2.1.

Fifty-seven (8.9%) of the 642 patients exposed to deferiprone experienced at least one SAE that was considered at least possibly related. Among them, the most commonly reported SAEs were neutropenia, observed in 6% patients, and agranulocytosis, observed in 1.7% patients.

**Table 6-8: Frequency of Serious Adverse Events - Non Fatal (irrespective of relationship to deferiprone) observed in 2 or more patients enrolled in clinical trials or in compassionate use programs.**

| | Deferiprone Exposure: 1338.8 yrs Total No. of patients exposed (N=642) Patients | |
|---|---|---|
| **Body System Preferred Term** | **N** | **%** |
| **Blood and lymphatic system disorders** | **56** | **8.7** |
| Neutropenia | 39 | 6.1 |
| Agranulocytosis | 11 | 1.7 |
| Lymphadenitis | 6 | 0.9 |
| Thrombocytopenia | 2 | 0.3 |
| **Cardiac disorders** | **9** | **1.4** |
| Cardiac failure congestive | 5 | 0.8 |
| Atrial fibrillation | 4 | 0.6 |
| Atrial flutter | 2 | 0.3 |
| **Gastrointestinal disorders** | **4** | **0.6** |
| Abdominal pain | 4 | 0.6 |
| **General disorders and administration site conditions** | **7** | **1.1** |
| Pyrexia | 7 | 1.1 |
| **Infections and infestations** | **20** | **3.1** |
| Cellulitis | 5 | 0.8 |
| Gastrointestinal infection | 3 | 0.5 |
| Infectious mononucleosis | 3 | 0.5 |
| Device related infection | 2 | 0.3 |
| Device related sepsis | 2 | 0.3 |
| Pharyngotonsillitis | 2 | 0.3 |
| Pneumonia | 2 | 0.3 |
| Sepsis | 2 | 0.3 |
| Urinary tract infection | 2 | 0.3 |
| **Injury, poisoning and procedural complications** | **6** | **0.9** |

| Body System<br>Preferred Term | Deferiprone<br>Exposure: 1338.8 yrs<br>Total No. of patients exposed (N=642)<br>Patients<br>N | <br><br><br>% |
|---|---|---|
| Femur fracture | 2 | 0.3 |
| Road traffic accident | 2 | 0.3 |
| Transfusion reaction | 2 | 0.3 |
| **Investigations** | **4** | **0.6** |
| Arthroscopy | 2 | 0.3 |
| Blood glucose increased | 2 | 0.3 |
| **Metabolism and nutrition disorders** | **7** | **1.1** |
| Diabetic ketoacidosis | 3 | 0.5 |
| Diabetes mellitus | 2 | 0.3 |
| Hypoglycaemia | 2 | 0.3 |
| **Musculoskeletal and connective tissue disorders** | **2** | **0.3** |
| Back pain | 2 | 0.3 |
| **Renal and urinary disorders** | **2** | **0.3** |
| Renal colic | 2 | 0.3 |
| **Surgical and medical procedures** | **14** | **2.2** |
| Splenectomy | 8 | 1.2 |
| Cholecystectomy | 3 | 0.5 |
| Knee operation | 3 | 0.5 |

### *6.2.1. **Withdrawals***

Table 6-9 summarizes patient withdrawals across pooled clinical studies by chelation regimen, age, and reason for withdrawal.

**Table 6-9: Withdrawals of patients in Pooled Clinical Studies**

| Disposition Category | Deferiprone 50 mg/kg/d n=25 (%) | Deferiprone 75 mg/kg/d n=407 (%) | Deferiprone 100 mg/kg/d n=108 (%) | Deferiprone (all doses) mg/kg/d n=642 (%) | Deferoxamine 50 mg/kg/d n=118 (%) | Alternate/ Combination Therapy n=89 (%) |
|---|---|---|---|---|---|---|
| Withdrawals by age group | | | | | | |
| 1 - 5 years | 1 ( 4.0) | 11 ( 2.7) | 5 ( 4.6) | 18 ( 2.8) | 0 ( 0.0) | 0 ( 0.0) |
| 6 - 11 years | 0 ( 0.0) | 18 ( 4.4) | 3 ( 2.8) | 24 ( 3.7) | 1 ( 0.8) | 1 ( 1.1) |
| 12 - 15 years | 0 ( 0.0) | 32 ( 7.9) | 0 ( 0.0) | 33 ( 5.1) | 0 ( 0.0) | 1 ( 1.1) |
| >= 16 years | 8 (32.0) | 147 (36.1) | 3 ( 2.8) | 170 (26.5) | 8 ( 6.8) | 10 (11.2) |
| **Withdrawals** | | | | | | |
| Total | 9 (36.0) | 208 (51.1) | 11 (10.2) | 245 (38.2) | 9 ( 7.6) | 12 (13.5) |
| Adverse event | 4 (16.0) | 81 (19.9) | 6 ( 5.6) | 99 (15.4) | 2 ( 1.7) | 6 ( 6.7) |
| Investigator decision | 0 ( 0.0) | 78 (19.2) | 0 ( 0.0) | 82 (12.8) | 0 ( 0.0) | 2 ( 2.2) |
| Lost to follow-up | 1 ( 4.0) | 5 ( 1.2) | 0 ( 0.0) | 6 ( 0.9) | 1 ( 0.8) | 0 ( 0.0) |
| Patient request | 4 (16.0) | 31 ( 7.6) | 5 ( 4.6) | 43 ( 6.7) | 2 ( 1.7) | 2 ( 2.2) |
| Protocol violation | 0 ( 0.0) | 13 ( 3.2) | 0 ( 0.0) | 15 ( 2.3) | 4 ( 3.4) | 2 ( 2.2) |

Approximately 13% of the deferiprone-treated patients discontinued their participation in the trials due to inadequate response, i.e., increasing serum ferritin or LIC or insufficient iron excretion. Those discontinuations were due mainly to the prohibition in the protocols, which forbade the investigator to adjust the deferiprone dose according to the patients' individual needs. Contrary to what was permitted in the deferoxamine treatment group, where the doses of deferoxamine could be varied to achieve the desired iron excretion, the design of the early studies did not permit the investigators to adjust the deferiprone dose to achieve optimum response. Without the possibility of making dose adjustments, investigators would have had to withdraw those patients on the fixed dose of deferiprone (75 mg/kg/d) if the body iron load was not being adequately controlled, as assessed by serum ferritin or LIC. No patients enrolled in studies where adjustment of the deferiprone dose was allowed were withdrawn due to increased serum ferritin or LIC.

Overall, 15.4% of the deferiprone-treated patients were withdrawn due to adverse events. Adverse events leading to treatment discontinuation are summarized in Table 6-10.

## Table 6-10: Pooled Clinical Studies: AEs irrespective of relationship to deferiprone leading to treatment discontinuation

| | Deferiprone<br>Total No. of patients withdrawn for AE (N=99)<br>Total No. of patients exposed (N=642)<br>Patients | |
|---|---|---|
| **Body System<br>Preferred Term** | **#** | **%** |
| **Blood and lymphatic system disorders** | **39** | **6.1** |
| Neutropenia | 27 | 4.2 |
| Agranulocytosis | 9 | 1.4 |
| Thrombocytopenia | 2 | 0.3 |
| Hypersplenism | 1 | 0.2 |
| **Cardiac disorders** | **10** | **1.6** |
| Cardiac failure | 2 | 0.3 |
| Cardiac failure congestive | 2 | 0.3 |
| Angina unstable | 1 | 0.2 |
| Arrhythmia | 1 | 0.2 |
| Cardiac failure chronic | 1 | 0.2 |
| Cardiogenic shock | 1 | 0.2 |
| Cardiomyopathy | 1 | 0.2 |
| Torsade de pointes | 1 | 0.2 |
| **Gastrointestinal disorders** | **10** | **1.6** |
| Nausea | 3 | 0.5 |
| Vomiting | 2 | 0.3 |
| Abdominal distension | 1 | 0.2 |
| Abdominal pain | 1 | 0.2 |
| Colitis | 1 | 0.2 |
| Diarrhoea | 1 | 0.2 |
| Intestinal obstruction | 1 | 0.2 |
| **General disorders and administration site conditions** | **2** | **0.3** |
| Asthenia | 1 | 0.2 |
| Multi-organ failure | 1 | 0.2 |
| **Hepatobiliary disorders** | **1** | **0.2** |
| Hepatitis | 1 | 0.2 |
| **Infections and infestations** | **2** | **0.3** |
| Cytomegalovirus hepatitis | 1 | 0.2 |
| Sepsis | 1 | 0.2 |
| **Injury, poisoning and procedural complications** | **2** | **0.3** |
| Internal injury | 1 | 0.2 |
| Post procedural complication | 1 | 0.2 |
| **Investigations** | **9** | **1.4** |
| Alanine aminotransferase increased | 4 | 0.6 |

| | Deferiprone<br>Total No. of patients withdrawn for AE (N=99)<br>Total No. of patients exposed (N=642)<br>Patients | |
|---|---|---|
| **Body System<br>Preferred Term** | **#** | **%** |
| Neutrophil count decreased | 3 | 0.5 |
| Blood creatinine increased | 1 | 0.2 |
| Hepatic enzyme increased | 1 | 0.2 |
| **Musculoskeletal and connective tissue disorders** | **12** | **1.9** |
| Arthralgia | 8 | 1.2 |
| Arthritis | 2 | 0.3 |
| Arthropathy | 1 | 0.2 |
| Polyarthritis | 1 | 0.2 |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **3** | **0.5** |
| Acute myeloid leukaemia | 1 | 0.2 |
| Adenocarcinoma | 1 | 0.2 |
| Leukaemia | 1 | 0.2 |
| **Pregnancy, puerperium and perinatal conditions** | **1** | **0.2** |
| Pregnancy | 1 | 0.2 |
| **Psychiatric disorders** | **3** | **0.5** |
| Depression | 2 | 0.3 |
| Confusional state | 1 | 0.2 |
| **Renal and urinary disorders** | **2** | **0.3** |
| Glomerulonephritis chronic | 1 | 0.2 |
| Nephrolithiasis | 1 | 0.2 |
| **Respiratory, thoracic and mediastinal disorders** | **1** | **0.2** |
| Pleural effusion | 1 | 0.2 |
| **Skin and subcutaneous tissue disorders** | **2** | **0.3** |
| Rash | 1 | 0.2 |
| Skin discolouration | 1 | 0.2 |

## *6.2.2. Adverse Events of Special Interest*

### *6.2.2.1. Neutropenia*

In the ApoPharma-sponsored clinical trials, neutropenia, defined as a confirmed absolute neutrophil count (ANC) between 0.5 and 1.5 x 109/L, occurred in 43 (6.7%) out of 642 patients (Table 6-11). Thirty seven cases of neutropenia in 34 patients (6.1 %) were observed in 560 thalassemia major patients and 12 cases in 9 (11 %) of 82 patients with other iron overload conditions. The rate of neutropenia in clinical studies was 3.0 events per 100 patient-years of exposure in patients with thalassemia major and 11.2 events per 100 patient-years of exposure in patients with conditions other than thalassemia major.

Neutropenia is a common event in thalassemia patients, particularly in those with hypersplenism, which may explain the comparable percentage of patients with neutropenia in deferiprone- and deferoxamine-treated patients in the ApoPharma clinical studies (i.e., 6.7% and 4%, respectively).

**Table 6-11: Pooled Safety Data: Neutropenia episodes reported in patients with Thalassemia Major versus Non Thalassemia Major.**

| Definition | Thalassemia Major N=560 | Non Thalassemia Major N=82 | Total N=642 |
|---|---|---|---|
| No. of Neutropenia Events | 37 | 12 | 49 |
| No. of patients with Neutropenia | 34 | 9 | 43 |
| % of patients with Neutropenia | 6.1 | 11.0 | 6.7 |
| Total Exposure (yrs) | 1231.9 | 107.0 | 1338.8 |
| Rate of Neutropenia (events)/100 pt-yrs | 3.0 | 11.2 | 3.7 |
| Median Age of patients reporting Neutropenia | 18 | 17 | 18 |
| Age (Min- Max) yrs of patients reporting Neutropenia | 2-33 | 4-77 | 2-77 |
| Sex of patients reporting Neutropenia - Male / Female / Unknown | 17 / 17 / 0 | 5 / 4 / 0 | 22 / 21 / 0 |
| Median Duration of DFP Exposure for patients reporting Neutropenia (days) | 368.5 | 246 | 327 |
| Range of Duration of DFP Exposure for patients reporting Neutropenia (days) | 9-2012 | 15-2854 | 9-2854 |
| Median Time to First Neutropenia (days) | 304.5 | 76 | 280 |
| Time to First Neutropenia (Min- Max) days | 8-1966 | 14-658 | 8-1966 |
| Median Duration of Neutropenia Events (days) | 10 | 11 | 10 |
| Duration of Neutropenia Events (Min-Max) days | 2-175 | 4-43 | 2-175 |
| G-CSF of Neutropenia Events - Yes / No/ Unknown | 1 / 30 / 3 | 1 / 6 / 2 | 2 / 36 / 5 |
| Hepatitis C status of Neutropenia patients - Yes / No / Unknown | 21 / 12 / 1 | 1 / 7 / 1 | 22 / 19 / 2 |
| Splenectomy status of Neutropenia patients - Yes / No / Unknown | 5 / 29 / 0 | 1 / 7 / 1 | 6 / 36 / 1 |

1) Seven cases in 4 patients were reported as non-serious.
2) Years of Exposure = ((end date of exposure - first date of exposure +1) - sum of interruption days)/365.25
3) Age is calculated as (First Exposure Date - Date of Birth)/365.25, rounded down to the nearest integer
4) Duration of event (days) calculated as (Date of AE Resolution - Date of AE Onset +1), where available.
5) Time to event calculated as (Date of AE Onset - First Date of Exposure). Time to first event is calculated.
6) Median duration of deferiprone exposure calculated as the median of the years of exposure for patients who had neutropenia.
7) Data cut-off date: 31 Aug 2010

In the initial ApoPharma studies, it was required that deferiprone be discontinued at onset of neutropenia and that the patients be withdrawn from the studies. All events resolved upon discontinuation of deferiprone. The more recent studies (LA-28 and LA30) investigated whether or not episodes of mild neutropenia (ANC less than $1.5 \times 10^9$/L but not less than $1.0 \times 10^9$/L) were transient events, similar to those observed during therapy with DFO. Patients who experienced mild neutropenia continued therapy with deferiprone, but had their neutrophil count monitored daily during those episodes. In these studies six patients experienced episodes of mild neutropenia, 4 of which were single episodes, and all of which resolved and did not recur despite continued deferiprone use. Another patient experienced two episodes of mild neutropenia that also resolved despite continuation of deferiprone use. None of these six cases progressed to agranulocytosis. One patient experienced 2 separate episodes of neutropenia that also resolved despite continuation of deferiprone use. This patient later experienced an episode of agranulocytosis. Deferiprone was discontinued at the onset of agranulocytosis and the event resolved. These findings show that mild episodes of neutropenia do not necessarily progress to agranulocytosis, even with continued deferiprone use.

#### *6.2.2.2. Agranulocytosis*

In the ApoPharma-sponsored clinical trials, agranulocytosis, defined as a confirmed ANC $< 0.5 \times 10^9$/L, occurred in 11 (1.7%) out of 642 patients (Table 6-12). All 11 episodes resolved upon discontinuation of deferiprone. Time to onset of agranulocytosis ranged from 65 days to 3352 days (median: 161 days). Six of the eleven episodes occurred within the first six months of treatment. Nine of the eleven episodes occurred within the first year of treatment. One of the 2 episodes observed after the first year of therapy was considered by the treating physician as unrelated to deferiprone therapy. This episode was observed after 1.6 years of therapy in a patient with MDS. Deferiprone therapy was interrupted at the onset of the event and re-initiated upon resolution. The patient continues to be treated with deferiprone up to date and has experienced no new episodes of agranulocytosis for these past 7 years. The other event was observed in a patient with thalassemia major, after 9 years of deferiprone use. The event occurred after treatment with interferon and ribavirin for treatment of chronic hepatitis C. This patient first developed neutropenia, when deferiprone, pegylated interferon and ribavirin were discontinued. The ANC improved and deferiprone was restarted. Twenty two days later agranulocytosis occurred and deferiprone was permanently discontinued.

**Table 6-12: Pooled Safety Data: Agranulocytosis episodes reported in patients with Thalassemia Major versus Non Thalassemia Major.**

| Definition | Thalassemia Major N=560 | Non Thalassemia Major N=82 | Total N=642 |
|---|---|---|---|
| No. of Agranulocytosis events | 8 | 3 | 11 |
| No. of patients with Agranulocytosis | 8 | 3 | 11 |
| % of patients with Agranulocytosis | 1.4 | 3.7 | 1.7 |
| Total Exposure (yrs) | 1231.9 | 107 | 1338.8 |
| Rate of Agranulocytosis (events)/100 pt-yrs | 0.6 | 2.8 | 0.8 |
| Median Age of patients reporting Agranulocytosis | 10 | 58 | 11 |
| Age (Min-Max) yrs of patients reporting Agranulocytosis | 4-18 | 12-64 | 4-64 |
| Sex of patients reporting Agranulocytosis - Male / Female / Unknown | 2 / 6 / 0 | 1 / 2 / 0 | 3 / 8 / 0 |
| Median Duration of DFP Exposure for patients reporting Agranulocytosis (days) | 157 | 302 | 181 |
| Range of Duration of DFP Exposure for patients reporting Agranulocytosis (days) | 67-3329 | 181-2854 | 67-3329 |
| Median Time to Agranulocytosis (days) | 160.5 | 301 | 161 |
| Time to Agranulocytosis (Min / Max) days | 65-3352 | 140-567 | 65-3352 |
| Median Duration of Agranulocytosis Events (days) | 9 | 19 | 10 |
| Duration of Agranulocytosis Events (Min-Max) days | 3-18 | 16-85 | 3-85 |
| G-CSF of Agranulocytosis events - Yes / No / Unknown | 6 / 2 / 0 | 2 / 1 / 0 | 8 / 3 / 0 |
| Hepatitis C status of Agranulocytosis patients - Yes / No / Unknown | 2 / 6 / 0 | 0 / 3 / 0 | 2 / 9 / 0 |
| Splenectomy status of Agranulocytosis patients - Yes / No / Unknown | 1 / 5 / 2 | 1 / 2 / 0 | 2 / 7 / 2 |

1) Years of Exposure = ((End Date of Exposure - First Date of Exposure +1) - sum of interruption days)/365.25
2 Age is calculated as (First Exposure Date - Date of Birth)/365.25, rounded down to the nearest integer
3) Duration of event (days) is calculated as (Date of AE Resolution - Date of AE Onset +1), where available.
4) Time to Event is calculated as (Date of AE Onset - First Date of Exposure).
5) Median Duration of DFP Exposure for patients reporting Agranulocytosis (days) calculates the years of exposure for subjects with agranulocytosis.
6) Data cut-off date: 31 Aug 2010.

The frequency of agranulocytosis (1-2%) generates difficulty in comparisons of subpopulations, when these are less than about 300 patients. The apparent lower frequency of agranulocytosis in patients with thalassemia major (1.4%) than in patients with other systemic iron overload conditions (3.7%) was not significant (p=0.1555). Nevertheless, if the difference is real, it may be due, at least in part, to the primary disease of those patients. Two of the 3 episodes of agranulocytosis in non-thalassemia major patients occurred in patients with myelodysplasia,

where there are other known causes for agranulocytosis. In one of those patients, there was no recurrence of agranulocytosis upon re-initiation of deferiprone treatment.

Deferiprone-associated agranulocytosis appears to be idiosyncratic, and the mechanism of deferiprone-associated agranulocytosis remains uncertain. Unlike the dose-related pancytopenia observed in some animal studies, clinical data reveal that the reduction is generally limited to neutrophils and it is not dose dependent within the recommended therapeutic doses: it has been reported at doses from 20 mg/kg/day to 100 mg/kg/day. No agranulocytosis was observed in two patients treated with deferiprone at doses greater than 200 mg/kg/day for up to two years. No evidence for an immune mechanism has been demonstrated. No increased *in vitro* sensitivity of myeloid precursors was observed in a patient who previously experienced deferiprone-associated agranulocytosis (Al-Refaie FN *et al.* 1993; Al-Refaie FN *et al.* 1994).

An attempt to identify predisposing factors, including those related to demographics, sex and age have been unsuccessful, although hampered by few cases in the controlled clinical settings. A study was commissioned by ApoPharma to find genetic markers that may identify patients predisposed to agranulocytosis. About 200 samples from deferiprone-treated patients with and without a history of agranulocytosis were collected. Genome-wide case-control analysis of SNP frequencies was performed. Cases were defined as patients who received deferiprone and developed agranulocytosis. Controls were defined as patients who received deferiprone for at least 24 months and did not develop agranulocytosis. No specific genetic markers were identified.

Clinical experience suggests that deferiprone-induced agranulocytosis is more severe in patients with Diamond-Blackfan anemia than in patients with other conditions underlying transfusional iron overload, although small numbers hamper the strength of that conclusion. Nevertheless, ApoPharma recommends that deferiprone therapy in patients with Diamond-Blackfan anemia should not be initiated except as a last resort.

Cases of agranulocytosis occurring in post-marketing setting are presented in section 6.3.

#### *6.2.2.3. Gastrointestinal Disorders*

Gastrointestinal upset such as nausea, vomiting, abdominal pain and diarrhea was observed in 258 (40.2%) of the 642 patients in the pooled safety database (Table 6-3). In general, gastrointestinal AEs occurred in the first few months of therapy (median time to onset 37 days of therapy), were mild to moderate, and resolved within a week of onset without discontinuation of therapy. Ten (1.6%) deferiprone-treated patients discontinued the studies due to any gastrointestinal event as the primary reason (nausea in 3 patients, vomiting in 2 patients, colitis in 1 patient, abdominal pain in 1 patient, abdominal distension in 1 patient, and the fatal cases of intestinal obstruction and of diarrhea previously described in Section 6.1.4).

#### *6.2.2.4. Musculoskeletal and Connective Tissue Disorders*

Arthropathies (including arthralgia, arthritis, and arthropathy) occurred in 17% of 642 patients exposed to deferiprone in the pooled safety database. Those events generally occurred within the first year of therapy (median time to first onset: 210 days) and were considered to be mild/moderate in severity in most patients. The median duration of those events was 9 days.

Twelve (1.9%) patients discontinued therapy due to arthropathies.

The sequential assessments of anti-nuclear antibody (ANA) titers, rheumatoid factors (RF), anti-double stranded DNA (anti-dsDNA) titers and anti-histone antibody (AHA) titers during one of the clinical studies indicated that the episodes of arthropathy are not associated with auto-immune disease.

#### *6.2.2.5. Increased ALT levels*

In the pooled safety data, baseline serum ALT levels greater than two times the upper limit of normal reference range (ULN) were present in 20.2% of deferiprone and 17.8% of deferoxamine-treated patients, reflecting a much higher than normal prevalence of increased enzymes due to long term deposition of iron in the liver and a high prevalence of hepatitis C from tainted blood used in transfusions in the past. Baseline ALT and Hepatitis C Status are found in Table 6-13.

**Table 6-13: Pooled Safety Data: Baseline ALT and Hepatitis C Status**

| | Deferiprone 50 mg/kg/d n=25 (%) | Deferiprone 75 mg/kg/d n=407 (%) | Deferiprone 100 mg/kg/d n=108 (%) | Deferiprone (all doses) mg/kg/d n=642 (%) | Deferoxamine 50 mg/kg/d n=118 (%) | Alternate/Combination Therapy with Deferiprone n=89 (%) |
|---|---|---|---|---|---|---|
| Baseline Hepatitis C Status [n (%)] | | | | | | |
| Positive | 0 ( 0.0) | 208 ( 51.1) | 30 ( 27.8) | 258 ( 40.2) | 52 ( 44.1) | 17 ( 19.1) |
| Negative | 1 ( 4.0) | 175 ( 43.0) | 64 ( 59.3) | 279 ( 43.5) | 66 ( 55.9) | 36 ( 40.4) |
| Missing Data | 24 ( 96.0) | 24 ( 5.9) | 14 ( 13.0) | 105 ( 16.4) | 0 ( 0.0) | 36 ( 40.4) |
| Baseline ALT [n (%)] | | | | | | |
| <= 2 x ULN | 21 ( 84.0) | 316 ( 77.6) | 95 ( 88.0) | 511 ( 79.6) | 97 ( 82.2) | 70 ( 78.7) |
| > 2 x ULN | 4 ( 16.0) | 90 ( 22.1) | 13 ( 12.0) | 130 ( 20.2) | 21 ( 17.8) | 19 ( 21.3) |
| Missing Data | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

In the pooled safety data, increased ALT was reported as an adverse event in 56 (8.7%) of 642 patients. Those events were generally transient, with a median duration of 21 days despite continued deferiprone therapy. Table 6-14 summarizes the patients in pooled clinical studies with ALT values within the normal range at baseline, but greater than 2, 3 or 5 times the ULN for two or more consecutive visits. Positive hepatitis C status at baseline was found to be a confounding factor in more than 50% of patients with elevated ALT values.

**Table 6-14: Pooled Safety Data: Summary of Patients with ALT values within the normal range at baseline, but greater than 2, 3 or 5 times the ULN at two or more consecutive visits.**

| ALT > 2 x ULN n (%) | | ALT > 3 x ULN n (%) | | ALT > 5 x ULN n (%) | |
|---|---|---|---|---|---|
| **Deferiprone (n = 330)** | **Deferoxamine (n = 73)** | **Deferiprone (n = 330)** | **Deferoxamine (n = 73)** | **Deferiprone (n = 330)** | **Deferoxamine (n = 73)** |
| 41 (12.4) | 2 (2.7) | 21 (6.4) | 1 (1.4) | 6 (1.8) | 0 (0.0) |

1) Analysis was done on patients with normal ALT at baseline
2) Percentage is calculated based on the number of patients with normal ALT at baseline
ULN = Upper Limit of Normal Reference Range
Cut-off Date: 31 Aug 2010

Study LA16-0102, where patients were randomized to either deferiprone or deferoxamine treatment, and where liver enzyme activity was monitored at similar intervals in both treatment groups permits comparison of ALT excursions above the ULN in patients treated with either chelator (Table 6-15).

**Table 6-15: Comparison of Number of Patients with ALT Levels Exceeding Three Times ULN between Deferiprone and DFO Treatment Groups during Study LA16-0102 at any visit.**

| | Randomized Treatment Groups | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | 3 Months | | 6 Months | | 9 Months | | 12 Months | |
| | DFP [n=29] | DFO [n=32] | DFP [n=28] | DFO [n=31] | DFP [n=28] | DFO [n=30] | DFP [n=27] | DFO [n=29] | DFP [n=29] | DFO [n=32] |
| ALT >3 times ULN* | | | | | | | | | | |
| Number of Patients | 0 | 0 | 2 | 2 | 5 | 1 | 3 | 1 | 3 | 4 |
| Percent | 0.0% | 0.0% | 7% | 6% | 18% | 3% | 11% | 4% | 10% | 13% |
| p-value | N/A | | 1.0000 | | 0.0968 | | 0.3434 | | 1.0000 | |

*No episodes of ALT > 5 times ULN were observed.

Four (0.6%) of 642 patients in pooled studies discontinued therapy due to elevation of serum ALT levels. One other patient (Study LA-02/06; Patient 434) with a history of chronic persistent hepatitis was withdrawn due to hepatitis and jaundice which included increased serum ALT, gamma-GT, nausea and vomiting. Concurrent medication at the time of the event included vitamin E and estradiol. An initial report of nausea and jaundice resolved after three days without interruption of therapy, however symptoms reappeared one week later with elevation in serum ALT. Her serum ALT level reached 669 IU/L and total bilirubin was 10.2 mg/dL (indirect bilirubin 8.9 mg/dL, direct bilirubin 1.3 mg/dL). Deferiprone and all other medications were discontinued. There was resolution of the nausea and jaundice and decline of the liver enzyme levels. Deferiprone therapy was reinitiated two weeks later, which was associated with recurrence of nausea, jaundice and increased serum ALT levels (346 IU/L) as well as AST (184 IU/L) and gamma-GT (111 IU/L). Therapy with deferiprone was discontinued and the patient was withdrawn from the trial. Symptoms gradually improved. Several weeks later, the patient started receiving deferoxamine and experienced an increase in serum ALT levels to approximately 300 IU/L. Therapy was continued. ALT gradually normalized over 3 months.

Subsequently the patient experienced increased ALT levels upon initiation of deferasirox. For the past 5 years the patient has been receiving alternating therapy of deferiprone and deferasirox with good tolerance. Fulfilment of Hy's law in this case is confounded by the pre-existing chronic persistent hepatitis and the high levels of indirect bilirubin.

One additional patient was withdrawn due to increased hepatic enzymes including ALT, AST and gamma-GT (LA16 A1-47).

This 19-year-old female with thalassemia major had a medical history of hepatitis C. Her baseline ALT value was within normal range. The patient started therapy with deferiprone 75mg/kg/day, the dose was increased to 100 mg/kg/day within 2 months. Approximately 3 months after therapy initiation serum ALT levels increased to 163 IU/L. There were also reports of increased AST and GGT (values not provided). Two months after onset of the events, deferiprone dose was reduced to 75 mg/kg/day. Therapy was interrupted. ALT and AST remained elevated and decreased zinc was also reported. The subject was withdrawn from the study. The ALT value at withdrawal was 220 IU/L. No re-challenge was attempted.

No episodes of liver failure have been reported related to the use of deferiprone during the past 23 years of its clinical experience.

### *6.2.3. **Zinc***

Deferiprone, like other iron chelators, is not wholly selective for iron, and will bind zinc, albeit with an affinity that is several orders of magnitude lower than for iron.

Thirty five of 291 (12%) of patients with normal zinc values at baseline had zinc values below the reference range at last assessment. Blood zinc decreased was reported as an adverse event in 4 (0.62%) deferiprone treated patients. One of those patients was withdrawn from the ApoPharma studies because of increased serum liver enzymes and at the time of withdrawal this patient also reported decreased blood zinc values. The decrease in zinc levels was considered probably related to deferiprone administration.

### *6.2.4. **Other Adverse Events***

The possibility that deferiprone may worsen liver fibrosis was suggested in an article published in 1998, in which hepatic biopsies from 14 thalassemia patients treated with deferiprone were retrospectively evaluated. The authors concluded that the progression of fibrosis in five of the patients could be due to deferiprone (Olivieri NF ***et al.*** 1998). The editorial that accompanied the article revealed several design deficiencies in this study, such as the evaluation of biopsy samples normally considered too small for adequate assessment, the lack of a true control population, and the presence of other factors, such as infectious hepatitis, parenchymal and reticuloendothelial iron deposition, and age, which may have influenced the assessment of progression of fibrosis (Kowdley KV & Kaplan. 1998), a condition well known to occur also in thalassemia patients (Berdoukas V ***et al.*** 2000; Cappellini MD ***et al.*** 1999; Harmatz P ***et al.*** 1999; Maggio A ***et al.*** 2002). Four of the five patients in whom progression of liver fibrosis was reported had evidence of hepatitis C infection. Subsequently, an independent and blinded review on the same biopsies found no worsening of liver fibrosis during deferiprone therapy (Callea F. 1998).

Since the initial report in 1998, several investigators have conducted independent studies to assess the liver histology in thalassemia patients treated with either deferiprone or deferoxamine for up to 12 years. None of these studies provided evidence that therapy with deferiprone is associated with progression of liver fibrosis (Table 6-16).

**Table 6-16: Published independent studies of liver fibrosis in patients treated with deferiprone**

| Publication | N patients | Time on deferiprone | Progression of liver fibrosis |
|---|---|---|---|
| Olivieri et al, 1998 | 14 | 2.3 years | Yes |
| Callea, 1998 | 14 | 2.3 years | No |
| Stella et al., 1998 | 10 | 2 ± 1 years | No |
| Piga et al., 1998 | 16 | 2 ± 0.5 years | No |
| Hoffbrand et al., 1998 | 17 | 2-4 years | No |
| Töndury et al., 1998, | 11 | 6-12 years | No |
| Galanello et al., 1999 | 18 | 1-2.4 years | No |
| Berdoukas et al., 1999 | 14 | 1 year | No |
| Maggio et al., 2002 | 21 | 2.5 ± 0.2 years | No |
| Wanless et al., 2002 | 56 | 2.5 years | No |
| Peng et al., 2003 | 11 | 3 years | No |
| Francis et al., 2003 | 11 | 2 years | No |
| Taher et al., 2004 | 12 | 5 years | No |
| Chen et al., 2006 | 45 | 2-5 years | No |
| Wu et al., 2006 | 17 | 3.3 years | No |
| Aydinok et al., 2007 | 12 | 1 year | No |

## 6.3. Post-Marketing Surveillance

The estimated post-marketing exposure to deferiprone from its first marketing authorization in 1999 until 31 Aug 2010 is 33,725 patient-years for the tablet and 318 patient-years for the oral solution, giving a total drug exposure of 34,043 patient-years.

All spontaneous reports of adverse events were catalogued by ApoPharma as related to deferiprone (i.e., to be adverse drug reactions - ADRs) unless specifically identified by the reporter as <Not Related>. Table 6-17 displays the number of post marketing serious adverse drug reactions (SADRs) received by ApoPharma from the time of the first marketing authorization for deferiprone in 1999 up to 31 Aug 2010.

**Table 6-17: Post-Marketing Serious Adverse Drug Reactions**

| Body System<br>Preferred Term | **Number of Events** |
|---|---|
| **Blood and Lymphatic System Disorders** | **190** |
| Neutropenia | 96 |
| Agranulocytosis | 94 |
| **Cardiac Disorders** | **5** |
| Cardiac failure | 3 |
| Atrial fibrillation | 1 |
| Cardiac failure congestive | 1 |
| **Congenital, familial and genetic disorders** | **1** |
| Congenital anomaly | 1 |
| **Eye disorder** | **2** |
| Diplopia | 1 |
| Retinal toxicity | 1 |
| **Gastrointestinal disorders** | **5** |
| Abdominal pain | 2 |
| Gastric ulcer | 1 |
| Pancreatitis | 1 |
| Vomiting | 1 |
| **General Disorders and Administration Site Conditions** | **2** |
| Asthenia | 1 |
| Chills | 1 |
| **Immune system disorders** | **2** |
| Hypersensitivity | 2 |
| **Infections and Infestations** | **4** |
| Fungal infection | 1 |
| Hepatitis infectious | 1 |
| Sepsis | 1 |
| Subcutaneous abscess | 1 |
| **Investigations** | **2** |
| Blood bilirubin increased | 1 |
| Aspartate aminotransferase increased | 1 |
| **Metabolism and Nutrition Disorders** | **1** |
| Metabolic acidosis | 1 |
| **Musculoskeletal and Connective Tissue Disorders** | **9** |
| Arthralgia | 2 |
| Polyarthritis | 2 |
| Arthritis | 1 |
| Bone pain | 1 |
| Joint Effusion | 1 |
| Muscular weakness | 1 |

| Body System<br>Preferred Term | **Number of Events** |
|---|---|
| Myositis | 1 |
| **Nervous System Disorders** | **8** |
| Cerebellar syndrome | 2 |
| Intracranial pressure increased | 2 |
| Altered state of consciousness | 1 |
| Convulsion | 1 |
| Headache | 1 |
| Pyramidal tract syndrome | 1 |
| **Psychiatric Disorders** | **1** |
| Depression | 1 |
| **Skin and Subcutaneous Tissue Disorders** | **2** |
| Henoch-Schonlein purpura | 1 |
| Urticaria | 1 |
| **All Body System Classification Total** | **234** |

In total, 19 fatal serious adverse reactions (SADRs) have been reported to ApoPharma in patients treated with deferiprone since 1999. Thirteen of the deaths followed reports of agranulocytosis (see below). Of the remaining 6 deaths, 4 were due to cardiac failure, 1 to due to sepsis not associated with agranulocytosis, and 1 due to fungal infection.

The most common SADRs reported to ApoPharma during post-marketing surveillance were neutropenia and agranulocytosis. Given the estimated 34,043 patient-years of deferiprone exposure, the 96 reported SADR reports of neutropenia and the 94 reported episodes of agranulocytosis represent a rate of approximately 0.28 reports per 100 subject-years of exposure.

Ninety four cases of agranulocytosis have been reported since 1999. Thirteen of those events resulted in a fatal outcome. All 13 episodes occurred in the first year of deferiprone therapy (20 days to 10 months after first exposure to deferiprone). All 13 patients experienced episodes of infection. In 8 patients, signs of infection (fever) were present up to six days prior to or on the day of diagnosis of agranulocytosis. Narratives of each fatal episode of agranulocytosis are in Appendix I. Further analyses of those events are presented in Appendix J. The information available to ApoPharma indicates that adequate monitoring of the neutrophil count and/or an adequate management of patient was not performed in the majority of the fatal cases (e.g., monitoring of the neutrophil count was not performed or deferiprone was not discontinued at onset of signs of infection or the physician who attended the patient was not aware the patient was being treated with a medicine that could cause agranulocytosis, and consequently managed the infection inappropriately).

Following the recognition of those factors in the occurrence of fatal cases of agranulocytosis, ApoPharma initiated an educational program in 2006 to health care professionals and to patients, in Europe, emphasizing the importance of monitoring of blood cell counts and of early discontinuation of deferiprone at the first sign of neutropenia. To emphasize the recommendations concerning monitoring of blood cell counts and early discontinuation of deferiprone at the first sign of neutropenia, a Dear Health Care Professional Letter (DHCPL) was distributed to deferiprone prescribers in the European Community. Other measures initiated around the same time as the distribution of the DHCPL included the creation of wallet-sized

cards for distribution to patients, emphasizing the importance of regular monitoring of the neutrophil count during treatment with deferiprone and of interruption of therapy at the first sign of neutropenia. Patients were advised to carry the card with them and to provide it to the health care professional overseeing them in case of infection. Subsequent surveys of health care professionals by ApoPharma indicated there was awareness of those measures by the majority of respondents. Although we cannot verify that this educational program was responsible for the observed decline in fatal cases of agranulocytosis after 2006, the decline coincided with the implementation of the program. The reported rate of agranulocytosis prior to and after the implementation of this program has remained consistent (0.30 vs 0.26 episodes per 100 patient-years, respectively). However, there was a decline in the reported rate of fatal cases of agranulocytosis from 0.07 to 0.01 episodes/100 patient-years in the period since the risk minimization activities were initiated. As of 31 August 2010, no reports of agranulocytosis with fatal outcome have been received by ApoPharma since 2008. Refer to Appendix J.

## 6.4. Use in Pregnancy

No formal studies of the safety of deferiprone in pregnant women or nursing mothers have been conducted by ApoPharma. Reproductive studies in animals are described in Section 3.2.4 and suggest that deferiprone is teratogenic and embryotoxic in non-iron-loaded rats and rabbits. Sporadic reports of pregnancies in women receiving deferiprone did not show congenital abnormalities or maternal complications. As of 31 August 2010, ApoPharma was aware of 6 reports of deferiprone use in pregnant women. Deferiprone was reported to have been discontinued between the 5th and 6th week of pregnancy in 3 of those patients. No information on time of deferiprone discontinuation is available on the other three pregnancies. Four of those pregnancies progressed uneventfully and healthy babies were born at term. One pregnancy terminated spontaneously and no information is available on the fetus. The outcome of the 6th pregnancy is unknown despite efforts to obtain follow up information.

Based on the available information, deferiprone use is contraindicated during pregnancy or breastfeeding, and women of childbearing potential are advised to avoid pregnancy and to stop taking deferiprone immediately if they become pregnant or plan to become pregnant.

## 6.5. LA-10 Study

An open label, single crossover study, named LA-10, was conducted to compare the clastogenic potential of deferiprone and deferoxamine in iron-overloaded, transfusion-dependent thalassemia patients (Marshall R *et al.* 2003)**.**

Measurement of chromosomal aberrations were made in 10 thalassemia major patients treated long-term with deferiprone (at least five years) and compared to an equal number of patients matched for age, sex and iron overload, treated long term with deferoxamine.

Two blood samples were collected from each patient, 7 and 20 days after a transfusion episode, and the frequency of chromosomal aberrations (gaps, breaks, and exchanges) in the patients' circulating lymphocytes was analyzed using standard cytogenetic staining techniques.

The frequency of reciprocal translocations was also analyzed using fluorescence *in situ* hybridization. After the second blood sample had been collected, all patients had their iron

chelation therapy switched to the other chelator, and two further blood samples were collected 7 and 20 days after transfusion for each of the next two transfusion cycles in all patients.

Chromosomal aberrations were less frequent in patients treated with deferiprone than in those treated with deferoxamine, although the difference did not reach statistical significance. At the first post-switch assessment, a statistically significant increase in cells with aberrations was observed in the group of patients whose therapy was switched from deferiprone to deferoxamine, whereas the switch from deferoxamine to deferiprone was associated with a decrease in the frequency of chromosomal aberrations.

The results of this study demonstrated that, in the clinical setting, deferiprone has no greater clastogenic potential than deferoxamine. The background incidence of chromosomal aberrations was likely to have been related, at least in part, to iron overloading in the patients studied. Iron has been shown to be clastogenic (production of structural chromosomal damage) in several test systems, including proliferating human lymphocytes in vitro, at concentrations as low as 1.25 ug/mL (Lima PDI *et al.* 2008; Shadab GGHA & Parveen. 2011).

# 7. Recommended Use

## 7.1. Proposed indication and dosage

Ferriprox® (deferiprone) is an iron chelator indicated for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate.

Inadequate response to an iron chelator is defined as a continuing increase in iron load or persistence of a clinically undesirable iron load, or intolerance of the chelator's use.

The effect of deferiprone in decreasing the total body iron load is directly influenced by the dose of the drug, the severity of the iron burden and the transfusion regimen (in essence, the iron input) delivering the iron overload. The recommended initial total daily dose of deferiprone is 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight. Dose adjustments to up to 100 mg/kg/day should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of the iron burden). It is recommended that serum ferritin concentrations be monitored every two to three months to assess the long-term effectiveness of the prescribed chelation regimen in controlling the body iron load.

Deferiprone as adjunctive therapy with deferoxamine should be used only for the treatment of patients who are at substantial risk of iron-induced toxicity, based on evidence of increasing iron overload despite robust monotherapy, or in whom there are clinical and/or biochemical signs of acute risk of severe morbidity or death.

Clinical experience suggests that deferiprone-induced agranulocytosis is more severe in patients with Diamond-Blackfan anemia than in patients with other conditions underlying transfusional iron overload. Given that myelodysplasia is frequently associated with neutropenia, it is possible that deferiprone use in patients with myelodysplasia could be associated with more frequent and severe episodes of agranulocytosis. ApoPharma recommends that deferiprone therapy in patients with Diamond-Blackfan anemia or in patients with myelodysplasia should not be initiated except

as a last resort.

The dosage form of deferiprone is a 500 mg film-coated tablet. The dose in mg/kg should be rounded to the nearest half-tablet.

### 7.2. Monitoring

Periodic monitoring of neutrophil counts and serum ALT values is required.

For early identification of neutropenia or agranulocytosis, the absolute neutrophil count must be monitored weekly (7 ± 3 days) during treatment with deferiprone. Patients treated with deferiprone should immediately interrupt deferiprone use and contact their health care provider upon experiencing signs of infection. Physicians should monitor the neutrophil count more frequently in such patients.

Although the clinical significance of elevated liver enzymes in some patients is unclear, all patients should have their serum ALT values monitored monthly during therapy with deferiprone, and interruption of therapy should be considered if a persistent increase in the serum ALT level occurs, in the absence of a known alternative cause of the increase.

## 8. Proposed Risk Management

Early detection of agranulocytosis and prevention of fatal outcomes as well as avoiding exposure to deferiprone during pregnancy are the most important foci of risk minimization during therapy with deferiprone.

To minimize those risks, ApoPharma is proposing use of a single centralized pharmacy distribution program with a registry of medical specialists prescribing deferiprone and registration of patients for implementation of an educational program on the risks associated with deferiprone therapy and the measures that mitigate those risks. The education program will be provided prior to the first dispensing of the medication and reminders of its key aspects will be sent to prescribers and users on a quarterly basis. In addition to facilitating risk management, the registry will collect information on previous chelation therapy, primary diagnosis, safety, tolerability and adequacy of response to deferiprone.

Since the main goal of the proposed risk minimization program is prevention of fatal consequences of agranulocytosis, ApoPharma proposes to focus on education of prescribers and patients regarding the need for the weekly monitoring of the neutrophil count, increased frequency of neutrophil count measurement at signs of infection, such as fever, flu-like symptoms, sore throat, etc, and interruption of therapy also at detection of neutropenia.

This plan is proposed with due regard to the targeted population, i.e., transfusion-dependent patients who are seen in the clinic every 2 to 4 weeks for their transfusions, and usually also seen between these occasions for type matching, and thus are unlikely to be lost to follow-up between prescriptions.

The elements of the proposed program include:

1. Product dispensed by a single central pharmacy.
2. Registration of deferiprone prescribers and acknowledgement from the physician that he/she understands the following:
    - The approved indication for deferiprone
    - The risks associated with deferiprone therapy including agranulocytosis and the potential for fetal toxicity.
    - The requirements for weekly (7 ± 3 days) monitoring of ANC, and for timely review of ANC results.
    - The management of deferiprone-treated patients at signs of infection, such as fever, flu-like symptoms, sore throat, etc.
    - The management of episodes of neutropenia or agranulocytosis.
    - The need for communicating those risks to each patient for whom deferiprone is prescribed.
    - Prompt reporting of adverse events occurring in the course of deferiprone therapy.
3. Registration of patients for whom deferiprone is being prescribed and acknowledgement from the patient that he/she understands the following:
    a. The risks associated with deferiprone therapy including agranulocytosis and the potential for fetal toxicity.
    b. The requirements for weekly (7 ± 3 days) monitoring of ANC and for immediately interruption of therapy at detection of neutropenia.
    c. The requirements for immediate interruption of therapy and of monitoring of the neutrophil count at signs of infections, such as fever, flu-like symptoms, sore throat, etc.
    d. Prompt reporting to their physician if they experience any symptoms of infection such as fever, sore throat or flu-like symptoms.
    e. The management of episodes of neutropenia or of agranulocytosis
    f. Mandatory use of contraceptive measures by women of childbearing potential while taking deferiprone, of interruption of therapy if they are trying to become pregnant, and of immediate interruption of therapy if they discover that they are pregnant while taking deferiprone.

g. To immediately notify their physician if they become pregnant, or if they plan to become pregnant during therapy.

h. The need for avoidance of breast feeding while taking deferiprone.

4. Detailed Communication Plan for those registered on the Program

a. Full Prescribing Information and Medication Guide provided to all physicians registered in the program.

b. Quarterly messages to registered prescribing medical specialists to remind them of the risk of agranulocytosis, the importance of ANC monitoring, and the recommended management of agranulocytosis, as well as the importance of notifying their patients of the need for prompt interruption of deferiprone and monitoring of the neutrophil count at the first sign of infection.

c. Quarterly messages to registered prescribing medical specialists that remind them of the risk of exposure to deferiprone during pregnancy and the importance of contraception counseling.

d. Quarterly reminders to registered patients as above.

e. Wallet size card reminding patients of the risk of agranulocytosis, the importance of monitoring their neutrophil count and the need to immediately contact their physician upon experiencing signs of infection. To be given to the patients with each prescription.

f. Toll-free hotline available to answer questions regarding deferiprone.

These steps are viewed as important to readily facilitate the acquisition and maintenance of therapy with deferiprone, without creating hurdles which might hinder its ongoing use by patients for whom previous chelation therapy has been inadequate. ApoPharma will continue to work with the FDA to further discuss the proposed risk minimization strategy.

In addition to the measures proposed above, ApoPharma will initiate a safety study and an active drug surveillance program for deferiprone-treated patients with primary conditions other than thalassemia. Safety data from the current ApoPharma compassionate use program and the published literature do not indicate the likelihood of an adverse events profile in these patients differing from that observed in patients with thalassemia, but no formal safety studies have been conducted. It is evident from these sources that there is a need for an alternative iron chelator in a segment of the non-thalassemia population, particularly in patients with sickle cell disease who are transfusion-dependent. To meet the current need while further determining the safety of deferiprone in those patients, ApoPharma commits to a post-approval safety study in patients with sickle cell disease, to be initiated within 9 months of FDA approval. A synopsis of the study is included in Appendix E. In addition to the proposed study, in order to facilitate immediate collection and assessment of safety data, ApoPharma proposes to conduct active

surveillance of adverse events in all patients with conditions other than thalassemia for whom deferiprone may be prescribed, prior to initiation of the trial. For those patients, the program will consist of proactive collection of adverse experiences using standardized data collection forms. Within 10 days of a patient's enrolment in the registry, prescribers with be required to complete a Patient Baseline Form, and a Medical Follow-up and Adverse Experience Reporting Form will be expected every 3 months during treatment with deferiprone. Prescribers will be required to report serious adverse events within 7 days of knowledge of them. All reported serious adverse events must be further investigated and followed by the ApoPharma Medical Safety department. ApoPharma will conduct analysis of collected data on a quarterly basis. Patients not eligible for the proposed sickle cell disease trial for any reason will continue in the active surveillance program. The active surveillance program in non-thalassemia patients will continue until the completion of the proposed study and the rendering of a decision by the FDA on the continued use of deferiprone in this patient group.

# 9. Integrated Summary of Risks and Benefits

Chronic blood transfusion programs lead to progressive iron accumulation (transfusional siderosis) with damage to, particularly, the heart, liver, and endocrine organs. Without effective chelation, death commonly occurs in the second or third decade of transfusions, predominantly due to iron-induced cardiac disease. In the USA, only two iron chelators, Desferal® (deferoxamine, DFO) and Exjade® (deferasirox, DFX), are available for the treatment of iron overload; both are marketed by Novartis and both have limitations related to efficacy and toxicity. There is an unmet medical need for the treatment of patients with transfusional iron overload for whom the current chelation therapy has been shown to be inadequate in controlling their iron burden or which is associated with intolerable side effects. Results of LA36 demonstrate that deferiprone is an effective treatment in patients with iron overload for whom previous chelation therapy has been inadequate. Results of the contributor study LA16 demonstrated that deferiprone is superior to deferoxamine in reducing cardiac iron load. The individual studies including LA16, and the natural history studies LA12 and Borgna-Pignatti et al, as well as the other ApoPharma studies and the published literature, provide additional evidence of the efficacy of deferiprone for the treatment of patients with transfusional iron overload.

The safety profile of deferiprone has been characterized by more than 23 years of clinical experience, including 11 years of post-marketing experience. The estimated drug exposure to deferiprone exceeds 34,000 patient-years, with some patients having received therapy for more than 14 years. There are now approximately 700 publications in the peer-reviewed literature referring to deferiprone (PubMed, 31 January 2011), most of which are independent of the involvement of ApoPharma, but provide safety information consistent with that reported by ApoPharma.

The most serious drug-induced adverse event associated with deferiprone, agranulocytosis, occurs in 1% to 2% of patients. In clinical trials, all episodes of agranulocytosis resolved upon discontinuation of deferiprone. No specific risk factors for agranulocytosis have been identified other than that most episodes have occurred during the first year of therapy. To minimize the consequences of agranulocytosis, ApoPharma proposes to implement an educational program to prescribers and patients on the requirements for the weekly monitoring of the neutrophil count,

increased frequency of neutrophil count measurement neutrophil monitoring and interruption of therapy at signs of infection.

The adverse events more commonly observed in deferiprone-treated patients than in DFO-treated patients, irrespective of their relationship to the study drug were gastrointestinal upset, such as abdominal pain, nausea, vomiting and diarrhea; respiratory infections such as influenza, tonsillitis and bronchitis; fever and arthralgia. In general, those events were mild to moderate in severity and resolved within a week despite continuous treatment with deferiprone. Episodes of increase in serum ALT levels are usually transient and occur most frequently during the first months of therapy. No episodes of liver failure have been reported with the use of deferiprone.

In summary, data generated during ApoPharma-sponsored clinical trials and published over the last decade reveal that the benefits of deferiprone therapy outweigh its potential risks. Therefore, the availability of deferiprone would fulfill the unmet medical need for an iron chelation for the treatment of transfusion siderosis in patients for whom previous chelation therapy has been inadequate.

# 10. References

1. ISMP QuarterWatch (Quarter 4 and 2009 totals) - Reported patients deaths increased by 14% in 2009. ISMP Medication Safety Alert. 2010;

2. Addis A, Loebstein R, Koren G, Einarson TR. Meta-analytic review of the clinical effectiveness of oral deferiprone (L1). Eur J Clin Pharmacol. 1999; 55:1-6.

3. Agarwal MB, Gupte SS, Viswanathan C, Vasandani D, Ramanathan J, Desai N, et al. Long-term assessment of efficacy and safety of L1, an oral iron chelator, in transfusion dependent thalassaemia: indian trial. Br J Haematol. 1992; 82:460-6.

4. al Refaie FN, Hershko C, Hoffbrand AV, Kosaryan M, Olivieri NF, Tondury P, et al. Results of long-term deferiprone (L1) therapy: a report by the International Study Group on Oral Iron Chelators. Br J Haematol. 1995; 91(1):224-9.

5. Al-Refaie FN, Hershko C, Hoffbrand AV, Kosaryan M, Olivieri NF, Töndury P, et al. Results of Long-Term Deferiprone (L1) Therapy: A Report by the International Study Group on Oral Iron Chelators. Br J Haematol. 1995; 91:224-9.

6. Al-Refaie FN, Veys PA, Wilkes S, Wonke B, Hoffbrand AV. Agranulocytosis in a patient with thalassaemia major during treatment with the oral iron chelator, 1,2-dimethyl-3-hydroxypyrid-4-one. Acta Haematol. 1993; 89:86-90.

7. Al-Refaie FN, Wonke B, Hoffbrand AV. Long-Term Assessment of Patients with Iron Overload Receiving Deferiprone (L1). Br J Haematol. 1994; 86(Suppl. 1):5.

8. Al-Refaie FN, Wonke B, Hoffbrand AV, Wickens DG, Nortey P, Kontoghiorghes GJ. Efficacy and Possible Adverse Effects of the Oral Iron Chelator 1,2-Dimethyl-3-Hydroxypyrid-4-One (L1) in Thalassemia Major. Blood. 1992; 80(3):593-9.

9. Alymara V, Bourantas D, Chaidos A, Bouranta P, Gouva M, Vassou A, et al. Effectiveness and safety of combined iron-chelation therapy with deferoxamine and deferiprone. Hematol J. 2004; 5(6):475-9.

10. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J. 2001; 22:2171-9.

11. Anderson LJ, Wonke B, Prescott E, Holden S, Walker JM, Pennell DJ. Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia. Lancet. 2002; 360:516-20.

12. Angelucci E, Brittenham GM, McLaren CE, Ripalti M, Baronciani D, Giardini C, et al. Hepatic iron concentration and total body iron stores in thalassemia major. N Engl J Med. 2000; 343(5):327-31.

13. Balveer K, Pyar K, Wonke B. Combined oral and parenteral iron chelation in beta thalassaemia major. Med J Malaysia. 2000; 55(4):493-7.

14. Berdoukas V, Bohane T, Eagle C, Lindeman R, DeSilve K, Tobias V, et al. The Sydney Children's Hospital experience with the oral iron chelator - deferiprone. Transfus Sci. 2000; 23(3):239-40.

15. Bergeron RJ, Streiff RR, Wiegand J, Luchetta G, Creary EA, Peter HH. A comparison of the iron-clearing properties of 1,2-dimethyl-3-hydroxypyrid-4-one, 1,2-diethyl-3-hydroxypyrid-4-one, and deferoxamine. Blood. 1992; 79(7):1882-90.

16. Borgna-Pignatti C, Cappellini MD, De Stefano P, Del Vecchio GC, Forni GL, Gamberini MR, et al. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. Blood. 2006; 107(9):3733-7.

17. Borgna-Pignatti C, Castriota-Scanderbeg A. Methods for evaluating iron stores and efficacy of chelation in transfusional hemosiderosis. Haematologica. 1991; 76:409-13.

18. Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica. 2004; 89(10):1187-93.

19. Borgna-Pignatti C, Rugolotto S, DeStefano P, Piga A, et al. Survival and disease complications in thalassemia major. Ann N Y Acad Sci. 1998; 850:227-31.

20. Borgna-Pignatti C, Zurlo MG, DeStefano P, DiGregorio F, Di Palma A, Piga A, et al. Survival in thalassemia with conventional treatment. Prog Clin Biol Res. 1989; 309:27-33.

21. Brittenham GM, Cohen AR, McLaren CE, Martin MB, Griffith PM, Nienhuis AW, et al. Hepatic iron stores and plasma ferritin concentration in patients with sickle cell anemia and thalassemia major. Am J Hematol. 1993; 42:81-5.

22. Brittenham GM, Danish EH, Harris J.W. Assessment of bone marrow and body iron stores: old techniques and new technologies. Semin Hematol. 1981; 18(3):194-221.

23. Brittenham GM, Sheth S, Allen CJ, Farrell DE. Noninvasive methods for quantitative assessment of transfusional iron overload in sickle cell disease. Semin Hematol. 2001; 38(1 Suppl 1):37-56.

24. Callea F. Iron chelation with oral deferiprone in patients with thalassemia [letter]. N Engl J Med. 1998; 339(23):1710-1.

25. Cappellini MD, Cerino M, Zatelli S, Fargion S, Sampietro M, Zanaboni L, et al. Liver damage in adult thalassemia major patients under regular chelation therapy with desferrioxamine. Proceedings of the 7th International Conference on Thalassaemia and the Haemoglobinopathies; 1999 May 31 - Jun 4; Bangkok, Thailand. p. 273.

26. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood. 2006; 107(9):3455-62.

27. Cappellini MD, Porter J, El Beshlawy A, Li CK, Seymour JF, Elalfy M, et al. Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. Haematologica. 2010; 95(4):557-66.

28. Carpenter JP, He T, Kirk P, Roughton M, Anderson LJ, de Noronha SV, et al. On T2* Magnetic Resonance and Cardiac Iron. Circulation. 2011;

29. Cassel DL, Hoxie JA, Cooper RA. Phorbol ester modulation of T-cell antigens in the Jurkat lymphoblastic leukemia cell line. Cancer Res. 1983; 43(10):4582-6.

30. Cazzola M, Borgna-Pignatti C, De Stefano P, Bergamaschi G, Bongo IG, Dezza L, et al. Internal Distribution of Excess Iron and Sources of Serum Ferritin in Patients with Thalassaemia. Scand J Haematol. 1983; 30:289-96.

31. Ceci A, Baiardi P, Catapano M, Felisi M, Cianciulli P, De S, V, et al. Risk factors for death in patients with beta-thalassemia major: results of a case-control study. Haematologica. 2006; 91(10):1420-1.

32. Ceci A, Baiardi P, Felisi M, Cappellini MD, Carnelli V, De Sanctis V, et al. The safety and effectiveness of deferiprone in a large-scale, 3-year study in Italian patients. Br J Haematol. 2002; 118(1):330-6.

33. Chan JC, Chim CS, Ooi CG, Cheung B, Liang R, Chan TK, et al. Use of the oral chelator deferiprone in the treatment of iron overload in patients with Hb H disease. Br J Haematol. 2006; 133(2):198-205.

34. Chenoufi N, Hubert N, Loreal O, Morel I, Pasdeloup N, Cillard J, et al. Inhibition of iron toxicity in rat and human hepatocyte cultures by the hydroxypyridin-4-ones CP20 and CP94. J Hepatol. 1995; 23:166-73.

35. Cohen AR, Galanello R, Piga A, De Sanctis V, Tricta F. Safety and effectiveness of long-term therapy with the oral iron chelator deferiprone. Blood. 2003; 102:1583-7.

36. Cohen AR, Galanello R, Piga A, DiPalma A, Vullo C, Tricta F. Safety profile of the oral iron chelator deferiprone: a multicentre study. Br J Haematol. 2000; 108:305-12.

37. Collins AF, Fassos FF, Stobie S, Lewis N, Shaw D, Fry M, et al. Iron-balance and dose-response studies of the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in iron-loaded patients with sickle cell disease. Blood. 1994; 83(8):2329-33.

38. Crosby WH. Editorial: Serum ferritin fails to indicate hemochromatosis--nothing gold can stay. N Engl J Med. 1976; 294(6):333-4.

39. D'Angelo E, Mirra N, Rocca A, Carnelli V. Combined Therapy With Desferrioxamine and Deferiprone: A New Protocol for Iron Chelation in Thalassemia. J Pediatr Hematol Oncol. 2004; 26(7):451-3.

40. Daar S, Pathare AV. Combined therapy with desferrioxamine and deferiprone in beta thalassemia major patients with transfusional iron overload. Ann Hematol. 2006; 85(5):315-9.

41. Del Vecchio GC, Crollo E, Schettini F, Schettini F, Fischer R, De Mattia D. Factors influencing effectiveness of deferiprone in a thalassaemia major clinical setting. Acta Haematol. 2000; 104(2-3):99-102.

42. El-Alfy M, Sari TT, Lee CL, Tricta F, El Beshlawy A. The Safety, Tolerability, and Efficacy of a Liquid Formulation of Deferiprone in Young Children With Transfusional Iron Overload. J Pediatr Hematol Oncol. 2010;

43. Eybl V, Kotyzova D, Kolek M, Koutensky J, Nielsen P. The influence of deferiprone (L1) and deferoxamine on iron and essential element tissue level and parameters of oxidative status in dietary iron-loaded mice. Toxicol Lett. 2002; 128(1-3):169-75.

44. Farmaki K, Tzoumari I, Pappa C. Oral chelators in transfusion-dependent thalassemia major patients may prevent or reverse iron overload complications. Blood Cells Mol Dis. 2011;

45. Farmaki K, Tzoumari I, Pappa C, Chouliaras G, Berdoukas V. Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major. Br J Haematol. 2009;

46. Fassos FF, Klein J, Fernandes D, Matsui D, Olivieri NF, Koren GR. The pharmacokinetics and pharmacodynamics of the oral iron chelator deferiprone (L1) in relation to hemoglobin levels. Int J Clin Pharmacol Ther Toxicol. 1996; 34(7):288-92.

47. Finch C. Regulators of iron balance in humans. Blood. 1994; 84(6):1697-702.

48. Finch CA, Bellotti V, Stray S, Lipschitz DA, Cook JD, Pippard MJ, et al. Plasma ferritin determination as a diagnostic tool. West J Med. 1986; 145(5):657-63.

49. Fischer R, Longo F, Nielsen P, Engelhardt R, Hider RC, Piga A. Monitoring long-term efficacy of iron chelation therapy by deferiprone and desferrioxamine in patients with β-thalassemia major: application of SQUID biomagnetic liver susceptometry. Br J Haematol. 2003; 121(6):938-48.

50. Florence A, Ward RJ, Peters TJ, Crichton RR. Studies of in vivo iron mobilization by chelators in the ferrocene-loaded rat. Biochem Pharmacol. 1992; 44(6):1023-7.

51. Fredenburg AM, Sethi RK, Allen DD, Yokel RAR. The pharmacokinetics and blood-brain-barrier permeation of the chelators 1,2-dimethyl-, 1,2 diethyl-, and 1-[ethan-1'ol]-2-methyl-3-hydroxypyridin-4-one in the rat. Toxicology. 1996; 108(3):191-9.

52. Fredenburg AM, Wedlund PJ, Skinner TL, Damani LA, Hider RC, Yokel RA. Pharmacokinetics of representative 3-hydroxypyridin-4-ones in rabbits: CP20 and CP94. Drug Metab Dispos. 1993; 21(2):255-8.

53. Gabutti V, Piga A. Results of long-term iron-chelating therapy. Acta Haematol. 1996; 95:26-36.

54. Galanello R, Kattamis A, Piga A, Fischer R, Leoni G, Ladis V, et al. A prospective randomized controlled trial on the safety and efficacy of alternating deferoxamine and deferiprone in the treatment of iron overload in patients with thalassemia. Haematologica. 2006;

55. Gale GR, Litchenberg WH, Smith AB, Singh PK, Campbell RA, Jones MM. Comparative iron mobilizing actions of deferoxamine, 1,2- dimethyl-3-hydroxypyrid-4-one, and pyridoxal isonicotinoyl hydrazone in iron hydroxamate-loaded mice. Res Commun Chem Pathol Pharmacol. 1991; 73(3):299-313.

56. Glickstein H, Ben El R, Shvartsman M, Cabantchik ZI. Intracellular labile iron pools as direct targets of iron chelators. A fluorescence study of chelator action in living cells. Blood. 2005; 106(9):3242-50.

57. Grady RW, Berdoukas VA, Rachmilewitz A, Galanello R, Borgna-Pignatti C, Ladis V, et al. Combinations of desferrioxamine and deferiprone markedly enhance iron excretion. Proceedings of the American Society of Hematology 44th Annual Meeting and Exposition; 2002 Dec 6-10; Philadelphia, Pennsylvania, USA. p. 241a.

58. Grady RW, Berdoukas VA, Rachmilewitz EA, Galanello R, Borgna-Pignatti C, Ladis V, et al. Iron chelation therapy: Metabolic aspects of combining deferiprone and desferrioxamine. Proceedings of the 11th International Conference on Oral Chelation in the Treatment of Thalassemia and Other Diseases; 2001 Mar 22-25; Catania, Italy. p. 74-8.

59. Grady RW, Hilgartner MW, Giardina PJV. Deferiprone: its effectiveness relative to that of desferrioxamine. Proceedings of the 6th International Conference on Thalassaemia and the Haemoglobinopathies; 1997 Apr 5-10; St. Paul's Bay, Malta. p. 2.

60. Grange S, Bertrand DM, Guerrot D, Eas F, Godin M. Acute renal failure and Fanconi syndrome due to deferasirox. Nephrol Dial Transplant. 2010;

61. Guo F. Report on Deferiprone Protein Binding Studies. 1998.

62. Harmatz P, Butensky E, Ferrell L, Foote D, Hackney-Stephens E, Vichinsky E. Hepatic injury in hypertransfused patients with sickle cell disease (SCD) or thalassemia. Blood; 1999; p. Abstract # 1875.

63. Hausler A, Monnet G, Peter O. Effects of iron chelators on hypothalamo-pituitary-adrenocortical (HPA) function in rats. J.Endocrinol.Invest.; 1993; p. 211.

64. Hershko C, Link G, Konijn AM, Huerta M, Rosenmann E, Reinus C. The iron-loaded gerbil model revisited: Effects of deferoxamine and deferiprone treatment. J Lab Clin Med. 2002; 139(1):50-8.

65. Hershko C, Link G, Pinson A, Peter HH, Dobbin P, Hider RC. Iron mobilization from myocardial cells by 3-hydroxypyridin-4-one chelators: studies in rat heart cells in culture. Blood. 1991; 77(9):2049-53.

66. Hileti D, Ward RJ, Peters TJ, Sheppard LN, Hoffbrand AV. Distribution of $^{14}$C-L1, in tissues of normal and iron-loaded rats . Proceedings of the 5th International Conference on Thalassemias and the Haemoglobinopathies; 1993 Mar 29 - Apr 3; Nicosia, Cyprus. p. 344.

67. Hoffbrand AV, Cohen A, Hershko C. Role of deferiprone in chelation therapy for transfusional iron overload. Blood. 2003; 102(1):17-24.

68. Hsieh MM, Everhart JE, Byrd-Holt DD, Tisdale JF, Rodgers GP. Prevalence of neutropenia in the U.S. population: age, sex, smoking status, and ethnic differences. Ann Intern Med. 2007; 146(7):486-92.

69. Kattamis C. Optimal use of desferrioxmine in the treatment of thalassaemia. In: Iron Overload and Chelation in Thalassaemia. Hans Huber Publishers; 1987. p. 11-25.

70. Kayyali R, Porter JB, Liu ZD, Davies NA, Nugent JH, Cooper CE, et al. Structure-function investigation of the interaction of 1- and 2-substituted 3-hydroxypyridin-4-ones with 5-lipoxygenase and ribonucleotide reductase. J Biol Chem. 2001; 276(52):48814-22.

71. Kersten MJ, Lange R, Smeets MEP, Vreugdenhil G, Roozendaal KJ, Lameijer W, et al. Long-term treatment of transfusional iron overload with the oral iron chelator deferiprone (L1): a dutch multicenter trial. Ann Hematol. 1996; 73(5):247-52.

72. Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J, et al. Cardiac T2* Magnetic Resonance for Prediction of Cardiac Complications in Thalassemia Major. Circulation. 2009;

73. Kolnagou A, Kontoghiorghes GJ. Maintenance of Normal Range Body Iron Store Levels for up to 4.5 Years in Thalassemia Major Patients Using Deferiprone Monotherapy. Hemoglobin. 2010; 34(3):204-9.

74. Kontoghiorghes GJ. Dose response studies using desferrioxamine and orally active chelators in a mouse model. Scand J Haematol. 1986a; 37:63-70.

75. Kontoghiorghes GJ. Orally active α-ketohydroxypyridine iron chelators: studies in mice. Mol Pharmacol. 1986b; 30:670-3.

76. Kontoghiorghes GJ, Barr J, Nortey P, Sheppard L. Selection of a new generation of orally active α-ketohydroxypyridine iron chelators intended for use in the treatment of iron overload. Am J Hematol. 1993; 42:340-9.

77. Kontoghiorghes GJ, Goddard JG, Bartlett AN, Sheppard L. Pharmacokinetic studies in humans with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one. Clin Pharmacol Ther. 1990; 48(3):255-61.

78. Kontoghiorghes GJ, Sheppard L. Simple synthesis of the potent iron chelators 1-alkyl-3-hydroxy-2-methylpyrid-4-ones. Inorg Chim Acta. 1987; 136:L11-L12.

79. Kontoghiorghes GJ, Sheppard L, Barr J. Synthetic methods and *in vitro* iron binding studies of the novel 1-alkyl-2-ethyl-3-hydroxypyrid-4-one iron chelators. Inorg Chim Acta. 1988; 152:195-9.

80. Kontoghiorghes GJ, Sheppard L, Hoffbrand AV, Charalambous J, Tikerpae J, Pippard MJ. Iron chelation studies using desferrioxamine and the potential oral chelator, 1,2-dimethyl-3-hydroxypyrid-4-one, in normal and iron loaded rats. J Clin Pathol. 1987; 40:404-8.

81. Kowdley KV, Kaplan MM. Iron-chelation therapy with oral deferiprone -toxicity or lack of efficacy? [Editorials]. N Engl J Med. 1998; 339(7):468-9.

82. Kwiatkowski JL. Oral Iron Chelators. Pediatr Clin North Am. 2008; 55(2):461-82.

83. Ladis V, Chouliaras G, Berdoukas V, Moraitis P, Zannikos K, Berdoussi E, et al. Relation of chelation regimes to cardiac mortality and morbidity in patients with thalassaemia major: an observational study from a large Greek unit. Eur J Haematol. 2010;

84. Lee MH, Means RT, Jr. Extremely elevated serum ferritin levels in a university hospital: associated diseases and clinical significance. Am J Med. 1995; 98(6):566-71.

85. Li CK, Luk CW, Ling SC, Chik KW, Yuen HL, Li CK, et al. Morbidity and mortality patterns of thalassaemia major patients in Hong Kong: retrospective study. Hong Kong Med J. 2002; 8(4):255-60.

86. Lima PDI, Vasconcellos MC, Montenegro RA, Sombra CML, Bahia MO, *et al.* Genotoxic and cytotoxic effects of iron sulfate in cultured human lymphocytes treated in different phases of cell cycle. Toxicology in Vitro. 2008; 22(3):723-9.

87. Link G, Konijn AM, Breuer W, Cabantchik ZI, Hershko C. Exploring the "iron shuttle" hypothesis in chelation therapy: effects of combined deferoxamine and deferiprone treatment in hypertransfused rats with labeled iron stores and in iron-loaded rat heart cells in culture. J Lab Clin Med. 2001; 138(2):130-8.

88. Link G, Konijn AM, Hershko C. Cardioprotective effect of alpha-tocopherol, ascorbate, deferoxamine, and deferiprone: mitochondrial function in cultured, iron-loaded heart cells. J Lab Clin Med. 1999; 133:179-88.

89. Link G, Pinson A, Hershko C. Ability of the orally effective iron chelators dimethyl- and diethyl-hydroxypyrid-4-one and of deferoxamine to restore sarcolemmal thiolic enzyme activity in iron-loaded heart cells. Blood. 1994; 83(9):2692-7.

90. Lipschitz DA, Cook JD, Finch CA. A clinical evaluation of serum ferritin as an index of iron stores. N Engl J Med. 1974; 290(22):1213-6.

91. Liu ZD, Khodr HH, Liu DY, Lu SL, Hider RC. Synthesis, physicochemical characterization, and biological evaluation of 2-(1'-hydroxyalkyl)-3-hydroxypyridin-4-ones: novel iron chelators with enhanced pFe(3+) values. J Med Chem. 1999a; 42:4814-23.

92. Liu ZD, Lu SL, Hider RC. *In vivo* iron mobilisation evaluation of hydroxypyridinones in 59 Fe-ferritin-loaded rat model. Biochem Pharmacol. 1999b; 57:559-66.

93. Maggio A, D'Amico G, Morabito A, Capra M, Ciaccio C, Cianciulli P, et al. Deferiprone versus deferoxamine in patients with thalassemia major: a randomized clinical trial. Blood Cells Mol Dis. 2002; 28(2):196-208.

94. Maggio A, Vitrano A, Capra M, Cuccia L, Gagliardotto F, Filosa A, et al. Improving survival with deferiprone treatment in patients with thalassemia major: A prospective multicenter randomised clinical trial Under the auspices of the Italian Society for Thalassemia and Hemoglobinopathies. Blood Cells Mol Dis. 2009a; 42(3):247-51.

95. Maggio A, Vitrano A, Capra M, Cuccia L, Gagliardotto F, Filosa A, et al. Long-term sequential deferiprone-deferoxamine versus deferiprone alone for thalassaemia major patients: a randomized clinical trial. Br J Haematol. 2009b; 145(2):245-54.

96. Marshall R, Tricta F, Galanello R, Leoni G, Kirkland D, Minto S, et al. Chromosomal aberration frequencies in patients with thalassaemia major undergoing therapy with deferiprone and deferoxamine in a comparative crossover study. Mutagenesis. 2003; 18(5):457-63.

97. Matsui D, Klein J, Hermann C, Grunau V, McClelland R, Chung D, et al. Relationship between the pharmacokinetics and iron excretion pharmacodynamics of the new oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one in patients with thalassemia. Clin Pharmacol Ther. 1991; 50(3):294-8.

98. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2008; 10(1):42.

99. Mostert LJ, Van Dorst JALM, Koster JF, Van Eijk HG, Kontoghiorghes GJ. Free radical and cytotoxic effects of chelators and their iron complexes in the hepatocyte. Free Radic Res Commun. 1987; 3(6):379-88.

100. Noetzli LJ, Carson SM, Nord AS, Coates TD, Wood JC. Longitudinal analysis of heart and liver iron in thalassemia major. Blood. 2008; 112(7):2973-8.

101. Nzouakou R, Habibi A, Lee K, Luciani A, Deux JF, Galacteros F, et al. Oral chelator deferiprone in adult with sickle cell disease. Blood; 2009;

102. Olive A, Junca J. Elevated serum ferritin levels: associated diseases and clinical significance. Am J Med. 1996; 101(1):120.

103. Olivieri NF. Randomized trial of deferiprone (L1) and deferoxamine (DFO) in thalassemia major [Abstract No. 2593]. Blood. 1996; 88(10 Suppl. 1):651a.

104. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood. 1997; 89(3):739-61.

105. Olivieri NF, Brittenham GM, Armstrong SAM, Basran RK, Daneman R, Daneman N, et al. First prospective randomized trial of the iron chelators deferiprone (L1) and deferoxamine. Proceedings of the American Society of Hematology 37th Annual Meeting; 1995a Dec 1-5; Seattle, WA, USA. p. 249a.

106. Olivieri NF, Brittenham GM, Koren G, Toronto Iron Chelation Research Group. Reduction in Hepatic Iron Stores with the Oral Iron Chelator L1 in Patients (PTS) with Transfusion-Dependent Thalassemia (HBT) and Sickle Cell Disease (SCD): First Three Years of the Canadian Trial. Blood; 1993; p. 313a.

107. Olivieri NF, Brittenham GM, Matsui D, Berkovitch M, Blendis LM, Cameron R, et al. Iron-chelation therapy with oral deferiprone in patients with thalassemia major. N Engl J Med. 1995b; 332(14):918-22.

108. Olivieri NF, Brittenham GM, McLaren CE, Templeton DM, Cameron RG, McClelland RA, et al. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. N Engl J Med. 1998; 339(7):417-23.

109. Olivieri NF, Koren G, Hermann C, Bentur Y, Chung D, Klein J, et al. Comparison of oral iron chelator L1 and desferrioxamine in iron-loaded patients. Lancet. 1990; 336:1275-9.

110. Olivieri NF, Nathan DG, MacMillan JH, Wayne AS, Liu P, McGee A, et al. Survival in medically treated patients with homozygous beta-thalassemia. N Engl J Med. 1994; 331(9):574-8.

111. Origa R, Bina P, Agus A, Crobu G, Defraia E, Dessi C, et al. Combined therapy with deferiprone and desferrioxamine in thalassemia major. Haematologica. 2005; 90(10):1309-14.

112. Overmoyer BA, McLaren CE, Brittenham GM. Uniformity of Liver Density and Nonheme (Storage) Iron Distribution. Arch Pathol Lab Med. 1987; 111:549-54.

113. Peng CT, Chow KC, Chen JH, Chiang YP, Lin TY, Tsai CH. Safety monitoring of cardiac and hepatic systems in ß-thalassemia patients with chelating treatment in Taiwan. Eur J Haematol. 2003; 70:392-7.

114. Pennell DJ, Berdoukas V, Karagiorga M, Ladis V, Piga A, Aessopos A, et al. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. Blood. 2006; 107(9):3738-44.

115. Pennell DJ, Porter JB, Cappellini MD, El Beshlawy A, Chan LL, Aydinok Y, et al. Efficacy of deferasirox in reducing and preventing cardiac iron overload in {beta}-thalassemia. Blood. 2010;

116. Perifanis V, Christoforidis A, Vlachaki E, Tsatra I, Spanos G, Athanassiou-Metaxa M. Comparison of Effects of Different Long-term Iron-Chelation Regimens on Myocardial and Hepatic Iron Concentrations Assessed with T2* Magnetic Resonance Imaging in Patients with beta-Thalassemia Major. Int J Hematol. 2007; 86(5):385-9.

117. Piga A, Gaglioti C, Fogliacco E, Tricta F. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. Haematologica. 2003; 88(5):489-96.

118. Porter JB, Gyparaki M, Burke LC, Huehns ER, Sarpong P, Saez V, et al. Iron mobilization from hepatocyte monolayer cultures by chelators: the importance of membrane permeability and the iron-binding constant. Blood. 1988; 72(5):1497-503.

119. Porter JB, Hoyes KP, Abeysinghe RD, Brooks PN, Huehns ER, Hider RC. Comparison of the subacute toxicity and efficacy of 3-hydroxypyridin-4-one iron chelators in overloaded and nonoverloaded mice. Blood. 1991; 78(10):2727-34.

120. Rafat C, Fakhouri F, Ribeil JA, Delarue R, Le Quintrec M. Fanconi Syndrome Due to Deferasirox. Am J Kidney Dis. 2009;

121. Ricchi P, Ammirabile M, Spasiano A, Costantini S, Cinque P, Di Matola T, et al. COMBINED CHELATION THERAPY IN THALASSEMIA MAJOR WITH DEFERIPRONE AND DESFERRIOXAMINE: A RETROSPECTIVE STUDY. Eur J Haematol. 2010;

122. Sajid R, Ghani F, Adil S, Khurshid M. Oral iron chelation therapy with deferiprone in patients with Thalassemia Major. J Pak Med Assoc. 2009; 59(6):388-90.

123. Sergejew T, Forgiarini P, Schnebli HP. Chelator-induced iron excretion in iron-overloaded marmosets. Br J Haematol. 2000; 110(4):985-92.

124. Shadab GGHA, Parveen N. Clastogenic Effects of Ferrous Sulfate on Human Lymphocyte Chromosomes in vitro. Journal of Applied Sciences Research. 2011; 7(2):125-8.

125. Singh S, Epemolu RO, Dobbin P, Tilbrook GS, Ellis BL, Damani LA, et al. Urinary metabolic profiles in human and rat of 1,2-dimethyl-and 1,2-diethyl-substituted 3-hydroxypyridin-4-ones. Drug Metab Dispos Biol Fate Chem. 1992; 20(2):256-61.

126. Sohn YS, Breuer W, Munnich A, Cabantchik ZI. Redistribution of accumulated cell iron. A modality of chelation with therapeutic implications. Blood. 2008; 111:1690-9.

127. St Pierre TG, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, Olynyk JK, et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. Blood. 2005; 105(2):855-61.

128. Stobie S, Tyberg J, Matsui D, Fernandes D, Klein J, Olivieri NF, et al. Comparison of the pharmacokinetics of 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in healthy volunteers, with and without co-administration of ferrous sulfate, to thalassemia patients. Int J Clin Pharmacol Ther Toxicol. 1993; 31(12):602-5.

129. Storey P, Thompson AA, Carqueville CL, Wood JC, De Freitas RA, Rigsby CK. R2* imaging of transfusional iron burden at 3T and comparison with 1.5T. J Magn Reson Imaging. 2007; 25(3):540-7.

130. Tanner MA, Galanello R, Dessi C, Smith GC, Westwood MA, Agus A, et al. A Randomized, Placebo-Controlled, Double-Blind Trial of the Effect of Combined Therapy With Deferoxamine and Deferiprone on Myocardial Iron in Thalassemia Major Using Cardiovascular Magnetic Resonance. Circulation. 2007; 115(14):1876-84.

131. Telfer P, Coen PG, Christou S, Hadjigavriel M, Kolnakou A, Pangalou E, et al. Survival of medically treated thalassemia patients in Cyprus. Trends and risk factors over the period 1980-2004. Haematologica. 2006; 91(9):1187-92.

132. Telfer PT, Prestcott E, Holden S, Walker M, Hoffbrand AV, Wonke B. Hepatic iron concentration combined with long-term monitoring of serum ferritin to predict complications of iron overload in thalassaemia major. Br J Haematol. 2000; 110(4):971-7.

133. Telfer PT, Warburton F, Christou S, Hadjigavriel M, Sitarou M, Kolnagou A, et al. Improved survival in thalassemia major patients on switching from desferrioxamine to combined chelation therapy with desferrioxamine and deferiprone. Haematologica. 2009;

134. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Disease of the heart and Great Vessels. In: Boston, Mass; Little, Brown & Co; 1994. p. 253-6.

135. Tricta F, Dougherty G, Diav-Citrin O, Loebstein R, Atanackovic G, Koren G. Randomized trial of deferiprone (L1) and deferoxamine (DFO) in thalassemia major. Proceedings of the 6th International Conference on Thalassaemia and the Haemoglobinopathies; 1997 Apr 5-10; St. Paul's Bay, Malta. p. 230.

136. Tsironi M, Assimakopoulos G, Polonofi K, Rigaki K, Aessopos A. Effects of Combined Deferiprone and Deferoxamine Chelation Therapy on Iron Load Indices in β-Thalassemia. Hemoglobin. 2008; 32(1):29-34.

137. Tsironi M, Polonifi K, Deftereos S, Farmakis D, Andriopoulos P, Moyssakis I, et al. Transfusional hemosiderosis and combined chelation therapy in sickle thalassemia. Eur J Haematol. 2005; 75(4):355-8.

138. Unal S, Hazirolan T, Beton B, Karabulut E, & Gumruk F. The cardiac effects of desferoxamine deferiprone combination therapy and desferoxamine monotherapy in thalassemic patients. 2009;

139. Voskaridou E, Douskou M, Terpos E, Stamoulakatou A, Meletis J, Ourailidis A, et al. Deferiprone as an oral iron chelator in sickle cell disease. Ann Hematol. 2005; 84(7):434-40.

140. Waldmeier PC, Buchle AM, Steulet AF. Inhibition of catechol-*O*-methyltransferase (COMT) as well as tyrosine and tryptophan hydroxylase by the orally active iron chelator, 1,2-dimethyl-3-hydroxypyridin-4-one (L1, CP20), in rat brain *in vivo*. Biochem Pharmacol. 1993; 45(12):2417-24.

141. Wong A, Alder V, Robertson D, Papadimitriou J, Maserei J, Berdoukas V, et al. Liver iron depletion and toxicity of the iron chelator Deferiprone ($L_1$, CP20) in the guinea pig. Biometals. 1997; 10:247-56.

142. Wonke B, Wright C, Hoffbrand AV. Combined therapy with deferiprone and desferrioxamine. Br J Haematol. 1998; 103(2):361-4.

143. Wood JC. Magnetic resonance imaging measurement of iron overload. Curr Opin Hematol. 2007; 14(3):183-90.

144. Wood JC, Otto-Duessel M, Gonzalez I, Aguilar MI, Shimada H, Nick H, et al. Deferasirox and deferiprone remove cardiac iron in the iron-overloaded gerbil. Transl Res. 2006; 148(5):272-80.

145. Wood JC, Thompson AA, Paley C, Kang B, Giardina P, Harmatz P, et al. Deferasirox (Exjade®) monotherapy signicantly reduces cardiac iron burden in chronically transfused β thalassemia patients: an MRI T2* study. 50th ASH Annual Meeting; 2008 Aug 12; San Francisco, CA. 3882

146. Worwood M, Cragg SJ, Jacobs A, McLaren C, Ricketts C, Economidou J. Binding of serum ferritin to concanavalin A: patients with homozygous beta thalassaemia and transfusional iron overload. Br J Haematol. 1980; 46(3):409-16.

147. Yokel RA, Fredenburg AM, Meurer KA, Skinner TL. Influence of lipophilicity on the bioavailability and disposition of orally active 3-hydroxypyridin-4-one metal chelators. Drug Metab Dispos. 1995; 23(10):1178-80.

148. Zakery H, Mormomen SH, Taghikhani H, Abolghassemi H. The Safety and Efficacy of Deferiprone for the Treatment of Iron Overloaded in Subjects With Transfusion Dependent Thalassemia in Iran. Proceedings of the 11th International Conference on Oral Chelation in the Treatment of Thalassemia and Other Diseases; 2001 Mar 22-25; Catania, Italy. p. 151.

149. Zurlo MG, De Stefano P, Borgna-Pignatti C, Di Palma A, Piga A, Melevendi C, et al. Survival and causes of death in thalassaemia major. Lancet. 1989; 2(8653):27-30.

# APPENDICES

# A ApoPharma Clinical Studies

Note: Studies LA21-BE, LA28-CMP, and LA30-0307 present data related to Ferriprox™ (deferiprone) Oral Solution. This formulation of deferiprone is bioequivalent to the deferiprone tablet formulation; however, it has not been submitted for approval as part of NDA 21-825.

## 1. Study LA-01: Randomized trial of deferiprone (L1, Ferriprox™) and deferoxamine (DFO) in thalassemia major

**Study Design**

- Multicenter, open label, randomized, active control

**Study Arm(s)**

- Deferiprone (75 mg/kg/d)
- DFO (50 mg/kg; 4-7 days/week)

**Study Population(s) (Entered / Completed)**

- Deferiprone (35/27)
- DFO (36/30)

**Duration (Study Start / Study End)**

- 2 years

**Subject Diagnosis / Main Inclusion Criteria**

- Homozygous β thalassemia

**Primary Objective**

- To compare the relative effectiveness and safety of DFP and DFO therapy, as reflected by the ability of each chelator to achieve net negative iron balance, reduce tissue iron stores, and reduce body iron stores

**Major Findings**

There was no significant difference (p = 0.8426) in the change in liver iron concentration (LIC) (combined superconducting quantum interference device (SQUID) (preferentially over biopsy values) and biopsy analysis) from baseline (8.54 ±3.64 mg/g, n= 13 vs. 7.09 ±4.06 mg/g, n= 13) to Month 24 (8.90 ±2.83 mg/g, n= 13 vs. 7.78 ±4.68 mg/g, n= 13) between the deferiprone (DFP) group (0.36 ±4.87 mg/g, n= 13) and the DFO group (0.69±3.40 mg/g, n= 13). Similarly, the results in LIC from baseline to Month 36 were not significantly different from zero in both groups. There was no significant difference (p = 0.6235) in the change of LIC (SQUID alone analysis) between the DFP group (2.03±4.67 mg/g, n= 9) and the DFO group (1.04 ±3.31 mg/g, n= 8). There was no significant difference (p = 0.3573) in the change of LIC (biopsy alone analysis) between the DFP group (-0.86 ±2.71 mg/g, n= 4) and the DFO group (-3.14 ±3.28

mg/g, n= 3). Similarly, the results in LIC from baseline to Month 36 were not significantly different from zero in both groups.

For the per protocol population, the serum ferritin levels in DFO and DFP subjects increased from baseline (2190 ±1450 µg/L, n= 20 vs. 1975 ±1107 µg/L, n= 21) to Month 24 (2294 ±1251 µg/L, n= 20 vs. 2192 ±1092 µg/L, n=21). There was no significant difference in the change of serum ferritin (105 ± 1217 µg/L, n= 20 vs. 217 ± 920 µg/L, n= 21) between DFO and DFP subjects (p = 0.7408).

For the intent-to-treat population, the serum ferritin levels in DFO and DFP subjects increased from baseline (2010 ±1201 µg/L, n= 36 vs. 1885 ±1043 µg/L, n= 35) to Month 24 (2012 ±1265 µg/L, n= 36 vs. 2071 ±1006 µg/L, n=35). There was no significant difference in the change of serum ferritin (2 ± 1104 µg/L, n= 36 vs. 187 ± 840 µg/L, n= 35) between DFO and DFP subjects (p = 0.4313).

The change in urinary iron excretion from baseline to Month 24 was not different between DFO and DFP subjects (p = 0.9849).

From baseline to Month 12, the mean change in left ventricular ejection fraction (LVEF) at rest was 6.1 ± 10.6% (n= 21) in DFP subjects and 1.2 ± 6.8% (n= 20) in DFO subjects. Only the change in DFP subjects differed significantly from zero (p = 0.0155); however, the difference between the two treatment groups was not statistically significant (p = 0.0893). From baseline to Month 24, the mean change in LVEF at rest was 8.5 ± 10.4% (n= 13) in DFP subjects and 0.9 ± 9.7% (n= 10) in DFO subjects. Only the change in the DFP subjects differed significantly from zero (p = 0.0123), but the difference between the two treatment groups was not statistically significant (p = 0.0879).

Two DFP-treated subjects experienced agranulocytosis, as defined by an absolute neutrophil count (ANC) $<0.5\times10^9$/L. Both subjects recovered fully after discontinuing the drug and treatment with granulocyte colony-stimulating factor.

**Publications**

Olivieri NF, Brittenham GM, Armstrong SAM, *et al*. First prospective randomized trial of the iron chelators deferiprone (L1) and deferoxamine. [Abstract] Blood 86[10 (Suppl. 1)], 249a, 1995. (Olivieri NF *et al.* 1995a)

Olivieri NF. Randomized trial of deferiprone (L1) and deferoxamine (DFO) in thalassemia major. [Abstract No. 2593] Blood 88[10 (Suppl. 1)], 1996. (Olivieri NF. 1996)

Tricta F, Dougherty G, Diav-Citrin O, *et al*. Randomized trial of deferiprone (L1) and deferoxamine (DFO) in thalassemia major. [Abstract] Proceedings of the 6th International Conference on Thalassemia and the Hemaglobinopathies 230. 1997. (Tricta F *et al.* 1997)

## 2. Study LA01-PK: Deferiprone Steady-State Pharmacokinetics in Thalassemia Patients under Long Term Oral Therapy

**Study Design**

- Single center, open labeled, single dose, uncontrolled, pharmacokinetic study

**Study Arm(s)**

- Deferiprone (25 mg/kg)

**Study Population(s) (Entered / Completed)**

- Deferiprone (7/7)

**Duration (Study Start / Study End)**

- July 1995 – July 1995 (Single Dose)

**Subject Diagnosis / Main Inclusion Criteria**

- Thalassemia major, under chronic treatment for at least one year with deferiprone

**Primary Objective**

- To determine the pharmacokinetic parameters of deferiprone in thalassemia patients treated long term with the drug and to assess the *in-vivo* performance of APO-66 500 mg tablets (Ferriprox®)

**Major Findings**

Deferiprone is readily bioavailable from oral tablets. The systemic availability of deferiprone from APO-66 500 mg tablets in this study is very similar to the published bioavailability data.

The absorption of deferiprone from the oral tablets was delayed by food, but the extent is similar to that in the fasted state of the gastrointestinal (GI) tract.

Deferiprone is primarily metabolized by glucuronidation and the glucuronide conjugate is excreted almost exclusively in the urine.

**Publications**

None.

**3. Study LA-02/06: Clinical study report for 7 years of therapy with Ferriprox™ in patients participating in studies LA-02/06**

**Study Design**

- Multicenter, open label, uncontrolled

**Study Arm(s)**

- Deferiprone (75 mg/kg/d)

**Study Population(s) (Entered / Completed)**

- Deferiprone (187/70) (13 of completed on deferoxamine therapy)

**Duration (Study Start / Study End)**

- 1 year/7 years

**Subject Diagnosis / Main Inclusion Criteria**

- Iron loaded subjects with thalassemia who completed LA-02 and wished to continue treatment with Ferriprox under Protocol LA 06.

**Primary Objective**

- To monitor long-term safety and effectiveness of a fixed dose of deferiprone

**Major Findings**

In 162 subjects who completed 1 year of therapy during study LA-02, mean serum ferritin concentrations at baseline and at 12 months were similar (p = 0.26). Ferritin values at baseline and at termination for all DFP recipients, whether or not they completed the study (intent-to-treat analysis), were also similar (2,696 ± 1,877 µg/L and 2,633 ± 1,815 µg/L, respectively; p = 0.58).

Analyses of the efficacy up to 7 years were based on the intent-to-treat population. Overall, serum ferritin values increased by a small but statistically significant amount from baseline to the seventh year of DFP treatment (p = 0.0393). The slope of the overall trend of serum ferritin for the ITT population, including all subjects and using the last observation carried forward for missing values, was estimated to be 3.2 ± 1.8 µg/L/month, which was not significantly different from zero.

In total 20 of the 187 subjects developed a serious adverse event (SAE) of neutropenia or agranulocytosis during the trial. Eighteen of the 20 subjects who experienced neutropenia had not been splenectomized. The difference in incidence of neutropenia or agranulocytosis was significant between the two groups of subjects (p = 0.0034); 2.7% and 15.9% of splenectomized and nonsplenectomized subjects respectively.

**Publications**

Cohen A, Galanello R, Piga A, DiPalma A, Vullo G, Tricta F. Safety profile of the oral iron chelator deferiprone: A multicentre study. *Br J Hematol* 2000;108:305-12. (Cohen AR *et al.* 2000)

Cohen A, Galanello R, Piga A, De Sanctis V, Tricta F. Safety and effectiveness of long-term therapy with the oral iron chelator deferiprone: Blood 2003; 102: 1583-87. (Cohen AR *et al.* 2003)

**4. Study LA-03: The long-term efficacy and safety of deferiprone (L1, Ferriprox®) in patients with thalassemia (formerly Compassionate use of Deferiprone in Thalassemia patients) Protocol LA-03**

**Study Design**

- Single center, open label, uncontrolled

**Study Arm(s)**

- Deferiprone (75 mg/kg/d)

**Study Population(s) (Entered / Completed)**

- Deferiprone (25/11)

**Duration (Study Start / Study End)**

- 7 years

**Subject Diagnosis / Main Inclusion Criteria**

- Thalassemia major (n=23), with iron overload and/or unable or unwilling to take DFO. Thalassemia intermedia (n=2)

**Primary Objective**

- To assess the long-term efficacy and safety of DFP in subjects with thalassemia and iron overload

**Major Findings**

There was a significant decrease in mean serum ferritin levels over time. On average, there was a significant decrease of 1,868.0 ± 2,898.9 µg/L from baseline to the last observation of subjects ($p = 0.0044$). A majority (79%, 19/24) of subjects exhibited a decreasing trend of serum ferritin that was confirmed by the overall trend analysis (slope ±SE: -26.6 ±11.0 µg/L/month, $p = 0.0159$). There was a significant decrease (5.7 ±6.6 mg Fe/g dry weight (dw) liver, $p = 0.0014$) in mean LIC from baseline to the last observation of the subjects. There was a statistically significant decreasing trend in LIC levels (slope ±SE: -0.16 ±0.04 mg Fe/g dw liver per month, $p = 0.0004$).

Three subjects experienced adverse events (AEs) (polyarticular arthritis, severe nausea, and worsening of cardiac disease) that resulted in discontinuation of the drug and withdrawal from the study.

**Publications**

Olivieri NF, Brittenham GM, Matsui D, et al. Iron-chelation therapy with oral deferiprone in patients with thalassemia major. N Eng J Med 1995; 332(14): 918-922. (Olivieri NF *et al.* 1995b)

Olivieri NF, Brittenham GM, McLaren CE, Templeton DM, Cameron RG, McClelland RA, et al. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. N Engl J Med. 1998; 339(7):417-23. (Olivieri NF *et al.* 1998)

### 5. Study LA-04/LA-06B: Compassionate Use of Deferiprone in Patients with Iron Overload

**Study Design**

- Multicenter, open-label, ongoing, compassionate use program

**Study Arm(s)**

- Deferiprone (75 mg/kg/d)

**Study Population(s) (Entered / Completed)**

- Deferiprone (174/23)

**Duration (Study Start / Study End)**

- 1996 – Present (Ongoing)

**Subject Diagnosis / Main Inclusion Criteria**

- Thalassemia major (n = 67) or other chronic iron overload conditions who required iron chelation and unable or unwilling to take DFO; myelodysplasia (n = 11), sickle cell disease (n = 3), myelofibrosis (n = 4), other (n = 11)

**Primary Objective**

- To provide subjects with thalassemia or other chronic iron overload conditions unable or unwilling to take DFO with an alternative treatment to control iron overload

**Major Findings**

Deferiprone treatment was able to control the body iron load, as measured by serum ferritin concentration over time.

**Publications**

None.

**6. Study LA08-9701: Safety and Efficacy of Alternating Deferoxamine and Deferiprone Compared to Deferoxamine Alone in the Treatment of Iron Overload in Thalassemia Patients**

**Study Design**

- Multicenter; open-label, randomized, parallel, active controlled

**Study Arm(s)**

- Deferiprone (75 mg/kg/d; 5 days/week) + DFO (20-60 mg/kg; 2 days/week) *(Add-On Therapy)*
- DFO (20-60 mg/kg; 5-7 days/week)

**Study Population(s) (Entered / Completed)**

- Deferiprone + DFO (29/29)
- DFO (30/30)

**Duration (Study Start / Study End)**

- 12 months

**Subject Diagnosis / Main Inclusion Criteria**

- Transfusion-dependent thalassemia major and received previous therapy with DFO

**Primary Objective**

- Evaluate efficacy and safety of alternating use of DFP and DFO compared with current standard therapy with DFO in treatment of iron overload

**Major Findings**

Over 12 months, the alternating regimen (n = 29) and the standard regimen of subcutaneous DFO infusion (n = 30) showed comparable reductions in serum ferritin (-248 ±791 µg/L for the alternating doses of DFP and DFO arm vs. -349 ±573 µg/L for the DFO arm; p = 0.5802). Rates

of therapeutic compliance did not differ between the two regimens. Trend analyses for serum ferritin revealed no significant differences between the two arms (p = 0.9808), but overall, there was a significant negative trend of serum ferritin concentration over time (p = 0.0469). The rate of decline was estimated to be -24.8 ± 12.4 µg/L/month (mean ± SD). Reductions in LIC (-65 ±615 vs. -239 ±474 µg/g) were not statistically significantly different between the alternating doses of DFP and DFO and DFO monotherapy cohorts (p = 0.2263). Splenectomy status, baseline serum ferritin concentration, and study site had no significant effect on similarity of efficacy between the two treatment arms.

There was similar incidence of AEs in both groups, although gastrointestinal symptoms were more prominent in the alternating doses of DFP and DFO arm, and headache, back pain, and dysmenorrhea were more evident in the DFO only arm. No significant changes in laboratory values were found.

**Publications**

Galanello R, Kattamis A, Piga A, Fischer R, Leoni G, Ladis V, et al. A prospective randomized controlled trial on the safety and efficacy of alternating deferoxamine and deferiprone in the treatment of iron overload in patients with thalassemia. Haematologica. 2006. (Galanello R *et al.* 2006)

**7. Study LA10-9902: An open label, single crossover design study to determine the clastogenic potential of deferiprone (L1) and compare that to the clastogenic potential of Desferal® (deferoxamine) in iron-overloaded, transfusion dependent individuals with thalassemia**

**Study Design**

- Single center, open label, single treatment, active controlled, crossover design with no intervening drug-free period

**Study Arm(s)**

- Group 1
  - Cycle 1: Current Deferiprone Treatment
  - Cycle 2: Deferoxamine (20-60 mg/kg; 4-7 days/week)
  - Cycle 3: Deferiprone (75 mg/kg/d)
- Group 2
  - Cycle 1: Current Deferoxamine Treatment
  - Cycle 2: Deferiprone (75 mg/kg/d)
  - Cycle 3: Deferoxamine (20-60 mg/kg; 4-7 days/week)

**Study Population(s) (Entered / Completed)**

- Group 1: (10/10)
- Group 2: (10/10)

**Duration (Study Start / Study End)**

- September 1999 – September 2000 (≥20 days per cycle)

**Subject Diagnosis / Main Inclusion Criteria**

- Subjects with a diagnosis of thalassemia major who are regularly transfused with blood filtered by a blood bank, for white blood cells, receiving ongoing chelation therapy with deferoxamine or deferiprone for the past three months

**Primary Objective**

- To determine if there is a significant change in the frequency of chromosomal aberrations in circulating lymphocytes in thalassemia major subjects receiving deferoxamine therapy following a switch in therapy to deferiprone, and to compare that frequency in subjects switched from deferiprone to deferoxamine.
- To determine the frequency of chromosomal aberrations in circulating lymphocytes in thalassemia major subjects following long term therapy with deferiprone compared to those on long term deferoxamine therapy.

**Major Findings**

Measurements of chromosomal aberrations were made in 10 thalassaemia major patients treated long-term with deferiprone (at least 5 years) and compared with an equal number of patients matched for age, sex and iron overload, treated long-term with deferoxamine. Two blood samples were collected from each patient, 7 and 20 days after a transfusion episode, and the frequency of chromosomal aberrations (gaps, breaks and exchanges) in the patients' circulating lymphocytes analysed in both samples using standard cytogenetic staining techniques. The frequency of reciprocal translocations was also analysed using fluorescence in situ hybridization. Relatively low frequencies of cells with stable and unstable aberrations were seen at both sampling times in all patients, with no statistically significant differences between sexes.

Chromosomal aberrations were less frequent in patients treated long-term with deferiprone than in patients treated with deferoxamine, although the difference did not reach statistical significance. After the second blood sample had been collected, all patients had their iron chelation therapy switched to the other chelator. Patients treated long-term with deferiprone had their therapy switched to deferoxamine and patients treated long-term with deferoxamine had their therapy switched to deferiprone. After the switch, two further blood samples were collected 7 and 20 days after transfusion for each of the next two transfusion cycles in all patients. Analysis of the post-switch samples also revealed a slightly higher frequency of chromosomal aberrations during therapy with deferoxamine than with deferiprone at all time points. A small, but statistically significant, increase in cells with aberrations was observed at the first post-switch assessment in the group of patients whose therapy was switched from deferiprone to deferoxamine, whereas the switch from deferoxamine to deferiprone was associated with a decrease in the frequency of chromosomal aberrations.

The results of the study demonstrate that, in a clinical setting, deferiprone has no greater clastogenic activity than that of deferoxamine.

**Publications**

Marshall R, Tricta F, Galanello R, Leoni G, Kirkland D, Minto S, et al. Chromosomal aberration

frequencies in patients with thalassaemia major undergoing therapy with deferiprone and deferoxamine in a comparative crossover study. Mutagenesis. 2003; 18(5):457-63. (Marshall R *et al.* 2003)

### 8. Study LA-11: Efficacy and safety of deferiprone (L1) in β-Thalassemia/Hemoglobin E diseases patients in Thailand

**Study Design**

- Open label, treated with deferiprone alone, uncontrolled

**Study Arm(s)**

- Deferiprone (25-50 mg/kg/d)

**Study Population(s) (Entered / Completed)**

- Deferiprone (24/16) (treated for greater than 3 months)

**Duration (Study Start / Study End)**

- 2 years

**Subject Diagnosis / Main Inclusion Criteria**

- Non-transfusion dependent or irregular transfused subjects with β thalassemia/hemoglobin E disease

**Primary Objective**

- To study the efficacy and toxicity of DFP in subjects β thalassemia/Hb E diseases in Thailand

**Major Findings**

DFP significantly reduced body iron load. After a mean treatment period of 334 ± 179 days (range 5 to 536 days), mean serum ferritin in 20 subjects who had at least two assessments (before the start, and at the end of treatment) decreased from 3,287 ± 1,927 μg/L to 1,221 ± 1,667 μg/L (mean change of -2,066 μg/L; $p < 0.0001$). LIC, analyzed in 16 subjects treated with DFP for more than 1 year, declined from 20.1 ± 8.4 mg/g dw liver to 7.5 ± 7.0 mg/g dw liver, with a mean change of 12.6 mg/g dw liver ($p < 0.0001$).

No cases of agranulocytosis occurred. One subject died during the study period as a result of septicemia with severe diarrhea after food poisoning. The investigator considered the death was not related to DFP.

**Publications**

None.

### 9. Study LA12-9907: Retrospective Assessment of Heart Failure and Survival During Iron Chelation with Deferiprone or Deferoxamine in Subjects with Transfusion-Dependent β-Thalassemia

**Study Design**

- Open-label, parallel, longitudinal, active controlled, single center

**Study Arm(s)**

- Deferiprone (75 mg/kg/d)
- DFO (20-60 mg/kg – 4-7 days/week)

**Study Population(s) (Entered / Completed)**

- Deferiprone (54/NA)
- DFO (75/NA)

**Duration (Study Start / Study End)**

- 5 years

**Subject Diagnosis / Main Inclusion Criteria**

- Transfusion dependent thalassemia major; ≥5 years old at time of start of review period

**Primary Objective**

- Evaluate incidence and progression of cardiac disease and survival in subjects treated with Ferriprox compared with DFO over the same period of time

**Major Findings**

At the end of the study, 7 subjects (13.0%) in the DFP group had cardiac disease (New York Heart Association (NYHA) Class I, II, III, or IV) compared with 22 subjects (29.3%) in the DFO group. Newly diagnosed cardiac disease was observed in 13 (20.6%) of the 63 DFO-treated subjects who were initially cardiac-disease free at the first study assessment, and in two (3.7%) of the 47 DFP-treated subjects who were cardiac disease free at the first study assessment ($p = 0.0133$). Overall, worsening of preexisting cardiac dysfunction or newly diagnosed cardiac disease was observed in two subjects in the DFP group and in 15 subjects (20%) in the DFO group ($p = 0.0069$). Improvement in NYHA class was observed in three of seven (43%) DFP-treated subjects compared with three of twelve (25%) DFO-treated subjects with cardiac disease at first assessment; the difference, however, was not statistically significant.

Subjects in the DFP group had significantly longer cardiac disease-free survival compared with subjects in the DFO group. Kaplan-Meier analysis of cardiac disease-free survival over a 5-year period was significantly more favorable in the DFP group ($p = 0.003$). By the end of the study, the two treatment groups did not show significant differences in mean serum ferritin concentrations ($p = 0.994$).

Four subjects, all treated with DFO, died during the study period; three had cardiac disease at first assessment, and death was attributed to irreversible progression of cardiac dysfunction. The fourth subject died within a few hours of being admitted to a provincial hospital for acute abdominal pain. No cause of death for this subject was provided to the sponsor.

Mean compliance was 89 ± 7% ($n = 53$) with DFP, and 85 ± 11% ($n = 73$) with DFO. Therefore, less favorable clinical outcomes in the DFO-treated group cannot be attributed to lack of compliance.

**Publications**

Piga A, Gaglioti C, Fogliacco E, Tricta F. Comparative effects of deferiprone and deferoxamine

on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. Hematologica 2003; 88:489-96. (Piga A *et al.* 2003)

### 10. Study LA14-9907: Pharmacokinetic Profile of Deferiprone in Subjects with Thalassemia Major and Cirrhosis

**Study Design**

- Open-label

**Study Arm(s)**

- Deferiprone (25 mg/kg)

**Study Population(s) (Entered / Completed)**

- Deferiprone (6/6)

**Duration (Study Start / Study End)**

- 8 hours (Single Dose)

**Subject Diagnosis / Main Inclusion Criteria**

- Patients with thalassemia major and cirrhosis

**Primary Objective**

- To obtain information on the absorption, metabolism and urinary excretion of deferiprone in at least 4 subjects with transfusion-dependent thalassemia and liver cirrhosis.

**Major Findings**

The results of LA14-9907 are consistent with the pharmacokinetic characteristics observed in a previous study for deferiprone, performed with thalassemia patients with no clear evidence of cirrhosis, suggesting that there is no decreased biotransformation of deferiprone in subjects with cirrhosis.

One subject (CF01) with a history of diabetes mellitus experienced an AE (hyperglycemia) before administration of DFP. The episode was treated with insulin and study drug was administered following resolution of the hyperglycemia.

Other AEs or SAEs were not reported in this study.

**Publications**

None.

### 11. Study LA15-0002: Safety and Efficacy of Ferriprox® for the Treatment of Iron Overload in Subjects with Transfusion-Dependent Thalassemia in Iran

**Study Design**

- Single center, open-label, uncontrolled

**Study Arm(s)**

- Deferiprone (75 mg/kg/d)

**Study Population(s) (Entered / Completed)**

- Deferiprone (29/26)

**Duration (Study Start / Study End)**

- 3 months

**Subject Diagnosis / Main Inclusion Criteria**

- Transfusion-dependent β thalassemia; Previously treated with DFO (50 mg/kg/d, on average 5 d/wk) for a minimum of 7 years

**Primary Objective**

- To monitor the efficacy and safety of DFP for the treatment of iron overload in subjects with transfusion dependent thalassemia, as reflected by:

  1) serum ferritin concentrations;

  2) the occurrence of AEs

**Major Findings**

Before administration of DFP, all subjects were treated with DFO (50 mg/kg/d, on average 5 d/wk) for at least 7 years. DFP reduced serum ferritin levels in all subjects. Data revealed a statistically significant decline in baseline serum ferritin from 3,364 ± 900 μg/L at baseline to 1,271 ± 302 μg/L after 3 months of treatment with DFP ($p = 0.0001$).

One subject experienced mild neutropenia (ANC = 1.45 × 109/L) and an unconfirmed neutropenia was detected in another subject. No unexpected adverse drug reactions (ADRs) were observed in this study.

**Publications**

Zakery H, Mirmomen SH, Taghikhani H, Abolghassemi H. The safety and efficacy of deferiprone for the treatment of iron overloaded in subjects with transfusion dependent thalassemia in Iran. Proceedings of the 11th International Conference on Oral Chelation in the Treatment of Thalassemia and other Diseases; 2001 Mar 22-25. Catania, Italy 2001. p. 151. (Zakery H *et al.* 2001)

### 12. Study LA16-0102: Randomized Trial Comparing the Relative Efficacy of Deferiprone to that of Deferoxamine in Removing Excess Cardiac Iron in Thalassemia Major Patients

**Study Design**

- Multicenter, Randomized, Open Label, Active Control

**Study Arm(s)**

- Deferiprone (100 mg/kg/d)
- DFO (50 mg/kg - 5-7 days/week)

**Study Population(s) (Entered / Completed)**

- Deferiprone (29/27)

- DFO (32/29)

**Duration (Study Start / Study End)**

- 12 months

**Subject Diagnosis / Main Inclusion Criteria**

- Thalassemia Major

**Primary Objective**

- To determine whether orally administered deferiprone exhibits superior efficacy in removing excess iron from the heart compared with that of standard subcutaneous infusions of DFO, as reflected by MRI T2* assessments of the heart in subjects treated with either chelator

**Major Findings**

This study showed that DFP is superior to DFO in decreasing cardiac iron overload, as measured by magnetic resonance imaging (MRI) T2*. At baseline, the difference of the geometric means (the anti-logs of the means of the log MRI T2* data) of the DFP (13.0 ms) and DFO (13.3 ms) treatment groups was not significant ($p = 0.77$). The geometric mean increased to 15.4 ms after 6 months, and to 16.5 ms after 12 months of treatment with DFP, with a significantly greater percentage increase from baseline compared to subjects treated with DFO (18% vs. 9%, $p = 0.0404$ [6 months]; 27% vs. 13%, $p = 0.0228$ [12 months]).

This study also showed greater beneficial effect of DFP (vs. DFO) on cardiac function, as measured by absolute changes from baseline to 12 months for LVEF by cardiac magnetic resonance (CMR) (DFP: 3.07% ± 3.58%, n = 29; DFO: 0.32% ± 3.38%, n = 31; $p = 0.0034$), for LVEF by echocardiography (ECHO) (DFP: 2.50% ± 6.04%, n = 28; DFO: -0.56% ± 4.90%, n = 31; $p = 0.0358$), and % change from baseline to 12 months for left ventricular shortening fraction (LVSF) by ECHO (DFP: 5.82 ± 15.62, n = 29; DFO: -2.64 ± 10.65; n = 32; $p = 0.0180$).

Comparable reductions in LIC and serum ferritin values were recorded in DFP and DFO treatment groups. After 12 months of treatment, the LIC of subjects treated with DFP and DFO showed mean reductions of 0.93 mg Fe/g dw liver and 1.54 mg Fe/g dw liver, respectively. The difference was not statistically significant ($p = 0.3961$). For serum ferritin, there was a decrease from baseline to 12 months in both the DFP and DFO groups (-181.0 µg/L vs. -466.1 µg/L, respectively). Again, the difference was not significant between the two groups ($p = 0.1598$). Therapeutic compliance was comparable between the DFP and DFO treatment groups (93.7% vs. 93.2%), indicating that differences in efficacy between the two groups is not attributable to differences in treatment compliance.

No subjects experienced agranulocytosis. There was one episode of neutropenia of mild severity possibly related to DFP, which resolved without discontinuation of the therapy. The majority of AEs and ADRs were mild to moderate in intensity.

**Publications**

Pennell DJ, Berdoukas V, Karagiorga M, Ladis V, Piga A, Aessopos A, et al. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. Blood. 2006; 107(9):3738-44. (Pennell DJ *et al.* 2006)

## 13. Study LA17-9701: The safety and effectiveness of deferiprone in a large-scale, 3-year study in Italian patients

**Study Design**

- Multicenter, open-label, uncontrolled, active drug surveillance program

**Study Arm(s)**

- Deferiprone (75 mg/kg/d)

**Study Population(s) (Entered / Completed)**

- Deferiprone (532/NA) (151 completed 3 years of therapy with DFP with no missing data at evaluated time points)

**Duration (Study Start / Study End)**

- 3 years

**Subject Diagnosis / Main Inclusion Criteria**

- Transfusion-dependent thalassemia major and serious toxicity with DFO therapy

**Primary Objective**

- To provide a program to control the distribution of DFP and to evaluate the long-term safety and efficacy of DFP use in subjects with thalassemia major

**Major Findings**

DFP (75 mg/kg/d) effectively reduced serum ferritin concentrations. Declines from baseline levels reached statistical significance after 36 months of therapy ($p = 0.01$). In particular, declines were statistically significant at all time points ($p < 0.001$) for the subgroup with ferritin levels greater than 4,000 μg/L at start of treatment, while the subgroup with baseline ferritin levels of between 2,000 and 4,000 μg/L showed a significant decrease ($p < 0.001$) after 24 months of treatment. Analysis of changes in circulating ferritin by means of shift tables showed that only 20% of subjects passed to a more severe class of ferritin level (Class I: < 2000 μg/L; Class II: ≤ 2000 μg/L to < 4000 μg/L; Class III: > 4000 μg/L) at 12 months.

The most serious ADR was agranulocytosis, which was observed in five (0.9%) subjects. All five episodes resolved upon interruption of therapy with DFP.

**Publications**

Ceci et al. The safety and effectiveness of deferiprone in a large- scale, 3 year study in Italian patients. British Journal of Haematology, 2002, 118, 330-336. (Ceci A *et al.* 2002).

## 14. LA20-BA: An Open Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution Under Fasting and Fed Conditions

**Study Design**

- Open label, single-dose, randomized, three-way crossover bioavailability study

**Study Arms**

- Group 1
  - Period 1: Deferiprone (1500mg) (Tablet Fasting)
  - Period 2: Deferiprone (1500mg) (Tablet Non-Fasting)
  - Period 3: Deferiprone (1500mg) (Solution Fasting)

**Study Population(s) (Entered / Completed)**

- Group 1 (15/13) (Two subjects withdrew for personal reasons following Period 2)

**Duration (Study Start / Study End)**

- 7.5 days (Single-Dose)

**Subject Diagnosis / Main Inclusion Criteria**

- All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who satisfied the screening evaluation, completed the baseline assessment and met all inclusion/exclusion criteria. The main inclusion criteria are:

  1. 18 to 55 years of age, healthy male or female non-smoking volunteers.

  2. Has a body weight of at least 50 kg.

  3. Has a Body Mass Index (BMI) between 21.0 and 28.0.

**Primary Objective**

- 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.

**Major Findings**

The pharmacokinetic results for deferiprone and deferiprone glucuronide demonstrated that the half-life results were comparable when the drug was administered under fasting or under fed conditions.

The apparent total body clearance of the parent after oral administration of deferiprone (CL/F) and mean residence time (MRT) slightly increased for deferiprone by approximately 14 and 17%, respectively, when the drug was administered with food.

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 mean 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 ln-transformed 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.

In addition, 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.

The reported adverse events were consistent with the known adverse event profile of deferiprone.

**Publications**

None.

**15. LA21-BE: Randomized, open-label, comparative, two-way crossover bioavailability study of deferiprone oral solution and Ferriprox® (deferiprone) tablets under fasting conditions**

**Study Design**

- Open label, single-dose, randomized, two-way crossover, comparative, BA study

**Study Arms**

- Group 1
  - Period 1: Deferiprone (1500mg) (Oral Solution)
  - Period 2: Deferiprone (1500mg) (Tablet)

**Study Population(s) (Entered / Completed)**

- Group 1 (42)

**Duration (Study Start / Study End)**

- 8 days (Single-Dose)

**Subject Diagnosis / Main Inclusion Criteria**

- Healthy subjects

**Primary Objective**

- Relative bioavailability of DFP oral solution and DFP tablet under fasting conditions

**Major Findings**

Based on the results of LA21-BE, deferiprone oral solution and Ferriprox® (deferiprone) tablets are bioequivalent under fasting conditions.

Fifteen healthy volunteers (36%, 42 subjects in total [mean weight: 74.1 kg (range: 52.2 to 91.9 kg)]) presented with 41 treatment-emergent AEs. Ten subjects (24%) had 26 AEs after dosing with the 1,500-mg DFP solution and 6 subjects (14%) had 15 AEs after receiving 1,500 mg of DFP tablets. Of 26 AEs in subjects receiving DFP solution, 22 (85%) were mild, and 4 (15%) were moderate. All AEs in subjects receiving DFP tablets were mild, and 12 (80%) AEs were judged related to study treatment. In subjects dosed with DFP solution, 20 (77%) AEs

were considered related to study treatment. The most frequently reported AEs (in more than 10% of subjects) were fatigue (19%), feeling cold (12%), and headache (12%).

**Publications**

None.

### 16. Borgna-Pignatti et al., 2006: Cardiac morbidity and mortality in deferoxamine- or deferiprone treated patients with thalassemia major

**Study Design**

- Retrospective, natural history

**Study Arms**

- Deferiprone (75 mg/kg/d)
- DFO (30-50 mg/kg – 5-6 days/week)

**Study Population(s) (Entered / Completed)**

- Deferiprone (157/NA)
- DFO (379/NA)

**Duration (Study Start / Study End)**

- Retrospective data collection over 8 year duration

**Subject Diagnosis / Main Inclusion Criteria**

- All subjects, treated for thalassemia major at the seven centers participating in this study, born between 1970 and 1993, who had their last follow-up between 31 JAN 1995 and 31 DEC 2003

**Primary Objective**

- To compare the occurrence of cardiac disease in subjects treated only with DFO to those whose therapy was switched to DFP during the period of observation, from 31JAN 1995 to 31 DEC 2003

**Major Findings**

Fifty-two cardiac events, including 15 cardiac deaths, were recorded in 14.5% of subjects treated only with DFO. By contrast, during the 9-year period of this study, no subject treated with DFP developed cardiac disease. To estimate the significance of the difference in occurrence of cardiac disease between the two treatment groups, the authors artificially created one cardiac event in a DFP patient. With the addition of this artificial case, the hazard ratio for DFP compared with DFO was 0.09 (CI 0.013, 0.66; p = 0.017).

Six subjects given DFP for periods ranging from 3 months to 5 years had cardiac events after completion of DFP treatment. One subject had an event 20 months after stopping DFP, and the remaining five had cardiac events more than 3 years after stopping DFP.

Fifteen patients, all on DFO, died of iron-induced cardiac disease during the review period. Cox regression analysis of total deaths did not show a significant difference in deaths between the

two therapy groups (p = 0.19), which was not unanticipated, given the relatively low number of events. When the noncardiac deaths (i.e., the two such deaths in patients on DFP) were included as failure events in addition to the cardiac events, Cox regression analysis provided an estimated hazard ratio of a cardiac event or death of 0.078 (CI 0.010, 0.56; p = 0.011) on DFP relative to DFO.

**Publications**

Borgna-Pignatti et al. Cardiac morbidity and mortality in deferoxamine –or deferiprone treated patients with thalassemia major. Blood, 2006,107(9):3733-3737. (Borgna-Pignatti C *et al.* 2006)

### 17. LA28-CMP: The compassionate use/named patient program of Ferriprox oral solution in iron-overloaded pediatric patients with transfusion-dependent anemias

**Study Design**

- Multicenter, open-label, single therapy, uncontrolled, compassionate use/named patient program

**Study Arms**

- Deferiprone (75-100 mg/kg/d)

**Study Population(s) (Entered / Completed)**

- Deferiprone (83/60); 75 subjects previously enrolled in LA30-0307

**Duration (Study Start / Study End)**

- February 2007 – March 2010

**Subject Diagnosis / Main Inclusion Criteria**

- Pediatric patients who is ≤ 16 years of age
- Confirmed diagnosis of transfusion-dependent anemia with iron overload requiring chelation therapy
- Iron overload as assessed by serum ferritin level and, if available, by hepatic iron concentration and/or cardiac MRI T2* value
- Patients for whom deferoxamine is contraindicated or inadequate
- Patients for whom Ferriprox™ tablet is inadequate
- Patients who do not meet the eligibility criteria for participation in any clinical trial of Ferriprox™

**Primary Objective**

- The primary objective of this program is to provide treatment with Ferriprox™ oral solution to iron overloaded pediatric patients with transfusion-dependent anemia for whom deferoxamine is contraindicated or inadequate.

- The secondary objective of this program is to assess the safety and efficacy of Ferriprox™ oral solution for the treatment of iron overload in pediatric patients with transfusion-dependent anemia.

**Major Findings**

Interim analysis has shown that Ferriprox™ (deferiprone) Oral Solution is well tolerated, safe, and effective in lowering serum ferritin in young children.

**Publications**

None.

**18. LA30-0307: A 24-week, open label, uncontrolled study of the safety and efficacy of Ferriprox™ (deferiprone) oral solution in iron-overloaded paediatric subjects with transfusion-dependent anemia**

**Study Design**

- Multi-center, open label, single treatment, uncontrolled study

**Study Arms**

- Deferiprone (up to 100 mg/kg/d)

**Study Population(s) (Entered / Completed)**

- Deferiprone (100/95)

**Duration (Study Start / Study End)**

- 24 weeks

**Subject Diagnosis / Main Inclusion Criteria**

- Subjects who were ≤ 10 years of age
- Subjects who had a confirmed diagnosis of transfusion-dependent anemia, other than Blackfan Diamond anemia, and had chronic iron overload requiring chelation therapy
- Subjects who were in a chronic transfusion program, and who had received at least 8 red blood cell transfusions per year for a minimum of one year
- Subjects who were iron overloaded as assessed by serum ferritin concentration greater than 1000 μg/L

**Primary Objective**

- The primary objective was to assess the safety of Ferriprox oral solution for the treatment of iron overload in paediatric subjects with transfusion-dependent anemia.
- The secondary objective was to assess the efficacy of Ferriprox oral solution in reducing iron overload in paediatric subjects with transfusion-dependent anemia.

**Major Findings**

This study demonstrated that the AE profile was consistent with what has been previously observed with the tablet formulation of deferiprone; this includes the incidence of neutropenia

(6%) and agranulocytosis (2%). There was a lower incidence of gastrointestinal adverse reactions than that previously observed with the tablet formulation in older subjects (>6 years of age; nausea 1% versus 17%; abdominal pain 6% versus 13%; vomiting 6% versus 12%; arthralgia 4% versus 11%). Overall, the treatment with Ferriprox oral solution for 24 weeks was effective in reducing serum ferritin concentrations in transfusion-dependent thalassemia subjects aged ≤ 10 years. The ferritin level at Week 24 had decreased more in subjects with baseline concentrations > 2500 µg/L than in those with baseline concentrations ≤2500 µg/L; however, this difference can be attributed to an effect of study design-mandated dosing. Splenectomy status at baseline did not significantly affect the change in serum ferritin levels over time.

**Publications**

The Safety, Tolerability, and Efficacy of a Liquid Formulation of Deferiprone in Young Children with Transfusional Iron Overload. El-Alfy M., Sari TT, Chan L, Tricta F., El-Beshlawy A. (El-Alfy M *et al.* 2010)

### 19. LA36-0310: Analysis of Data from Clinical Studies of Ferriprox to Evaluate its Efficacy in Patients with Iron Overload for Whom Previous Chelation Therapy Has Been Inadequate

**Study Design**

- Re-analysis of data from clinical studies of Ferriprox based on historical reference performance criteria in the form of using patient as their own control.

**Study Arms**

- N/A

**Study Population(s) (Entered / Completed)**

- Total: 747
- Serum ferritin: 264
- LIC: 117
- MRI T2*: 39

**Duration (Study Start / Study End)**

- 1 year

**Subject Diagnosis / Main Inclusion Criteria**

- Receive standard chelation; prior to being treated with Ferriprox, and SF >2500µg/L or MRI T2* <20ms or LIC >7mg/g dw

**Primary Objective**

- To evaluate the efficacy of deferiprone in patients who had previously failed therapy with other iron chelators

**Major Findings**

- For each of the 3 efficacy measures (SF, LIC and MRI T2*), the lower limit of the 95% confidence interval for the percentage of patients with significant improvement was greater than the pre-defined treatment success criterion of 20% (SF: 45%, 58%;

LIC: 32%, 51%; MRI T2*: 45%, 77%). Long-term effectiveness of Ferriprox (iron overload treatment) was supported.

**Publications**

None.

# B.1 Effect of Add-On Deferiprone Therapy on Serum Ferritin Reported in Literature

| Reference | Duration | Chelator | N | Serum Ferritin (µg/l) mean ± SD | | |
|---|---|---|---|---|---|---|
| | | | | Initial | Final | P |
| (Wonke B *et al.* 1998) | 10.2 | DFP 88-110 mg/kg/d<br>DFO 4g/48h/wk;<br>2g/24h 5d/wk;<br>3g/24h 6d/wk | 5 | 7500 | 2438.8 | 0.0791 |
| (Alymara V *et al.* 2004) | 13.5 | DFP 60 mg/kg 6d/wk<br>DFO 40-50mg/kg 4-6d/wk | 25 | 2637±1291 | 1580±1023 | 0.002 |
| (Origa R *et al.* 2005) | 12-57 | DFP 70-80 mg/kg/d<br>DFO 40-50mg/kg 5-6d/wk | 64 | 5243±2345 | 3439±2426 | <0.001 |
| (Daar S & Pathare. 2006) | 60-48 | DFP 75 mg/kg/d<br>DFO 40mg/kg/d 4-5d/wk | 55 | 3088±1299 | 2051±935 | <0.001 |
| (Tanner MA *et al.* 2007) | 12 | DFP 75 mg/kg/d<br>DFO 34.9mg/kg 5d/wk | 32 | 1574 | 598 | <0.001 |
| (Tsironi M *et al.* 2008) | 18 | DFP 70-80 mg/kg/d<br>DFO 35 mg/kg 5d/wk | 5 | 2654.8±1583.7 | 289.4±87.9 | <0.026 |
| (Farmaki K *et al.* 2009) | 60-84 | DFP 70-100 mg/kg/d<br>DFO 20-60 mg/kg/d | 52 | 3421.6±882.0 | 87±25 | <0.001 |
| (Ricchi P *et al.* 2010) | 2.7-96 | DFP 75 mg/kg/d<br>DFO 25-35mg/kg 5d/wk | 36 | 2592±1701 | 899±833 | <0.001 |
| | | DFP 50 mg/kg/d<br>DFO 25-35mg/kg 5d/wk | | | | |
| | | DFP 75 mg/kg/d<br>DFO 25-35mg/kg 3d/wk | | | | |
| | | DFP 50 mg/kg/d<br>DFO 25-35mg/kg 3d/wk | | | | |
| (Cassel DL *et al.* 1983) | 12-24 | DFP 75-100 mg/kg/d<br>DFX 20-25 mg/kg/d | 15 | 581±346 | 103±60 | 0.0001 |

# B.2 Effect of Add-On Deferiprone Therapy on Myocardial T2* and LVEF Reported in Literature

| Reference | Duration | Chelator | N | Myocardial T2* (ms) | | | LVEF (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Initial | Final | P | Initial | Final | P |
| (Tanner MA *et al.* 2007) | 12 | DFP 75 mg/kg/d<br>DFO 34.9 mg/kg 5d/wk | 32 | 11.7 | 17.7 | <0.001 | 65.8 ± 6.2 | 68.4 ± 4.7 | 0.05 |
| (Tsironi M *et al.* 2008) | 18 | DFP 70-80 mg/kg/d<br>DFO 35 mg/kg 5d/wk | 5 | 20.50±12.85 | 23.66±10.45 | <0.05 | 63.92±13.36 | 71.89±4.77 | |
| (Unal S *et al.* 2009) | 22.2±7.8 | DFP 20-25 mg/kg/dose<br>DFO 30-40 mg/kg 3-5d/wk | 26 | 8.8±4.1 | 12.8±7.3 | <0.001 | 48.7±9.2 | 56.6±8.6 | 0.001 |
| (Farmaki K *et al.* 2009) | 60-84 | DFP 75-100 mg/kg/d<br>DFP 20-60 mg/kg/d | 52 | 13.8±9.8 | 35.5±8.1 | <0.001 | | | |
| (Ricchi P *et al.* 2010) | 2.7-96 | DFP 75 mg/kg/d<br>DFO 25-35 mg/kg 5d/wk | 36 | 18.9±13.4 | 22.2±12.5 | | 55.7±8.8 | 58.2±9.25 | |
| | | DFP 50 mg/kg/d<br>DFO 25-35 mg/kg 5d/wk | | | | | | | |
| | | DFP 75 mg/kg/d<br>DFO 25-35 mg/kg 3d/wk | | | | | | | |
| | | DFP 50 mg/kg/d<br>DFO 25-35 mg/kg 3d/wk | | | | | | | |
| (Farmaki K *et al.* 2011) | 12-24 | DFP 75-100 mg/kg/d<br>DFX 20-25 mg/kg/d | 15 | 34.1±5.8 | 36.9±5.6 | 0.0381 | | | |

## B.3 Effect of Add-On Deferiprone Therapy on LIC Reported in Literature

| Reference | Duration | Chelator | N | Liver T2* (ms) | | | LIC (mg/g dw) mean ± SD | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Initial | Final | P | Initial | Final | P |
| (Tanner MA *et al.* 2007) | 12 | DFP 75 mg/kg/d<br>DFO 34.9mg/kg 5d/wk | 32 | 4.9 | 10.7 | <0.001 | | | |
| (Tsironi M *et al.* 2008) | 28 | DFP 70-80 mg/kg/d<br>DFO 35mg/kg 5d/wk | 5 | 2.78±1.67 | 9.17±8.89 | | | | |
| (Farmaki K *et al.* 2009) | 60-84 | DFP 70-100 mg/kg/d<br>DFP 20-60 mg/kg/d | 52 | 1.5±8.2 | 34.4±5.4 | <0.001 | 15.7±11.1 | 0.9±0.2 | <0.001 |
| (Ricchi P *et al.* 2010) | 2.7-96 | DFP 75 mg/kg/d<br>DFO 25-35mg/kg 5d/wk | 36 | | | | 7.4±3.2 | 3.3±1.6 | <0.001 |
| | | DFP 50 mg/kg/d<br>DFO 25-35mg/kg 5d/wk | | | | | | | |
| | | DFP 75 mg/kg/d<br>DFO 25-35mg/kg 3d/wk | | | | | | | |
| | | DFP 50 mg/kg/dDFO 25-35mg/kg 3d/wk | | | | | | | |
| (Farmaki K *et al.* 2011) | 12-24 | DFP 75-100 mg/kg/d<br>DFX 20-25 mg/kg/d | 15 | 18.6±8.9 | 30.5±5.9 | 0.0012 | 1.6±1.1 | 1.0±0.2 | 0.0019 |

# C.1 Controlled Clinical Studies from Literature

| Reference | N | Primary Disease | Duration (Months) | Chelator Regimen (mg/kg/d) | Serum Ferritin (mean ± SD (µg/L)) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Initial | Final | P value | |
| | | | | | | | Difference from Baseline | Difference between Groups |
| (Maggio A *et al.* 2002) | DFP: 71 | TM | 12 | 75 DFP | 2283 ± 754 | 2061 ± 853 | <0.05 | not available |
| | DFO: 73 | | | 50 DFO | 2019 ±678 | 1787 ± 893 | <0.05 | |
| (Fischer R *et al.* 2003) | DFP: 54 | TM | 48.5 ± 3.3 | 75 DFP | 1897 ± 885 | 2519 ± 2582 | not available | not available |
| | DFO: 51 | | 23.0 ± 8.3 | 34.2 ± 4.6 DFO | 1422 ± 795 | 1631 ± 951 | not available | |
| (D'Angelo E *et al.* 2004)3) | DFP: 6 | TM | 21 | 75 DFP | 3083 ± 505 | 1248 ± 286 | <0.01 | not available |
| | DFP+DFO: 7 | | 16.28 | 75 DFP 40-50 DFO | 2864 ± 326 | 1,475 ± 92 | <0.01 | |
| (Chan JC *et al.* 2006) | DFP: 16 | Hb H disease | 18 | 50 increased to 75 DFP | 1,492.3 ± 901.4 | 519.4 ± 405.4 | 0.0008 | not available |
| | Control: 16 | | | not available | 482.6 ± 225.8 | 525.4 ± 260.7 | 0.6230 | |
| (Maggio A *et al.* 2009b) | DFP:108 | TM | 60 | 75 7d/wk DFP | 1868 ± 845 | 1588 ± 1217 | not available | 0.805 |
| | DFP/DFO:105 | | | 75 4d/wk DFP 50 3d/wk DFO | 1727 ± 669 | 1369 ± 816 | not available | |

# C.2 Uncontrolled Clinical Studies from Literature

| Reference | N | Primary Disease | Duration (Months) | Chelator Regimen (mg/kg/d) | Serum Ferritin (mean ± SD (µg/L)) | | |
|---|---|---|---|---|---|---|---|
| | | | | | Initial | Final | P value |
| (Balveer K *et al.* 2000) | 3 | TM | 12 | 75 - 80 | 8109 ± 4822 | 2205 ± 1724 | 0.07 |
| (Del Vecchio GC *et al.* 2000) | 9 | TM | 18 | 75 | 3180 ± 1570 | 3260 ± 1310 | N/A |
| (Kolnagou A & Kontoghiorghes. 2010) | 8 | TM | 21.3 | 80-100 | 1085 | 1737 | N/A |
| (Sajid R *et al.* 2009) | 87 | TM | 14 | 75 | 4656 ± 2052.5 | 4139 ± 1710.4 | <0.001 |

# D Summary of published literature of interest

The results of the Borgna-Pignatti study and of Study LA12-9907 are consistent with those of the published literature on the assessment of survival in patients with thalassemia treated with deferiprone or DFO. The most relevant are briefly addressed below:

1. Ceci et al. evaluated risk factors for death in patients with transfusion-dependent thalassemia treated in 31 Italian centers in the period during which deferiprone became available in Italy through an Italian Ministry of Health Active Drug Surveillance Program and during the first years that deferiprone became commercially available. Inclusion of deferiprone in patients' therapeutic regimens was associated with a 3-fold reduction in the risk of death (Ceci A *et al.* 2006). The 31 centers that participated in Ceci's study, and the patients reported by her were different from those reported by Borgna-Pignatti, demonstrating a consistent effect on survival across different samples of Italy's thalassemia population.

2. Telfer et al. (2006) also documented enhanced survival in thalassemia subjects after the introduction of deferiprone in Europe. In that study, most patients employed a chelation regimen that added deferiprone to DFO. This regimen was introduced in 1999 due to an increasing number of cardiac deaths in DFO-treated subjects. Their study addressed survival of 539 β-thalassemia subjects in Cyprus from 1980 to 2004 and showed a significant trend of increasing cardiac deaths between 1980 and 2000 ($p<0.001$) and a decline after 2000 ($p = 0.06$), the first year of introduction of therapy with deferiprone in the country. No cardiac deaths were observed in the subjects who switched to DFO + deferiprone combination chelation therapy (0 deaths per 1000 person-years follow-up, 95% confidence interval: 0 - 8.2). These authors concluded that enhanced survival may be attributed, at least in part, to the introduction of a deferiprone and DFO combination treatment (Telfer P *et al.* 2006).

3. Subsequently, Telfer et al. (2009) also published the results of two additional years of follow up of the patients enrolled in the study above. Sixty-five patients died between 1980 and 2006. Thirty-two (49% of deaths) were from cardiac causes. There was only one death in the group of patients for whom deferiprone was added to deferoxamine. This death was due to E. coli sepsis and was not associated with neutropenia or agranulocytosis. Overall, the hazard ratio of 0.14 equated to 7.4 fold improved survival for each year on therapy with deferiprone. For the birth cohort of 284 patients born after 1st January 1974, deferiprone treatment was the only independent factor significantly associated with survival. For cardiac deaths, the effect of adding deferiprone on the hazard ratio could not be calculated since there were no events in this group of patients. Making an arbitrary assumption that the patient with the median duration of deferiprone therapy had in fact died of cardiac disease, deferiprone is associated with a 4-fold increased chance of survival from cardiac death (Telfer PT *et al.* 2009).

4. Another study (Modell B *et al.* 2008) reported on a retrospective analysis of CMR T2* findings and of death certificate reports for thalassemia patients enrolled in the UK Thalassaemia Register, comparing periods prior to the year 2000 to the period 2000–

2003. This latter time period is of interest because of changes occurring after 1999 in the routine care of transfused thalassemia patients, namely: reduced reliance on serum ferritin as the sole marker of iron burden; routine CMR monitoring with T2*; and use of deferiprone, either as monotherapy or in combination with DFO. The authors found that, after 1970, when adequate transfusion schemes became the norm, iron overload replaced anemia as the most common cause of death. Iron chelation therapy by subcutaneous infusion of DFO was standard practice after 1980, but iron-induced cardiac disease remained the most common cause of death. After 1999, with the routine use of deferiprone in patients with cardiac siderosis, the annualized death rate from iron overload declined by 71%.

5. Maggio et al. (Maggio A *et al.* 2009a) evaluated the survival of 265 consecutive patients with thalassemia major who were admitted to 25 treatment centers in Italy between 2000 and 2008. One hundred and twenty four patients received deferoxamine and 141 patients received deferiprone (N=55 deferiprone alone, N=68 deferiprone sequential with deferoxamine, N=18 deferiprone combined with deferoxamine). Ten deaths were reported during the deferoxamine treatment; no deaths occurred with the DFP-alone or the combined DFP–DFO treatments. One death was reported during the deferiprone–deferoxamine sequential treatment in a patient that had experienced an episode of heart failure one year earlier. The hazard ratio of death for patients treated with deferoxamine vs. deferiprone was 29.4 with a 95% confidence interval of 3.6 to 240 (p-value=0.0016).

6. Most recently, Ladis et al. (Ladis V et al. 2010) analyzed the risk of cardiac death during 1990-1999 and 2000-2008 in more than 500 patients with thalassemia major. Their study also analyzed morbidity, mortality and reversal of heart failure during 2000-2008 according to chelation regime: deferoxamine, deferiprone and combination therapy of deferoxamine and deferiprone. Three hundred and fifty four patients older than 10 years and free of cardiac disease on January 1st 1999, were included in the de novo cardiac event evaluation, while 86 were included in the evaluation of reversal of cardiac disease. There was an approximately threefold significant reduction in the annual risk of cardiac death after the year 2000: the annual risk of cardiac death reduced from 1.52% to 0.67% (p= 0.0095) in patients aged between 20-30 years and 1.87% to 0.56% (p=0.052) in patients aged between 30-40 years. The risk for a de novo cardiac event for deferoxamine was 9.1 times greater than that of deferiprone and 23.6 than with the combination of deferiprone and deferoxamine. The risk of cardiac death was 9.5 per 1000 patient-years for deferoxamine, 2.5 on deferiprone, 1.4 on combination. The odds of reversal of cardiac disease were 8.5 times greater with deferiprone and 6.1 with combination therapy compared to deferoxamine.

# E Draft synopsis for proposed study

**Study Title** A Randomized, Parallel Arm, Active-Controlled, Comparison study of Deferiprone and Deferasirox for the Treatment of Transfusional Iron Overload in Sickle Cell Disease

**Rationale** About 10% of patients with sickle cell disease are dependent on chronic blood transfusion therapy. In the absence of effective iron chelation, chronic blood transfusion leads to progressive iron accumulation (transfusional siderosis) with damage to the heart, liver, and endocrine organs, and ultimately premature death. Deferiprone is an iron chelator that has been demonstrated to be effective in reducing iron load in transfusional siderosis, and in the US its proposed indication is for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate. The safety profile of deferiprone has been characterized by more than 23 years of clinical experience, including 11 years of post-marketing experience in Europe, Australia and other territories. The clinical trial and post-marketing populations comprise predominantly patients with thalassemia, although a few publications have reported on the safety and efficacy of patients with sickle cell disease in clinical studies. The current study is designed to collect information on both the safety and the efficacy of deferiprone in transfusionally iron overloaded patients with sickle cell disease.

**Objective(s)** The primary objective is to evaluate the safety and tolerability of deferiprone in comparison with deferasirox in transfusionally iron overloaded sickle cell patients.

The secondary objective is to compare the efficacy of deferiprone with that of deferasirox in reducing iron load in transfusionally iron overloaded patients with sickle cell disease, as determined by effects on serum ferritin and liver iron concentrations.

**Design Overview** This is a 52-week multi-centre, randomized, active-controlled, open-label study. Patients who sign an informed consent form will undergo screening. In patients who meet other screening requirements, eligibility to enter the study will include at least one of the following measures of iron overload:

1. Serum ferritin concentration > 500 µg/L; or
2. Liver iron concentration of > 2 mg/g dry weight, determined by MRI T2*

Patients will be randomized to receive deferiprone or deferasirox in a 2:1 ratio, and stratified by the following age groups: up to 11 years, 12 to 16 years and 16 years and older.

Patients randomized to the deferiprone arm will receive study medication orally three times a day at a recommended starting dose of 75 mg/kg/day. Dose adjustment will be allowed up to 100 mg/kg/day, based on body iron levels as determined by serum ferritin, or liver iron concentrations and investigator's judgment. The doses should be adjusted to the nearest half tablet and as per the participant's tolerability to changes in the dose regimen. A lower dose may be prescribed based on the occurrence of treatment emergent adverse events.

Patients randomized to the deferasirox arm will receive study medication once a day orally at a recommended starting dose of 20 mg/kg/day. Dose adjustment will be allowed up to 40 mg/kg/day, based on excess iron body content (serum ferritin and liver iron concentration) and investigator's judgment.

A lower dose may be prescribed based on the occurrence of treatment emergent adverse events.

Safety and efficacy evaluations will occur according to the schedule of evaluation. Safety assessments will include monitoring of the absolute neutrophil count, serum creatinine, liver enzymes, bilirubin, alkaline phosphatase and proteinuria. Body weight, height and sexual development will be monitored at baseline and repeated at 26 and 52 weeks of therapy, or at the time of early withdrawal. Efficacy assessments will include measurement of serum ferritin at baseline and repeated every 12 weeks and liver iron concentration at baseline and repeated at 52 weeks of therapy, or at the time of early withdrawal.

**Number of Subjects** Approximately 200 patients will be enrolled (approx. 127 patients on deferiprone and 63 patients on deferasirox).

**Patient Population / Eligibility Criteria**

Key Inclusion Criteria

Patients who meet all the following criteria will be eligible to enter the study:

1. Patients with sickle cell disease ≥ 2 years of age and with iron overload from repeated blood transfusions;
2. Patients on a regular blood transfusion regimen;
3. Prior chelation therapy permitted but not mandatory;

4. Serum ferritin level > 500 µg/L, or LIC of ≥ 2 mg Fe/g dry weight;
5. Patients and parent or legal guardian (when applicable) for whom a signed and witnessed written informed consent has been provided prior to the first study intervention.

Main Exclusion Criteria

1. Anemia other than sickle cell disease;
2. Transfusion regimen that includes exchange transfusions;
3. Evidence of abnormal liver function (liver enzyme > 3 times upper limit of normal);
4. Evidence of impaired renal function;
5. Disorders associated with neutropenia (ANC < 1.5 x $10^9$/L) or thrombocytopenia (platelet count < 50 x $10^9$/L) in the 12 months preceding the initiation of the study medication, except for patients who have been treated with interferon and in whom the ANC has fully recovered;
6. History of malignancy;
7. Treatment with an investigational drug within 30 days or 10 half-lives (which ever is longer) preceding the first dose of study medication;
8. Pregnant, nursing females and females of childbearing potential who are sexually active and unwilling, or unable to use an acceptable method of contraception.

**Primary endpoints** Frequency and severity of adverse events, discontinuation due to adverse events and on the number of laboratory values that fall outside the predetermined ranges.

**Secondary endpoints** Change in serum ferritin concentration from baseline to week 52.

Change in LIC from baseline to week 52.

# F Pooled Safety Data: Summary of Adverse Events, irrespective of causality, in at least one deferiprone treated patient

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| **Patients with any AE** | **23 (92.0)** | **346 (85.0)** | **94 (87.0)** | **538 (83.8)** | **100 (84.7)** | **68 (76.4)** |
| **Blood and lymphatic system disorders** | **2 ( 8.0)** | **76 (18.7)** | **11 (10.2)** | **99 (15.4)** | **11 ( 9.3)** | **8 ( 9.0)** |
| Neutropenia | 1 ( 4.0) | 29 ( 7.1) | 8 ( 7.4) | 43 ( 6.7) | 5 ( 4.2) | 5 ( 5.6) |
| Lymphadenopathy | 0 ( 0.0) | 11 ( 2.7) | 0 ( 0.0) | 13 ( 2.0) | 6 ( 5.1) | 0 ( 0.0) |
| Agranulocytosis | 0 ( 0.0) | 9 ( 2.2) | 2 ( 1.9) | 11 ( 1.7) | 0 ( 0.0) | 0 ( 0.0) |
| Lymphadenitis | 1 ( 4.0) | 8 ( 2.0) | 0 ( 0.0) | 9 ( 1.4) | 0 ( 0.0) | 0 ( 0.0) |
| Thrombocytopenia | 0 ( 0.0) | 6 ( 1.5) | 2 ( 1.9) | 9 ( 1.4) | 0 ( 0.0) | 1 ( 1.1) |
| Leukopenia | 0 ( 0.0) | 7 ( 1.7) | 0 ( 0.0) | 7 ( 1.1) | 0 ( 0.0) | 0 ( 0.0) |
| Blood disorder | 0 ( 0.0) | 5 ( 1.2) | 0 ( 0.0) | 5 ( 0.8) | 0 ( 0.0) | 0 ( 0.0) |
| Thrombocytosis | 0 ( 0.0) | 5 ( 1.2) | 0 ( 0.0) | 5 ( 0.8) | 0 ( 0.0) | 0 ( 0.0) |
| Hypersplenism | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Leukocytosis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Splenomegaly | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 2 ( 1.7) | 1 ( 1.1) |
| Anaemia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Lymph node pain | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Cardiac disorders** | **0 ( 0.0)** | **22 ( 5.4)** | **7 ( 6.5)** | **44 ( 6.9)** | **13 (11.0)** | **14 (15.7)** |
| Cardiac failure congestive | 0 ( 0.0) | 4 ( 1.0) | 1 ( 0.9) | 11 ( 1.7) | 1 ( 0.8) | 6 ( 6.7) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Palpitations | 0 ( 0.0) | 5 ( 1.2) | 2 ( 1.9) | 9 ( 1.4) | 2 ( 1.7) | 1 ( 1.1) |
| Atrial fibrillation | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 5 ( 0.8) | 0 ( 0.0) | 3 ( 3.4) |
| Cardiac failure | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 4 ( 0.6) | 1 ( 0.8) | 2 ( 2.2) |
| Atrial flutter | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 2 ( 2.2) |
| Cardiomyopathy | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 3 ( 0.5) | 3 ( 2.5) | 1 ( 1.1) |
| Tachycardia | 0 ( 0.0) | 2 ( 0.5) | 1 ( 0.9) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Extrasystoles | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Sinus tachycardia | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Angina unstable | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Arrhythmia | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Bradycardia | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Bundle branch block right | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Cardiac failure chronic | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Cardiac siderosis | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Cardiogenic shock | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Cardiomegaly | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Cor pulmonale | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Dilatation ventricular | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 3 ( 2.5) | 1 ( 1.1) |
| Intracardiac thrombus | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Restrictive cardiomyopathy | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Supraventricular extrasystoles | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Tachyarrhythmia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Torsade de pointes | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Congenital, familial and genetic disorders** | **1 ( 4.0)** | **1 ( 0.2)** | **0 ( 0.0)** | **2 ( 0.3)** | **0 ( 0.0)** | **0 ( 0.0)** |
| Dermatofibrosis lenticularis disseminata | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Thyroglossal cyst | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Ear and labyrinth disorders** | **0 ( 0.0)** | **20 ( 4.9)** | **3 ( 2.8)** | **28 ( 4.4)** | **12 (10.2)** | **5 ( 5.6)** |
| Ear pain | 0 ( 0.0) | 12 ( 2.9) | 0 ( 0.0) | 14 ( 2.2) | 4 ( 3.4) | 2 ( 2.2) |
| Vertigo | 0 ( 0.0) | 3 ( 0.7) | 1 ( 0.9) | 5 ( 0.8) | 3 ( 2.5) | 1 ( 1.1) |
| Deafness | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 3 ( 0.5) | 1 ( 0.8) | 1 ( 1.1) |
| Ear congestion | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 1 ( 1.1) |
| Tinnitus | 0 ( 0.0) | 0 ( 0.0) | 2 ( 1.9) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Deafness unilateral | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hearing impaired | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Hypoacusis | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 1 ( 1.1) |
| Otorrhoea | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Endocrine disorders** | **0 ( 0.0)** | **22 ( 5.4)** | **0 ( 0.0)** | **23 ( 3.6)** | **5 ( 4.2)** | **1 ( 1.1)** |
| Hypothyroidism | 0 ( 0.0) | 13 ( 3.2) | 0 ( 0.0) | 14 ( 2.2) | 3 ( 2.5) | 1 ( 1.1) |
| Hypogonadism | 0 ( 0.0) | 7 ( 1.7) | 0 ( 0.0) | 8 ( 1.2) | 0 ( 0.0) | 1 ( 1.1) |
| Goitre | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Hypoparathyroidism | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| **Eye disorders** | **1 ( 4.0)** | **39 ( 9.6)** | **4 ( 3.7)** | **50 ( 7.8)** | **9 ( 7.6)** | **6 ( 6.7)** |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Conjunctivitis | 1 ( 4.0) | 23 ( 5.7) | 4 ( 3.7) | 31 ( 4.8) | 4 ( 3.4) | 3 ( 3.4) |
| Conjunctivitis allergic | 0 ( 0.0) | 6 ( 1.5) | 0 ( 0.0) | 6 ( 0.9) | 2 ( 1.7) | 0 ( 0.0) |
| Eye pain | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 4 ( 0.6) | 0 ( 0.0) | 0 ( 0.0) |
| Ocular icterus | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 3 ( 0.5) | 2 ( 1.7) | 1 ( 1.1) |
| Vision blurred | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 2 ( 2.2) |
| Blepharitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Chalazion | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Conjunctival hyperaemia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Eye pruritus | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Eye swelling | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Macular oedema | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Myopia | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Uveitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Vitreous adhesions | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Vitreous haemorrhage | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Vitreous opacities | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| **Gastrointestinal disorders** | **16 (64.0)** | **215 (52.8)** | **39 (36.1)** | **300 (46.7)** | **43 (36.4)** | **27 (30.3)** |
| Nausea | 9 (36.0) | 87 (21.4) | 13 (12.0) | 117 (18.2) | 3 ( 2.5) | 7 ( 7.9) |
| Vomiting | 2 ( 8.0) | 76 (18.7) | 17 (15.7) | 108 (16.8) | 14 (11.9) | 12 (13.5) |
| Abdominal pain upper | 0 ( 0.0) | 64 (15.7) | 11 (10.2) | 79 (12.3) | 10 ( 8.5) | 2 ( 2.2) |
| Abdominal pain | 0 ( 0.0) | 63 (15.5) | 10 ( 9.3) | 76 (11.8) | 11 ( 9.3) | 2 ( 2.2) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Diarrhoea | 7 (28.0) | 46 (11.3) | 10 ( 9.3) | 73 (11.4) | 5 ( 4.2) | 10 (11.2) |
| Toothache | 0 ( 0.0) | 47 (11.5) | 3 ( 2.8) | 53 ( 8.3) | 9 ( 7.6) | 3 ( 3.4) |
| Dyspepsia | 0 ( 0.0) | 22 ( 5.4) | 1 ( 0.9) | 25 ( 3.9) | 3 ( 2.5) | 1 ( 1.1) |
| Abdominal discomfort | 0 ( 0.0) | 5 ( 1.2) | 5 ( 4.6) | 12 ( 1.9) | 2 ( 1.7) | 1 ( 1.1) |
| Abdominal distension | 0 ( 0.0) | 6 ( 1.5) | 2 ( 1.9) | 12 ( 1.9) | 0 ( 0.0) | 3 ( 3.4) |
| Constipation | 0 ( 0.0) | 10 ( 2.5) | 2 ( 1.9) | 12 ( 1.9) | 0 ( 0.0) | 0 ( 0.0) |
| Gastritis | 0 ( 0.0) | 4 ( 1.0) | 2 ( 1.9) | 8 ( 1.2) | 0 ( 0.0) | 2 ( 2.2) |
| Enteritis | 0 ( 0.0) | 6 ( 1.5) | 0 ( 0.0) | 7 ( 1.1) | 0 ( 0.0) | 1 ( 1.1) |
| Gingivitis | 0 ( 0.0) | 6 ( 1.5) | 0 ( 0.0) | 6 ( 0.9) | 0 ( 0.0) | 0 ( 0.0) |
| Epigastric discomfort | 0 ( 0.0) | 1 ( 0.2) | 4 ( 3.7) | 5 ( 0.8) | 3 ( 2.5) | 0 ( 0.0) |
| Abdominal pain lower | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 4 ( 0.6) | 1 ( 0.8) | 0 ( 0.0) |
| Eructation | 0 ( 0.0) | 0 ( 0.0) | 4 ( 3.7) | 4 ( 0.6) | 0 ( 0.0) | 0 ( 0.0) |
| Stomatitis | 0 ( 0.0) | 2 ( 0.5) | 1 ( 0.9) | 3 ( 0.5) | 1 ( 0.8) | 0 ( 0.0) |
| Abdominal tenderness | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Aerophagia | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Dental caries | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Dysphagia | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Flatulence | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Gastrooesophageal reflux disease | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Hyperchlorhydria | 1 ( 4.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Lip swelling | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Abdominal adhesions | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Anal pruritus | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Aphthous stomatitis | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 2 ( 1.7) | 0 ( 0.0) |
| Colitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Dry mouth | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Food poisoning | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Gastric ulcer | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Gastrointestinal pain | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Glossodynia | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Inguinal hernia | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Intestinal obstruction | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Lip blister | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Lip dry | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Pancreatitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Reflux oesophagitis | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Teething | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Tongue discolouration | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **General disorders and administration site conditions** | **3 (12.0)** | **183 (45.0)** | **23 (21.3)** | **232 (36.1)** | **50 (42.4)** | **20 (22.5)** |
| Pyrexia | 3 (12.0) | 147 (36.1) | 14 (13.0) | 181 (28.2) | 15 (12.7) | 15 (16.9) |
| Fatigue | 0 ( 0.0) | 26 ( 6.4) | 2 ( 1.9) | 31 ( 4.8) | 10 ( 8.5) | 2 ( 2.2) |
| Asthenia | 0 ( 0.0) | 18 ( 4.4) | 3 ( 2.8) | 21 ( 3.3) | 9 ( 7.6) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Chest pain | 0 ( 0.0) | 15 ( 3.7) | 4 ( 3.7) | 20 ( 3.1) | 3 ( 2.5) | 1 ( 1.1) |
| Oedema peripheral | 0 ( 0.0) | 10 ( 2.5) | 2 ( 1.9) | 13 ( 2.0) | 3 ( 2.5) | 1 ( 1.1) |
| Chills | 0 ( 0.0) | 2 ( 0.5) | 3 ( 2.8) | 9 ( 1.4) | 1 ( 0.8) | 4 ( 4.5) |
| Malaise | 0 ( 0.0) | 7 ( 1.7) | 0 ( 0.0) | 8 ( 1.2) | 10 ( 8.5) | 0 ( 0.0) |
| Influenza like illness | 0 ( 0.0) | 5 ( 1.2) | 1 ( 0.9) | 7 ( 1.1) | 0 ( 0.0) | 1 ( 1.1) |
| Pain | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 6 ( 0.9) | 3 ( 2.5) | 2 ( 2.2) |
| Hunger | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 4 ( 0.6) | 0 ( 0.0) | 0 ( 0.0) |
| Chest discomfort | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Infusion site hypersensitivity | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Local swelling | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Medical device complication | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 2 ( 2.2) |
| Thirst | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Catheter site pain | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Catheter site related reaction | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Discomfort | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hypothermia | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Infusion site inflammation | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Multi-organ failure | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Hepatobiliary disorders** | **1 ( 4.0)** | **33 ( 8.1)** | **1 ( 0.9)** | **37 ( 5.8)** | **3 ( 2.5)** | **2 ( 2.2)** |
| Hepatomegaly | 0 ( 0.0) | 7 ( 1.7) | 0 ( 0.0) | 9 ( 1.4) | 0 ( 0.0) | 2 ( 2.2) |
| Hepatitis chronic persistent | 0 ( 0.0) | 7 ( 1.7) | 0 ( 0.0) | 7 ( 1.1) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Cholelithiasis | 0 ( 0.0) | 4 ( 1.0) | 1 ( 0.9) | 5 ( 0.8) | 0 ( 0.0) | 0 ( 0.0) |
| Biliary colic | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 4 ( 0.6) | 0 ( 0.0) | 0 ( 0.0) |
| Hepatic pain | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 4 ( 0.6) | 0 ( 0.0) | 0 ( 0.0) |
| Jaundice | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 4 ( 0.6) | 2 ( 1.7) | 0 ( 0.0) |
| Hepatitis | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Chronic hepatitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hepatic congestion | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hepatic failure | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hepatic mass | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hepatitis toxic | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Liver tenderness | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Immune system disorders** | **1 ( 4.0)** | **7 ( 1.7)** | **1 ( 0.9)** | **10 ( 1.6)** | **5 ( 4.2)** | **1 ( 1.1)** |
| Hypersensitivity | 0 ( 0.0) | 3 ( 0.7) | 1 ( 0.9) | 4 ( 0.6) | 3 ( 2.5) | 0 ( 0.0) |
| Seasonal allergy | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 3 ( 0.5) | 1 ( 0.8) | 1 ( 1.1) |
| Allergy to arthropod bite | 1 ( 4.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Multiple allergies | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Allergy to animal | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Allergy to arthropod sting | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Infections and infestations** | **12 (48.0)** | **250 (61.4)** | **55 (50.9)** | **360 (56.1)** | **84 (71.2)** | **41 (46.1)** |
| Nasopharyngitis | 1 ( 4.0) | 154 (37.8) | 15 (13.9) | 182 (28.3) | 44 (37.3) | 11 (12.4) |
| Pharyngitis | 0 ( 0.0) | 113 (27.8) | 26 (24.1) | 149 (23.2) | 23 (19.5) | 10 (11.2) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Influenza | 0 ( 0.0) | 120 (29.5) | 1 ( 0.9) | 127 (19.8) | 15 (12.7) | 6 ( 6.7) |
| Tonsillitis | 1 ( 4.0) | 35 ( 8.6) | 1 ( 0.9) | 40 ( 6.2) | 2 ( 1.7) | 3 ( 3.4) |
| Bronchitis | 1 ( 4.0) | 31 ( 7.6) | 2 ( 1.9) | 36 ( 5.6) | 3 ( 2.5) | 1 ( 1.1) |
| Upper respiratory tract infection | 8 (32.0) | 14 ( 3.4) | 6 ( 5.6) | 35 ( 5.5) | 7 ( 5.9) | 6 ( 6.7) |
| Ear infection | 0 ( 0.0) | 31 ( 7.6) | 0 ( 0.0) | 33 ( 5.1) | 1 ( 0.8) | 1 ( 1.1) |
| Rhinitis | 0 ( 0.0) | 17 ( 4.2) | 11 (10.2) | 30 ( 4.7) | 6 ( 5.1) | 2 ( 2.2) |
| Sinusitis | 0 ( 0.0) | 24 ( 5.9) | 1 ( 0.9) | 27 ( 4.2) | 3 ( 2.5) | 1 ( 1.1) |
| Pharyngotonsillitis | 0 ( 0.0) | 20 ( 4.9) | 0 ( 0.0) | 23 ( 3.6) | 6 ( 5.1) | 3 ( 3.4) |
| Viral infection | 0 ( 0.0) | 10 ( 2.5) | 7 ( 6.5) | 19 ( 3.0) | 10 ( 8.5) | 1 ( 1.1) |
| Tooth abscess | 0 ( 0.0) | 14 ( 3.4) | 3 ( 2.8) | 18 ( 2.8) | 4 ( 3.4) | 0 ( 0.0) |
| Gastroenteritis | 0 ( 0.0) | 12 ( 2.9) | 3 ( 2.8) | 17 ( 2.6) | 7 ( 5.9) | 2 ( 2.2) |
| Urinary tract infection | 0 ( 0.0) | 13 ( 3.2) | 1 ( 0.9) | 17 ( 2.6) | 0 ( 0.0) | 2 ( 2.2) |
| Otitis media | 0 ( 0.0) | 13 ( 3.2) | 1 ( 0.9) | 16 ( 2.5) | 1 ( 0.8) | 1 ( 1.1) |
| Oral herpes | 0 ( 0.0) | 9 ( 2.2) | 0 ( 0.0) | 10 ( 1.6) | 5 ( 4.2) | 1 ( 1.1) |
| Tracheitis | 0 ( 0.0) | 6 ( 1.5) | 0 ( 0.0) | 10 ( 1.6) | 4 ( 3.4) | 4 ( 4.5) |
| Cystitis | 1 ( 4.0) | 7 ( 1.7) | 1 ( 0.9) | 9 ( 1.4) | 1 ( 0.8) | 0 ( 0.0) |
| Infectious mononucleosis | 0 ( 0.0) | 7 ( 1.7) | 0 ( 0.0) | 7 ( 1.1) | 0 ( 0.0) | 0 ( 0.0) |
| Measles | 0 ( 0.0) | 7 ( 1.7) | 0 ( 0.0) | 7 ( 1.1) | 0 ( 0.0) | 0 ( 0.0) |
| Sepsis | 1 ( 4.0) | 5 ( 1.2) | 0 ( 0.0) | 7 ( 1.1) | 0 ( 0.0) | 1 ( 1.1) |
| Varicella | 0 ( 0.0) | 6 ( 1.5) | 0 ( 0.0) | 7 ( 1.1) | 4 ( 3.4) | 1 ( 1.1) |
| Gastroenteritis viral | 0 ( 0.0) | 6 ( 1.5) | 0 ( 0.0) | 6 ( 0.9) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Acute tonsillitis | 0 ( 0.0) | 1 ( 0.2) | 4 ( 3.7) | 5 ( 0.8) | 0 ( 0.0) | 0 ( 0.0) |
| Cellulitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 5 ( 0.8) | 2 ( 1.7) | 3 ( 3.4) |
| Laryngitis | 0 ( 0.0) | 4 ( 1.0) | 1 ( 0.9) | 5 ( 0.8) | 1 ( 0.8) | 0 ( 0.0) |
| Otitis externa | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 5 ( 0.8) | 2 ( 1.7) | 1 ( 1.1) |
| Pneumonia | 0 ( 0.0) | 5 ( 1.2) | 0 ( 0.0) | 5 ( 0.8) | 0 ( 0.0) | 0 ( 0.0) |
| Vaginal infection | 0 ( 0.0) | 2 ( 0.5) | 3 ( 2.8) | 5 ( 0.8) | 2 ( 1.7) | 0 ( 0.0) |
| Gastrointestinal infection | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 4 ( 0.6) | 3 ( 2.5) | 0 ( 0.0) |
| Herpes simplex | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 4 ( 0.6) | 1 ( 0.8) | 0 ( 0.0) |
| Bronchopneumonia | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Device related infection | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 3 ( 3.4) |
| Device related sepsis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 2 ( 2.2) |
| Furuncle | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Parotitis | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Pyelonephritis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 1 ( 1.1) |
| Tooth infection | 0 ( 0.0) | 2 ( 0.5) | 1 ( 0.9) | 3 ( 0.5) | 2 ( 1.7) | 0 ( 0.0) |
| Abscess limb | 0 ( 0.0) | 0 ( 0.0) | 2 ( 1.9) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Acute sinusitis | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Bacterial infection | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Bacterial sepsis | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 2 ( 2.2) |
| Catheter site infection | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Fungal skin infection | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Herpes zoster | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Infection | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Localised infection | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 2 ( 1.7) | 0 ( 0.0) |
| Nail infection | 2 ( 8.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Paronychia | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Pharyngitis streptococcal | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 2 ( 2.2) |
| Roseola | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Staphylococcal infection | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Viral pharyngitis | 0 ( 0.0) | 0 ( 0.0) | 2 ( 1.9) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Viral upper respiratory tract infection | 0 ( 0.0) | 0 ( 0.0) | 2 ( 1.9) | 2 ( 0.3) | 2 ( 1.7) | 0 ( 0.0) |
| Wound infection | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Yersinia infection | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Acarodermatitis | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Anal abscess | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Appendicitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Ascariasis | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Bacteraemia | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Body tinea | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Breast abscess | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Bronchiolitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Corneal abscess | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Cytomegalovirus hepatitis | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Cytomegalovirus infection | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Dengue fever | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Diabetic foot infection | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Endocarditis | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Enterobiasis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Escherichia urinary tract infection | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Eye infection | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 2 ( 1.7) | 1 ( 1.1) |
| Folliculitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Fungal infection | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Genital infection female | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hepatitis a | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hepatitis b | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hordeolum | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Impetigo | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Infected bites | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Lobar pneumonia | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Lyme disease | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Meningitis | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Meningitis bacterial | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Oral candidiasis | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Otitis media acute | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Pertussis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Postoperative wound infection | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Pulpitis dental | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Pyoderma | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Rotavirus infection | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Serratia sepsis | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Splenic abscess | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Viral tonsillitis | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Vulvovaginal candidiasis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Vulvovaginal mycotic infection | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Injury, poisoning and procedural complications** | **4 (16.0)** | **63 (15.5)** | **17 (15.7)** | **93 (14.5)** | **25 (21.2)** | **7 ( 7.9)** |
| Transfusion reaction | 0 ( 0.0) | 10 ( 2.5) | 4 ( 3.7) | 15 ( 2.3) | 6 ( 5.1) | 1 ( 1.1) |
| Road traffic accident | 1 ( 4.0) | 9 ( 2.2) | 0 ( 0.0) | 10 ( 1.6) | 0 ( 0.0) | 0 ( 0.0) |
| Joint injury | 0 ( 0.0) | 9 ( 2.2) | 0 ( 0.0) | 9 ( 1.4) | 1 ( 0.8) | 0 ( 0.0) |
| Fall | 0 ( 0.0) | 3 ( 0.7) | 4 ( 3.7) | 7 ( 1.1) | 1 ( 0.8) | 0 ( 0.0) |
| Joint sprain | 0 ( 0.0) | 7 ( 1.7) | 0 ( 0.0) | 7 ( 1.1) | 1 ( 0.8) | 0 ( 0.0) |
| Limb injury | 1 ( 4.0) | 3 ( 0.7) | 2 ( 1.9) | 6 ( 0.9) | 2 ( 1.7) | 0 ( 0.0) |
| Contusion | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 4 ( 0.6) | 6 ( 5.1) | 1 ( 1.1) |
| Allergic transfusion reaction | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 3 ( 0.5) | 4 ( 3.4) | 3 ( 3.4) |
| Foot fracture | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Head injury | 0 ( 0.0) | 1 ( 0.2) | 2 ( 1.9) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Rib fracture | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Upper limb fracture | 0 ( 0.0) | 1 ( 0.2) | 2 ( 1.9) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Arthropod bite | 0 ( 0.0) | 0 ( 0.0) | 2 ( 1.9) | 2 ( 0.3) | 2 ( 1.7) | 0 ( 0.0) |
| Excoriation | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Eye injury | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Femur fracture | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Fracture | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Hand fracture | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Hip fracture | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Muscle injury | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Muscle strain | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Procedural pain | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 2 ( 1.7) | 0 ( 0.0) |
| Skin laceration | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Tibia fracture | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Abdominal injury | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Back injury | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Burns second degree | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Chemical burn of skin | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Epicondylitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Face injury | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Femoral neck fracture | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Forearm fracture | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Heat stroke | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Internal injury | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Joint dislocation | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Limb crushing injury | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Meniscus lesion | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Neck injury | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Open fracture | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Periorbital haematoma | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Post procedural complication | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Skeletal injury | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Sternal fracture | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Thoracic vertebral fracture | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Wound | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Investigations** | **3 (12.0)** | **124 (30.5)** | **55 (50.9)** | **203 (31.6)** | **25 (21.2)** | **17 (19.1)** |
| Biopsy liver | 0 ( 0.0) | 66 (16.2) | 0 ( 0.0) | 70 (10.9) | 1 ( 0.8) | 2 ( 2.2) |
| Neutrophil count decreased | 0 ( 0.0) | 28 ( 6.9) | 21 (19.4) | 57 ( 8.9) | 4 ( 3.4) | 7 ( 7.9) |
| Alanine aminotransferase increased | 0 ( 0.0) | 29 ( 7.1) | 22 (20.4) | 56 ( 8.7) | 5 ( 4.2) | 4 ( 4.5) |
| Weight increased | 0 ( 0.0) | 3 ( 0.7) | 12 (11.1) | 17 ( 2.6) | 6 ( 5.1) | 1 ( 1.1) |
| Cardiac murmur | 0 ( 0.0) | 12 ( 2.9) | 0 ( 0.0) | 13 ( 2.0) | 3 ( 2.5) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Aspartate aminotransferase increased | 0 ( 0.0) | 3 ( 0.7) | 6 ( 5.6) | 10 ( 1.6) | 1 ( 0.8) | 1 ( 1.1) |
| Electrocardiogram t wave inversion | 0 ( 0.0) | 0 ( 0.0) | 6 ( 5.6) | 6 ( 0.9) | 0 ( 0.0) | 0 ( 0.0) |
| White blood cell count decreased | 0 ( 0.0) | 1 ( 0.2) | 5 ( 4.6) | 6 ( 0.9) | 6 ( 5.1) | 0 ( 0.0) |
| Gamma-glutamyltransferase increased | 0 ( 0.0) | 1 ( 0.2) | 4 ( 3.7) | 5 ( 0.8) | 2 ( 1.7) | 0 ( 0.0) |
| Blood zinc decreased | 0 ( 0.0) | 1 ( 0.2) | 3 ( 2.8) | 4 ( 0.6) | 1 ( 0.8) | 0 ( 0.0) |
| Electrocardiogram qt prolonged | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 4 ( 0.6) | 1 ( 0.8) | 2 ( 2.2) |
| Blood creatinine increased | 1 ( 4.0) | 0 ( 0.0) | 1 ( 0.9) | 3 ( 0.5) | 0 ( 0.0) | 1 ( 1.1) |
| Electrocardiogram repolarisation abnormality | 0 ( 0.0) | 0 ( 0.0) | 3 ( 2.8) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Platelet count increased | 0 ( 0.0) | 0 ( 0.0) | 3 ( 2.8) | 3 ( 0.5) | 2 ( 1.7) | 0 ( 0.0) |
| Weight decreased | 2 ( 8.0) | 0 ( 0.0) | 1 ( 0.9) | 3 ( 0.5) | 9 ( 7.6) | 0 ( 0.0) |
| Arthroscopy | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Blood bilirubin increased | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Blood glucose increased | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 2 ( 2.2) |
| Heart rate increased | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Investigation | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Platelet count decreased | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Activated partial thromboplastin time prolonged | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Alanine aminotransferase abnormal | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Aspartate aminotransferase abnormal | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Bilirubin conjugated | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Blood alkaline phosphatase increased | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Blood glucose decreased | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Blood lactate dehydrogenase increased | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Blood phosphorus increased | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Blood potassium decreased | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Blood urea increased | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Electrocardiogram t wave abnormal | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Haemoglobin decreased | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Hepatic enzyme increased | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hepatitis b core antigen positive | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hepatitis c antibody positive | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| International normalised ratio abnormal | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| International normalised ratio increased | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Laboratory test abnormal | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Liver function test abnormal | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Lymph node palpable | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Neutrophil count abnormal | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Neutrophil count increased | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Prothrombin time prolonged | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Serum ferritin abnormal | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Spleen palpable | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 2 ( 1.7) | 0 ( 0.0) |
| Vitamin e decreased | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| **Metabolism and nutrition disorders** | **3 (12.0)** | **42 (10.3)** | **14 (13.0)** | **68 (10.6)** | **4 ( 3.4)** | **9 (10.1)** |
| Increased appetite | 0 ( 0.0) | 18 ( 4.4) | 14 (13.0) | 32 ( 5.0) | 0 ( 0.0) | 0 ( 0.0) |
| Decreased appetite | 3 (12.0) | 7 ( 1.7) | 0 ( 0.0) | 10 ( 1.6) | 3 ( 2.5) | 0 ( 0.0) |
| Hyperglycaemia | 0 ( 0.0) | 4 ( 1.0) | 1 ( 0.9) | 6 ( 0.9) | 0 ( 0.0) | 1 ( 1.1) |
| Diabetes mellitus | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 5 ( 0.8) | 0 ( 0.0) | 1 ( 1.1) |
| Hypocalcaemia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 4 ( 0.6) | 0 ( 0.0) | 3 ( 3.4) |
| Dehydration | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 1 ( 1.1) |
| Diabetic ketoacidosis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 2 ( 2.2) |
| Hypoglycaemia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 2 ( 2.2) |
| Fluid retention | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Hypokalaemia | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 2 ( 2.2) |
| Hypomagnesaemia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 1 ( 1.1) |
| Malnutrition | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Electrolyte imbalance | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Failure to thrive | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Folate deficiency | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 1 ( 1.1) |
| Glucose tolerance impaired | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Hyponatraemia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Obesity | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Selenium deficiency | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Type 1 diabetes mellitus | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Vitamin a deficiency | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Vitamin b6 deficiency | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Vitamin c deficiency | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Vitamin d deficiency | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| **Musculoskeletal and connective tissue disorders** | **5 (20.0)** | **142 (34.9)** | **25 (23.1)** | **194 (30.2)** | **43 (36.4)** | **19 (21.3)** |
| Arthralgia | 2 ( 8.0) | 76 (18.7) | 14 (13.0) | 101 (15.7) | 9 ( 7.6) | 7 ( 7.9) |
| Back pain | 3 (12.0) | 66 (16.2) | 12 (11.1) | 90 (14.0) | 29 (24.6) | 9 (10.1) |
| Pain in extremity | 0 ( 0.0) | 23 ( 5.7) | 2 ( 1.9) | 29 ( 4.5) | 8 ( 6.8) | 3 ( 3.4) |
| Myalgia | 0 ( 0.0) | 14 ( 3.4) | 3 ( 2.8) | 18 ( 2.8) | 4 ( 3.4) | 1 ( 1.1) |
| Joint swelling | 0 ( 0.0) | 10 ( 2.5) | 0 ( 0.0) | 12 ( 1.9) | 1 ( 0.8) | 2 ( 2.2) |
| Musculoskeletal pain | 0 ( 0.0) | 11 ( 2.7) | 0 ( 0.0) | 11 ( 1.7) | 2 ( 1.7) | 0 ( 0.0) |
| Arthropathy | 0 ( 0.0) | 7 ( 1.7) | 1 ( 0.9) | 10 ( 1.6) | 0 ( 0.0) | 2 ( 2.2) |
| Muscle spasms | 0 ( 0.0) | 7 ( 1.7) | 1 ( 0.9) | 10 ( 1.6) | 2 ( 1.7) | 2 ( 2.2) |
| Bone pain | 1 ( 4.0) | 6 ( 1.5) | 1 ( 0.9) | 9 ( 1.4) | 0 ( 0.0) | 1 ( 1.1) |
| Musculoskeletal chest pain | 0 ( 0.0) | 8 ( 2.0) | 1 ( 0.9) | 9 ( 1.4) | 0 ( 0.0) | 0 ( 0.0) |
| Neck pain | 0 ( 0.0) | 8 ( 2.0) | 1 ( 0.9) | 9 ( 1.4) | 2 ( 1.7) | 0 ( 0.0) |
| Osteoporosis | 0 ( 0.0) | 7 ( 1.7) | 1 ( 0.9) | 8 ( 1.2) | 0 ( 0.0) | 0 ( 0.0) |
| Arthritis | 0 ( 0.0) | 2 ( 0.5) | 2 ( 1.9) | 5 ( 0.8) | 0 ( 0.0) | 0 ( 0.0) |
| Flank pain | 0 ( 0.0) | 5 ( 1.2) | 0 ( 0.0) | 5 ( 0.8) | 1 ( 0.8) | 0 ( 0.0) |
| Muscular weakness | 0 ( 0.0) | 3 ( 0.7) | 1 ( 0.9) | 4 ( 0.6) | 1 ( 0.8) | 0 ( 0.0) |
| Haemarthrosis | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 1 ( 1.1) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Osteopenia | 0 ( 0.0) | 2 ( 0.5) | 1 ( 0.9) | 3 ( 0.5) | 1 ( 0.8) | 0 ( 0.0) |
| Groin pain | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Growing pains | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Joint effusion | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 1 ( 1.1) |
| Joint range of motion decreased | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Joint stiffness | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 2 ( 0.3) | 2 ( 1.7) | 0 ( 0.0) |
| Metatarsalgia | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Pain in jaw | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Tendonitis | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Bone infarction | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Bursitis | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Coccydynia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Intervertebral disc protrusion | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Joint crepitation | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Limb discomfort | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Musculoskeletal stiffness | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Polyarthritis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Scoliosis | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Synovial cyst | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Tenosynovitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Torticollis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **0 ( 0.0)** | **6 ( 1.5)** | **2 ( 1.9)** | **10 ( 1.6)** | **0 ( 0.0)** | **0 ( 0.0)** |
| Lung neoplasm malignant | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Acute myeloid leukaemia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Adenocarcinoma | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Benign breast neoplasm | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Haemangioma | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Haemangioma of liver | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Leukaemia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Melanocytic naevus | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Skin papilloma | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Nervous system disorders** | **0 ( 0.0)** | **152 (37.3)** | **18 (16.7)** | **183 (28.5)** | **41 (34.7)** | **12 (13.5)** |
| Headache | 0 ( 0.0) | 129 (31.7) | 17 (15.7) | 156 (24.3) | 38 (32.2) | 9 (10.1) |
| Dizziness | 0 ( 0.0) | 17 ( 4.2) | 2 ( 1.9) | 23 ( 3.6) | 4 ( 3.4) | 4 ( 4.5) |
| Somnolence | 0 ( 0.0) | 18 ( 4.4) | 0 ( 0.0) | 18 ( 2.8) | 1 ( 0.8) | 0 ( 0.0) |
| Migraine | 0 ( 0.0) | 5 ( 1.2) | 0 ( 0.0) | 6 ( 0.9) | 1 ( 0.8) | 1 ( 1.1) |
| Hypoaesthesia | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 3 ( 0.5) | 1 ( 0.8) | 0 ( 0.0) |
| Neuralgia | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 1 ( 1.1) |
| Sinus headache | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 3 ( 0.5) | 3 ( 2.5) | 0 ( 0.0) |
| Syncope | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Burning sensation | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Formication | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Hemicephalalgia | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Paraesthesia | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Convulsion | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Depressed level of consciousness | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Encephalitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Facial palsy | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hypersomnia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hypogeusia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Lethargy | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Sciatica | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Tremor | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Pregnancy, puerperium and perinatal conditions** | **1 ( 4.0)** | **0 ( 0.0)** | **0 ( 0.0)** | **1 ( 0.2)** | **1 ( 0.8)** | **0 ( 0.0)** |
| Pregnancy | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| **Psychiatric disorders** | **0 ( 0.0)** | **15 ( 3.7)** | **2 ( 1.9)** | **20 ( 3.1)** | **3 ( 2.5)** | **3 ( 3.4)** |
| Anxiety | 0 ( 0.0) | 5 ( 1.2) | 1 ( 0.9) | 7 ( 1.1) | 1 ( 0.8) | 1 ( 1.1) |
| Depression | 0 ( 0.0) | 5 ( 1.2) | 0 ( 0.0) | 6 ( 0.9) | 1 ( 0.8) | 1 ( 1.1) |
| Insomnia | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Suicidal ideation | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 2 ( 2.2) |
| Confusional state | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Depressed mood | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Elevated mood | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Homicidal ideation | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Major depression | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Mood altered | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Nervousness | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Oppositional defiant disorder | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Self injurious behaviour | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Stress | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Renal and urinary disorders** | **2 ( 8.0)** | **110 (27.0)** | **2 ( 1.9)** | **116 (18.1)** | **5 ( 4.2)** | **2 ( 2.2)** |
| Chromaturia | 0 ( 0.0) | 94 (23.1) | 0 ( 0.0) | 94 (14.6) | 0 ( 0.0) | 0 ( 0.0) |
| Renal colic | 0 ( 0.0) | 8 ( 2.0) | 1 ( 0.9) | 9 ( 1.4) | 3 ( 2.5) | 0 ( 0.0) |
| Dysuria | 1 ( 4.0) | 5 ( 1.2) | 0 ( 0.0) | 8 ( 1.2) | 0 ( 0.0) | 2 ( 2.2) |
| Nephrolithiasis | 1 ( 4.0) | 3 ( 0.7) | 0 ( 0.0) | 4 ( 0.6) | 0 ( 0.0) | 0 ( 0.0) |
| Pollakiuria | 0 ( 0.0) | 2 ( 0.5) | 1 ( 0.9) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Renal pain | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Strangury | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Costovertebral angle tenderness | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Glomerulonephritis chronic | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Haematuria | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hydronephrosis | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Nephrocalcinosis | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Oliguria | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Polyuria | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Reproductive system and breast disorders** | **1 ( 4.0)** | **25 ( 6.1)** | **7 ( 6.5)** | **33 ( 5.1)** | **11 ( 9.3)** | **0 ( 0.0)** |
| Dysmenorrhoea | 0 ( 0.0) | 12 ( 2.9) | 3 ( 2.8) | 15 ( 2.3) | 7 ( 5.9) | 0 ( 0.0) |
| Amenorrhoea | 0 ( 0.0) | 11 ( 2.7) | 2 ( 1.9) | 13 ( 2.0) | 3 ( 2.5) | 0 ( 0.0) |
| Menstruation irregular | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Balanoposthitis | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Breast swelling | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Dyspareunia | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Menorrhagia | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Metrorrhagia | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Pelvic pain | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Premenstrual syndrome | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Prostatitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Prostatomegaly | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Vulvovaginal discomfort | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **2 ( 8.0)** | **168 (41.3)** | **16 (14.8)** | **202 (31.5)** | **43 (36.4)** | **13 (14.6)** |
| Cough | 0 ( 0.0) | 117 (28.7) | 4 ( 3.7) | 129 (20.1) | 25 (21.2) | 6 ( 6.7) |
| Oropharyngeal pain | 2 ( 8.0) | 83 (20.4) | 1 ( 0.9) | 89 (13.9) | 18 (15.3) | 2 ( 2.2) |
| Epistaxis | 0 ( 0.0) | 14 ( 3.4) | 3 ( 2.8) | 17 ( 2.6) | 3 ( 2.5) | 0 ( 0.0) |
| Dyspnoea | 0 ( 0.0) | 10 ( 2.5) | 1 ( 0.9) | 12 ( 1.9) | 1 ( 0.8) | 1 ( 1.1) |
| Nasal congestion | 0 ( 0.0) | 12 ( 2.9) | 0 ( 0.0) | 12 ( 1.9) | 4 ( 3.4) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Asthma | 0 ( 0.0) | 8 ( 2.0) | 1 ( 0.9) | 10 ( 1.6) | 2 ( 1.7) | 1 ( 1.1) |
| Rhinorrhoea | 0 ( 0.0) | 6 ( 1.5) | 3 ( 2.8) | 10 ( 1.6) | 3 ( 2.5) | 1 ( 1.1) |
| Dysphonia | 0 ( 0.0) | 4 ( 1.0) | 1 ( 0.9) | 5 ( 0.8) | 0 ( 0.0) | 0 ( 0.0) |
| Productive cough | 0 ( 0.0) | 4 ( 1.0) | 1 ( 0.9) | 5 ( 0.8) | 0 ( 0.0) | 0 ( 0.0) |
| Rhinitis allergic | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 5 ( 0.8) | 2 ( 1.7) | 1 ( 1.1) |
| Bronchospasm | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 2 ( 1.7) | 0 ( 0.0) |
| Pharyngeal erythema | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Tonsillar hypertrophy | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 1 ( 0.8) | 0 ( 0.0) |
| Wheezing | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 3 ( 0.5) | 1 ( 0.8) | 1 ( 1.1) |
| Bronchitis chronic | 1 ( 4.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Haemoptysis | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Pulmonary hypertension | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Respiratory distress | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 2 ( 2.2) |
| Upper respiratory tract inflammation | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Choking | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Chylothorax | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Dry throat | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Dyspnoea exertional | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hypoxia | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Pleural effusion | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Pulmonary congestion | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Pulmonary oedema | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Pulmonary toxicity | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Sinus congestion | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Sleep apnoea syndrome | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Upper airway obstruction | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Skin and subcutaneous tissue disorders** | **1 ( 4.0)** | **53 (13.0)** | **10 ( 9.3)** | **69 (10.7)** | **21 (17.8)** | **4 ( 4.5)** |
| Urticaria | 0 ( 0.0) | 15 ( 3.7) | 3 ( 2.8) | 18 ( 2.8) | 3 ( 2.5) | 0 ( 0.0) |
| Rash | 0 ( 0.0) | 13 ( 3.2) | 1 ( 0.9) | 14 ( 2.2) | 3 ( 2.5) | 0 ( 0.0) |
| Pruritus | 0 ( 0.0) | 4 ( 1.0) | 2 ( 1.9) | 6 ( 0.9) | 4 ( 3.4) | 0 ( 0.0) |
| Dermatitis contact | 0 ( 0.0) | 2 ( 0.5) | 3 ( 2.8) | 5 ( 0.8) | 1 ( 0.8) | 0 ( 0.0) |
| Skin ulcer | 1 ( 4.0) | 3 ( 0.7) | 0 ( 0.0) | 4 ( 0.6) | 0 ( 0.0) | 0 ( 0.0) |
| Alopecia | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Dermatitis | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 2 ( 1.7) | 0 ( 0.0) |
| Dermatitis allergic | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 3 ( 2.5) | 0 ( 0.0) |
| Hidradenitis | 0 ( 0.0) | 3 ( 0.7) | 0 ( 0.0) | 3 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Acne | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.9) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Dry skin | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Erythema | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 2 ( 1.7) | 1 ( 1.1) |
| Pityriasis rosea | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Rash pruritic | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Skin discolouration | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Yellow skin | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Dermatitis atopic | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Eczema | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Hyperhidrosis | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Ingrowing nail | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Pruritus generalised | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Rash generalised | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Rash macular | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Skin hyperpigmentation | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Skin hypopigmentation | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Skin lesion | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Skin nodule | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Skin plaque | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Sweat discolouration | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Sweat gland disorder | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Swelling face | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Xeroderma | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 3 ( 2.5) | 0 ( 0.0) |
| **Social circumstances** | **0 ( 0.0)** | **0 ( 0.0)** | **0 ( 0.0)** | **1 ( 0.2)** | **0 ( 0.0)** | **0 ( 0.0)** |
| Treatment noncompliance | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Surgical and medical procedures** | **1 ( 4.0)** | **37 ( 9.1)** | **8 ( 7.4)** | **52 ( 8.1)** | **3 ( 2.5)** | **4 ( 4.5)** |
| Splenectomy | 0 ( 0.0) | 10 ( 2.5) | 2 ( 1.9) | 12 ( 1.9) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Cholecystectomy | 0 ( 0.0) | 5 ( 1.2) | 1 ( 0.9) | 6 ( 0.9) | 0 ( 0.0) | 0 ( 0.0) |
| Tooth extraction | 0 ( 0.0) | 1 ( 0.2) | 4 ( 3.7) | 6 ( 0.9) | 1 ( 0.8) | 0 ( 0.0) |
| Knee operation | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 4 ( 0.6) | 0 ( 0.0) | 0 ( 0.0) |
| Catheter placement | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Mole excision | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Nail operation | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Renal stone removal | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Surgery | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) |
| Tonsillectomy | 0 ( 0.0) | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 1 ( 0.8) | 0 ( 0.0) |
| Adenotonsillectomy | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Appendicectomy | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Catheter removal | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Catheterisation venous | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Circumcision | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Endodontic procedure | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Eye operation | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Hernia repair | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Inguinal hernia repair | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Keratomileusis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Keratotomy | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Lipoma excision | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

| Body System<br>Preferred Term | DFP<br>50 mg/kg/d<br>n=25 (%) | DFP<br>75 mg/kg/d<br>n=407 (%) | DFP<br>100 mg/kg/d<br>n=108 (%) | DFP<br>(all doses)<br>mg/kg/d<br>n=642 (%) | DFO<br>50 mg/kg/d<br>n=118 (%) | Alternate/Combination<br>Therapy with DFP<br>n=89 (%) |
|---|---|---|---|---|---|---|
| Lithotripsy | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Mass excision | 1 ( 4.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Meniscus operation | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Packed red blood cell transfusion | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Suture insertion | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Tympanoplasty | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Ureterolithotomy | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Urethral repair | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Vitrectomy | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 1.1) |
| Wart excision | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Wisdom teeth removal | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| **Vascular disorders** | **0 ( 0.0)** | **7 ( 1.7)** | **1 ( 0.9)** | **14 ( 2.2)** | **5 ( 4.2)** | **4 ( 4.5)** |
| Hypotension | 0 ( 0.0) | 4 ( 1.0) | 0 ( 0.0) | 7 ( 1.1) | 0 ( 0.0) | 3 ( 3.4) |
| Hypertension | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 3 ( 0.5) | 1 ( 0.8) | 1 ( 1.1) |
| Pallor | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.3) | 2 ( 1.7) | 1 ( 1.1) |
| Haematoma | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) | 1 ( 0.2) | 1 ( 0.8) | 0 ( 0.0) |
| Phlebitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Vasculitis | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |

1) Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of patients exposed with systemic iron overload primary diagnoses in each dosing group.
3) Patients exposed to more than one DFP dose are classified by their maximum dose.
4) There are 13 patients whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These patients are included in DFP (all doses)
5) Data cutoff date: 31AUG2010

# G Narratives of fatal cases from clinical trials

## Cardiac Disorders

Subject 38 (Case 2002AP000373)— Cardiac Failure

Case 2002AP000373 concerns episodes of cardiac failure and abnormal hepatic function experienced by a 23-year-old splenectomized female subject (Subject 38; height: 152 cm; weight: 42 kg) with thalassemia enrolled in Study LA-04 (The Compassionate-use of Deferiprone in Subjects with Transfusion-Dependent Anemia and Chronic Iron Overload). ApoPharma received reports of this event on 23 MAY 1997.

The subject was hospitalized and treated in FEB 1997 for congestive heart failure. At that time, the subject's iron chelation, intensive intravenous therapy with deferoxamine, was permanently discontinued because of recurrent infection of the central catheter, and subcutaneous therapy was not pursued because of the subject's previous experience with severe local reactions. On 27 MAR 1997, the subject started treatment with deferiprone for iron overload (hepatic iron concentration was 6.1 mg/g liver wet weight and serum ferritin 9,946 µg/L) at a total daily dose of 75 mg/kg orally. In APR 1997, the subject presented with symptoms of worsening of cardiac function (intense asthenia, fatigue, nocturnal partial orthopnea, and poor quality of life), and she was hospitalized for the treatment of congestive heart failure. On 28 APR 1997, deferiprone was interrupted to facilitate the preparation of the subject for a heart and liver transplant. On 02 MAY 1997, there was a progressive worsening of cardiac function. Therapy with defriprone was restarted. On 03 MAY 1997, AST was 231 U/L, ALT was 203 U/L, and total bilirubin was 1.86 mg/dL. From 10 MAY 1997 to 12 MAY 1997, the subject experienced chills and fever (39°C-40°C), and further deterioration of cardiac function. ANCs performed on 07 and 14 MAY 1997 were $8.31 \times 10^9$/L and $6.49 \times 10^9$/L, respectively. deferiprone was permanently discontinued on 11 MAY 1997. The subject's general condition continued to deteriorate progressively and she died on from cardiac failure.

The subject had a medical history of hepatitis C, cardiac disease, hepatomegaly, hypogonadism, and diabetes mellitus.

The investigator described the event as severe with doubtful relationship to DFP.

Subject 61 (Case 2002AP000451)— Congestive Cardiac Failure

Case 2002AP000451 concerns an episode of congestive cardiac failure experienced by a 26-year-old splenectomized male subject (Subject 61; weight: 50 kg, height: 179 cm) with thalassemia major enrolled in Study LA-01 (Randomized Trial of Deferiprone and Deferoxamine in Thalassemia Major).

On 08 NOV 1993, the subject began deferiprone for the treatment of iron overload at a dose of 4,000 mg/d (75 mg/kg/d) orally. In OCT 1993, 1 month before the start of treatment with deferiprone, he initiated therapy with nadolol 40 mg/d for the treatment of heart failure. On 21 FEB 1994, the subject was diagnosed to have diabetes mellitus secondary to iron overload. Concomitant medication included vitamin C 100 mg/d orally, folate 5 mg/d orally, and insulin

44 U/d subcutaneously.

On the subject presented with increasing shortness of breath and extreme fatigue. He was admitted to the hospital for right-sided congestive heart failure. The exercise radionuclide angiogram (RNA) multiacquisition-gated scan showed abnormal systolic and diastolic function in the right and left ventricles. MRI of the heart and liver showed severe iron overload. The subject was administered digoxin 0.025 mg/d orally and Lasix 20 mg/d orally. The subject's total daily dose of nadolol was reduced to 20 mg/d orally. Treatment with deferiprone was not discontinued. After an unspecified number of days, the subject was discharged from the hospital in stable condition.

Deferiprone was discontinued on 26 APR 1994. On the subject died during a heart transplant because of allograft heart failure.

The subject had a medical history of iron-induced cardiomyopathy with previous arrhythmias and supraventricular tachycardia. The subject was positive for hepatitis B and C antibodies.

The investigator considered the death to be an outcome of the congestive cardiac failure episode and assessed the relationship of the event to deferiprone as doubtful.

Subject 109 (Case 2004AP000508)— Cardiomyopathy

Case 2004AP000508 concerns episodes of sepsis, cardiomyopathy, and endocarditis experienced by a 38-year-old splenectomized male subject (Subject 109; height: 168.2 cm; weight: 64.6 kg) with β-thalassemia major and multiple organ toxicities from iron overload enrolled in Study LA-04 (The Compassionate use of Deferiprone in Subjects with Transfusion-Dependent Anemia and Chronic Iron Overload).

On 15 DEC 2003, deferiprone at a total daily dose of 4,750 mg orally was added to the subject's iron chelation because of worsening of cardiac disease despite therapy with deferoxamine. Before initiating deferiprone the subject maintained a compliant regimen of subcutaneous deferoxamine 3 g/d (17.5 g/wk).

On the subject was admitted to the hospital with sepsis. A blood culture on was positive for *Streptococcus mitis*. At the onset of the event, the subject was receiving deferoxamine 3 g subcutaneous, Altace (lovastatin) 5 mg orally, Coreg (carvedilol) 50 mg orally, Coumadin (warfarin sodium) 5 mg orally, digoxin 250 mg orally, folic acid 3 mg orally, Paxil (paroxetine) 20 mg orally, Singulair (montelukast) 10 mg orally, testosterone 1 mg intramuscular, Ambien (zolpidem tartrate) 10 mg orally, Cardizem (diltiazem hydrochloride) 180 mg orally, Lasix (furosemide) 20 mg orally, Xanax (alprazolam) 0.25 mg orally, Xopenex (levalbuterol hydrochloride) 1.25 mg high-flow nebulizer, and Azmacort high-flow nebulizer (triamcinolone acetonide) two puffs daily.

Deferiprone was not interrupted at the onset of the event.

On the subject died. The primary cause of death as reported by the investigator was complications of cardiomyopathy and endocarditis related to complications of thalassemia and sepsis.

The subject had a medical history of β-thalassemia major, multiple organ toxicities from iron overload, asthma, hypogonadism, congestive heart failure, endocarditis, mitral regurgitation, cardiomyopathy, tachyarrhythmias including atrial fibrillation, atrial flutter, and ventricular tachycardia. The subject had a past medical history of attempted flutter ablation in 1999, and since 19 SEP 2003 had an implantable defibrillator.

The investigator described this event as severe and not related to DFP.

Subject 114 (Case 2005AP000112)— Cardiac Failure

Case 2005AP000112 concerns an episode of cardiac failure experienced by a 45-year-old, splenectomized female subject (Subject 114; weight: 66.0 kg, height: 172.7 cm), with myelofibrosis enrolled in Study LA-04 (The Compassionate-use of Deferiprone in Subjects with Transfusion-Dependent Anemia and Chronic Iron Overload).

On 11 JUN 2004, the subject started deferiprone at a total daily dose of 4,000 mg orally for iron overload associated with end-stage myelofibrosis. Concomitant medications taken at the time of the onset of this event included Oxycontin (oxycodone HCl) 320 mg, Neurontin (gabapentin) 900 mg, Lovenox (enoxaparin) 100 mg, Lasix (furosemide) 160 mg, Ditropan (oxybutynin chloride) 10 mg, Bactrim DS (sulfamethoxazole/trimetho) 1,920 mg, Urocit (potassium citrate) 12 tablets, lactulose 60 cc, Urised (methenamine combinations) 8 tablets, Senokot S (senna) 4 tablets, K Dur (potassium chloride) 40 meq daily, and Dilaudid (hydromorphone HCl) 24 mg.

On the subject was admitted to the hospital after falling and suffering head trauma. A head CT showed no intracerebral bleeding; however, the subject was hospitalized because of severe weakness and shortness of breath. A chest CT showed moderate right-sided pleural effusion and questionable subclavian vein thrombosis and findings consistent with early pulmonary edema. She recovered and was discharged from the hospital on On the subject was admitted to the hospital for severe weakness, shortness of breath, and failure to thrive after falling and striking her head on . An ECG was obtained and showed sinus rhythm with a right axis deviation, incomplete right bundle branch block, and right ventricular hypertrophy. Chest x-ray showed a large consolidation at the right base. The subject recovered and was discharged from the hospital on .

On the subject died. The physician reported the primary cause of death as heart failure and cor pulmonale associated with end-stage myeloid fibrosis.

The subject had a medical history of myeloid metaplasia, hypercoagulable state leading to chronic pulmonary embolus, pulmonary hypertension and cor pulmonale with chronic hypoxemia, massive hepatomegaly and ascites secondary to myeloid fibrosis, chronic interstitial cystitis with urinary incontinence, perineal maceration, and acute myelogenous leukemia presently in remission.

The physician assessed the event as not related to therapy of deferiprone.

Subject 172 (Case 2005AP000512)— Cardiac Failure

Case 2005AP000512 concerns an episode of cardiac failure experienced by a 20-year-old nonsplenectomized male subject (Subject 172; weight: 48 kg; height: 165.1 cm) enrolled in Study LA-04 (The Compassionate-use of Deferiprone in Subjects with Transfusion-Dependent Anemia and Chronic Iron Overload). ApoPharma received reports of these events on 20 JUN 2005.

On , the subject was admitted to the hospital for continuous infusion of deferoxamine because of gradual worsening of his echocardiogram secondary to noncompliance with deferoxamine therapy. On 25 MAY 2005, deferiprone at a daily dose of 3,000 mg orally, was added to his regimen of deferoxamine for his end-stage cardiac disease secondary to iron overload. During hospitalization, he had one episode of transient unresponsiveness, which appeared to be related to Benadryl (diphenhydramine) and anxiety medication. He had progression of his pulmonary symptoms with respiratory distress and deteriorating left ventricular function (shortening fraction 22%). Ventilatory support was required. The concomitant medications included oral acetaminophen, albuterol, albumin, oral ascorbic acid , oral calcium carbonate, oral levocarnitine, oral diphenhydramine, dopamine, enoxaparin subcutaneous, oral ergocalcitriol, oral furosemide, heparin intravenous, insulin aspart, insulin NPH, metoclopramide, milrinone, ondansetron, oral psyllium, oral sertraline, oral spironolactone, testosterone, and oral zinc acetate.

On , the subject was transferred to a cardiac transplant facility because of progressive worsening of cardiac disease. While there, he developed a urinary tract infection and small growth of methicillin-resistant *Staphylococcus aureus* (MRSA) was observed in his sputum. On treatment, his condition improved; he was weaned off dopamine, and his milrinone dose was reduced. He commenced carvedilol, was extubated and transferred back to the original hospital on . Upon transfer, he was weaned off milrinone, and had daily monitoring of lactate levels. No changes were observed in the echocardiograms. He became able to sit, talk and walk in the intensive care unit. On , following his birthday party, he developed rapid increase in breathing and a falling blood pressure. At 11:30 p.m., he had a pulse oximetry of 99%, slow heart rate with a junctional rhythm in the 30s, and no pulse. Cardiopulmonary resuscitation was performed (6 doses epinephrine, one dose atropine, 2 doses calcium, and 3 doses bicarbonate were administered). Despite the interventions, he died at on . The cardiologist reported the terminal symptoms were secondary to the severe underlying cardiac disease. A stash of unswallowed medication was found hidden in his drawer.

During therapy with deferiprone CBC and liver function were regulary monitored. The lowest ANC was on 19 JUN 2005, WBC count of $4,800 \times 10^9$/L with 80% polymorphonuclear leukocytes. Platelet count ranged from 150,000 to $280,000 \times 10^6$/L. Creatinine ranged from 0.7 to 1.2 mg/dL; SGOT - from 48 to 250 and SGPT - from 60 to 150 U/L. There were occasional periods of nausea and one episode of vomiting.

The subject had a medical history of transfusion-dependant Aase syndrome, diabetes, panhypopituitarism, growth failure, pulmonary edema, and severe cardiomyopathy secondary to his iron overload.

The physician assessed this event as not related to deferiprone.

Case 2007AP000577 – Congestive Cardiac Failure

Case 2007AP000577 concerns an episode of fatal congestive heart failure complicated by sepsis in an 18 year old splenectomized male subject.

On 18 APR 2007, the subject was enrolled in the study (enrollment # 220) and started deferiprone at a total daily dose of 6500 mg orally (Lot # HD2374) for the treatment of transfusion-induced iron overload in combination with Desferal (deferoxamine mesylate) at a total daily dose of 9000 mg intravenously.

Relevant medical history included cardiomyopathy with severe congestive heart failure secondary to iron overload. Shortly after enrollment in the study, the patient experienced worsening of cardiac function. The subject had received transfusions every two months since childhood.

On he was transferred from Hackensack University Medical Center to Newark Beth Israel Medical Center for consideration of further treatment. On admission, the subject's blood pressure was 80/50 mm Hg with respiratory rate of 24 breaths per minute. Physical examination was notable for regular heart rhythm with clear lungs, and enlarged liver. On initial right heart catheterization with a Swan Ganz catheter showed a pulmonary artery (PA) pressure of 44/17 mm Hg with a mean of 27 mm Hg, a pulmonary capillary wedge pressure (PCWP) of 1 mm Hg, and PA oxygen saturation of 62%. Thermodilution cardiac output index was 2.68. The subject came on a variety of drips and these were adjusted over the course of the first day. Continuous wide gradient between pulmonary artery diastolic and wedge pressure was suggestive for a possible veno occlusive disease.

The subject developed a temperature spike with an elevated white count. Cultures grew gram positive cocci in clusters. Echocardiogram showed severely decreased left and right ventricular function as well as tricuspid regurgitation. Impression of infectious disease specialist was that it was necessary to change all lines.

On the subject was brought to the catheterization lab for placement of his right internal jugular latex free Swan Ganz catheter. In addition, his Port A Cath was removed by Interventional Radiology. The subject decompensated after placement of a new Swan Ganz catheter, and all efforts to resuscitate him were unsuccessful.

On the subject died of a combination of septic and cardiogenic shock despite all resuscitative efforts. Concomitant medications at the time of the event included K phos (potassium phosphate) orally, KCL (potassium chloride) 120 MEq orally daily, carvedilol 25 mg orally daily, captopril 18.5 orally daily, Lovenox (a low molecular weight heparin) 90 mg subcutaneously daily, Nexium (esomeprazole magnesium) 40 mg daily, furosemide 500 mg intravenously daily, milrinone 50 mg intravenously daily, M.V.I (multivitamin infusion) orally daily, Aldactone (spironolactone) 25mg orally daily, midodrine 30 mg orally daily, digoxin, maalox, and ibuprofen 1600 mg daily.

Allergies: severe allergy to latex.

The physician assessed the event as severe, serious and not related to the use of deferiprone. In the opinion of the investigator the subject died of congestive heart failure complicated by sepsis despite all resuscitative efforts.

Case 2008AP000592- Arrhythmia and Cardiac failure

Concerns an episode of arrhythmia and cardiac failure in 31-year old male subject with beta thalassemia major enrolled in Study LA 04 (Subject # 240): The Compassionate Use of deferiprone in Patients with Transfusion Dependent Anemia and Chronic Iron Overload.

On the patient was admitted to the Cardiac Intensive Care Unit at the University of California, San Francisco for the second time in a period of one month for heart failure and atrial fibrillation. Treatment with deferoxamine was initiated, but the patient's cardiac function continued to deteriorate. The patient's ejection fraction had fallen to 20% with a decline in blood pressure, which required placement of a balloon pump on . In the months prior to this admission, his cardiac MRI/T2* showed 7.1 ms, his liver SQUID showed an iron level of 13-14 mg/g dry weight, and the most recent ferritin level results were over 6000 ug/L.

On 27 Feb 2008 the treating physician requested ApoPharma for urgent release of deferiprone for compassionate use. The subject started deferiprone on at a total daily dose of 95.9 mg/kg orally (Lot # HD2374) in combination with Desferal (deferoxamine mesylate) at a total daily dose of 96 mg/kg but died the following day.

Medications at the time of the event included midazolam, sodium phosphate, ondansetron, heparin, potassium chloride), magnesium sulphate, calcium gluconate, dextrose 50% water, glucose chew-tab, haloperidol, dopamine HCL/dextrose 5% water, heparin sodium porcine, insulin aspart, testosterone, lidocaine, Aspirin (acetylsalicylic acid), cefazolin, Nephrovite (vitamin B complex), famotidine, Heparin-Loc, magnesium sulfate, hydromorphine, calcium gluconate, amiodarone, thrombin, Ducolax, multivitamins.

The physician assessed the event as severe, serious and not related to the use of deferiprone.

Case 2009AP002097- Cardiogenic shock

Concerns an episode of cardiogenic shock experienced by a 32-year old splenectomized female subject with thalassemia major.

The subject had a medical history of splenectomy (1983- at age 6 years), chronic hepatitis C (1998- at age 21 years), liver iron overload with hepatic iron concentration of 4.7 mg/gram dry weight liver (24 JAN 2008), cardiac iron overload with cardiac T2* of 6.41 milliseconds (24 JUL 2008) and babesiosis (17 JAN 2009), and on 31 JAN 2009, the ejection fraction from ECHO was 65 %. She was regularly transfused with approximately 3 units of packed red blood cells every 3 weeks. She was on chelation therapy with deferoxamine.

On the subject was admitted to the hospital for chronic iron overload with cardiac dysfunction. She had episodes of hypotension, arrhythmia, congestive heart failure and ascites during her stay in the hospital. On the subject began treatment with Desferal (deferoxamine mesylate) at a total daily dose of 4000 mg for heart failure. Cardiac MRI

performed on showed stable iron overload with cardiac T2* of 8.30 milliseconds. Her serum ferritin level ranged from 2000 to 6000 ng/mL between JAN 2008 and JAN 2009. She was transferred to cardiac care unit (CCU) with tachycardia on . The patient was treated with continuous intravenous infusion of Desferal at a dose of 4000 mg/day (75 mg/kg/day) for heart failure.

Concomitant medications from 23APR2009 included: amiodarone 400 mg/day orally and digoxin 0.125 mg/day orally for heart failure, Lovenox (heparin-fraction, sodium salts) 55 mg/day subcatuneous for prophylaxis, ergocalciferol 50,000 units for vitamin D deficiency, celexa (citralopram hydrobromide) 10 mg/day for depression and anxiety, nicotine 7 mg/day intradermal for withdrawal (tobacco withdrawal symptoms), Lantus (insulin glargine) 15 units subcutaneously for hyperglycemia, levothyroxine 125 mcg orally for hypothyroidisim, calcium carbonate 2500 mg/day orally for hypocalcemia, dopamine 2 mcg/ per minute for continuous hypotension, Levodopa, and Lasix 5 mg per hour continuous intravenous infusion for fluid overload.

On 12 MAY 2009 the subject's serum ferritin level was 1145 ng/mL and ejection fraction from echocardiogram (ECHO) was 15 %. On 15 MAY 2009, the subject's physician contacted ApoPharma requesting emergency release of deferiprone for her patient who was being treated in a step down unit for chronic iron overload with cardiac dysfunction.

On 15 MAY 2009, subject began therapy with deferiprone at a daily dose of 4000 mg/day (75.45 mg/kg/day) in combination with Desferal at a total daily dose of 4000 mg cardiac iron overload and on 19 MAY 2009 the dose of deferiprone reduced to 3500 mg/day (56.6 mg/kg/day) and the dose of Desferal was reduced to 3000 mg/day from 18 MAY 2009 to 20 MAY 2009.

On she developed worsening hypotension, edema, oliguria and acidosis. On she was treated with dopamine, 20 mcg/kg/min intravenously and levodopa 20 mcg/kg intravenously for hypotension and was moved to the Intensive Care Unit. Treatment with deferiprone was permanently discontinued on . The ejection fraction from ECHO was 15 % on . The subject died of cardiogenic shock on .

The Investigator considered the event severe and possibly related to the treatment with deferiprone.

**Neoplasms**

Subject 127 (Case 2005AP000749)— Lung Neoplasm Malignant

Case 2005AP000749 concerns an episode of malignant lung neoplasm experienced by a 65-year-old, nonsplenectomized female subject (Subject 127; weight: 51.8 kg, height: 155 cm) enrolled in Study LA-04 (The Compassionate-use of Deferiprone in Subjects with Transfusion-Dependent Anemia and Chronic Iron Overload).

The subject started deferiprone (total daily dose of 3,750 mg orally) on 19 APR 2004 for iron overload secondary to blood transfusions. On 14 FEB 2005, at the onset of the SAE (agranulocytosis), deferiprone was permanently discontinued. Concomitant medications

included oral nitroglycerine 20 mg, Protonix (pantoprazole) 40 mg, multivitamin 1 tablet, ASA 81 mg, Bisoprolol 2.5 mg, Actonel (risedronate sodium) 35 mg, Oscal (calcium carbonate) 1 tablet, Altace (lovastatin) 10 mg, Zocor (simvastatin) 20 mg, Celebrex (celecoxib) 200 mg, Compazine (prochlorperazine edisylate, dose and route are unknown), Arava (leflunomide, dose and route are unknown), thalidomide 100 mg/d, Vidaza (5-azacitidine) 75 mg/d subcutaneous for 7 days, and quinine 324 mg/d orally.

On the basis of the results of the left lung core biopsy performed on the subject was diagnosed with non–small-cell lung cancer on . For the lung cancer, she received only radiation therapy because she was not able to receive any chemotherapy.

At the physical exam on she presented with a swollen left calf and ankle. The ultrasound of the deep veins of the left leg demonstrated no evidence of deep vein thrombosis. On the subject was admitted to the emergency department after having been found lying on her kitchen floor. The following diagnosis, symptoms and signs were recorded: abnormal ECG, dehydration, hepatic enzyme abnormalities, significant thrombocytopenia, hyperglycemia, and chronic back pain secondary to compression fractures and osteoporosis. The same day, the subject was transferred to the medical unit. On the subject died.

She had a medical history of refractory anemia with ring sideroblasts, osteoporosis, gastroesophageal reflux, peripheral vascular disease, left femoral arterial occlusion and bypass surgery, bilateral carotid disease and left carotid endarterectomy in JUN 2004, coronary artery disease and angioplasty for unstable angina in AUG 2001, and breast and cervical cancer, presently in remission.

The physician assessed the event not related to the use of deferiprone.

<u>Subject ID# LA04-224 (Case 2009AP004320)- Pleural Effusion</u>

Concerns an event of pleural effusion secondary to lung neoplasm experienced by a 72-year old male subject diagnosed with myelodysplastic syndrome.

On 09 OCT 2007, the subject started deferiprone at a daily dose of 100 mg/kg/ day (7500 mg/day) for the treatment of transfusion-induced iron overload.

In JUN 2009, the subject started to develop left-sided pleural effusions. He experienced chest pains on the left side with shortness of breath. A chest x-ray showed a large pleural effusion. On subject had a thoracentesis and 1.6 liter of citrine fluid which was on the left side and located by ultrasound was removed. On the subject was admitted to emergency room for left-sided chest pain. The chest X-ray exam on the same day confirmed the new accumulation of minimal fluid but also a shadow on the left lung field. He had a protrusion on one of the ribs at the level of the 8th to 6th intercostals space on the posterior axillary line. On the CT scan of the chest with IV contrast confirmed large left pleural effusion and revealed new accumulation of fluid, the presence of few slightly prominent nodes in mediastinum, an irregular focal density in the periphery of the right mid lung, structural lung changes with the impression of underlying chronic obstructive pulmonary disease (COPD) and enlargement of the spleen. On the cytology report revealed the presence of atypical cells based on microscopic examination of smear cells, and recurrent pleural effusions

were proved to be malignant.

On the subject was hospitalized for malignant pleural effusion and lung cancer and developed atrial fibrillation and congestive heart failure. Therapy with deferiprone was discontinued on the same day. No tissue diagnosis was done due to the frailty of the subject. He also had a fall with fracture of his shoulder and right hip. From the date of his admission, the subject had chosen to be on palliative care with comfort measures and not aggressive medications or procedures. From 20 SEP 2009, he was treated with morphine 10 mg/hour subcutaneously using CAD infusion pump, intravenously as needed for pain control, budesonide, 0.5 mg/twice a day by inhalation and combivent, 0.5 to 2.5 mg by inhalation four times a day for chronic obstructive pulmonary disease, digoxin, 0.125 mg/day orally for atrial fibrillation, Lasix, 40 mg/day orally, for atrial fibrillation and congestive heart failure, and Tinzaparine, 4500 units, subcutaneously for prevention of deep vein thrombosis. On the subject died of pleural effusion due to lung cancer. No autopsy was done.

Relevant medical history includes refractory anemia diagnosed on 04 AUG 2004, benign prostate hypertrophy, hypertension, myelodysplastic syndrome, acute respiratory disease. The subject is a long life smoker.

The concomitant medication was reported as tamsulosin, 0.4 mg/day orally, for benign prostatic hypertrophy.

The investigator considered the malignancy of the lung not to be related to use of deferiprone; the subject had risk factors for lung malignancy. He was a smoker for many years with chronic obstructive pulmonary disease (COPD).

Subject ID# LA04/06B-98 (Case 2009AP004924) - Adenocarcinoma

Concerns an episode of adenocarcinoma experienced by a 53-year old splenectomized female with thalassemia major.

The subject has been on treatment with deferiprone since MAY 1995 with history of hepatitis C. The subject had a medical history of chronic arthritic pain in knees, hip, back and more recently in abdomen and chest.

At the time of the event the subject was treated with deferiprone at a dose of 96.93 mg/kg/day (6000 mg/day), for iron overload. On the subject was admitted to hospital due to pneumonia and hepatic mass L5 vertebra and retroperitoneal intra-abdominal lymphadenopathy. The last dose of deferiprone was admininistred on 19 NOV 2009. On 20 NOV 2009, treatment with deferiprone was discontinued. On the chest X-ray showed bilateral interstitial and alveolar lung opacities and the physical exam showed significant 2+ pitting edema of the lower extremities. At this time, the subject's diagnosis remained unclear. The subject remained in the hospital and received antibacterial treatment. The follow-up chest CT showed some clearing of the airspace opacities with residual minimal patchy lower lung airspace opacities and some linear atelectatic opacities. The subject also presented with ongoing abdominal and back pain and MRI showed an expansile lesion involving the L5 vertebra and extensive retroperitoneal and intra-abdominal lymphadenopathy. The subject remained on treatment with 4 liters of oxygen by nasal cannula, and she continued to have shortness of breath

on exertion and remained afebrile.

On the subject had a liver biopsy confirming the presence of malignant tumor cells. The slides, including cell block, showed clusters of highly pleomorphic cells, with irregular, enlarged, hyperchromatic nuclei with coarse chromatin, and vague gland formation was present in some areas. These findings were consistent with adenocarcinoma, and immunostains showed that carcinoma was positive for AE1-AE3, cytokeratin 7 (CK-7), and carcinoembryonic antigen (CEA) (diffuse pattern), but negative for α-fetoprotein (AFP) and HepPar-1. Although hepatocellular carcinoma was in the morphologic differential, this staining pattern was considered not typical, and the final diagnosis was of metastatic liver cancer. The subject's condition became progressively worse and the patient passed away on

The final diagnosis provided by the reporter for the subject was "metastatic adenocarcinoma of unknown primary origin". The death certificate specifies metastatic liver carcinoma as immediate cause of death. No autopsy was performed.

The investigator considered the events serious, and not related to the use of deferiprone.

Subject ID: CF-41 (Case 2007AP000570) – Hepatic cirrhosis; Hepatocellular Carcinoma

Case 2007AP000570 concerns a 35 year old splenectomized male subject with beta thalassemia major who developed hepatocellular carcinoma (HCC) while receiving deferiprone for transfusion –induced iron overload in compassionate use programs LA-03 and LA-04 sponsored by Apotex (Subject ID: CF-41).

The subject first began treatment with a non-Apotex formulation of deferiprone in 1991 in an investigator-initiated program conducted at the Hospital for Sick Children in Toronto. The subject had previously received Desferal (deferoxamine) which he stopped taking in SEP 1991 due to a skin rash. As the weight of the subject remained stable at about 70 kg, he received a steady daily dose of deferiprone at approximately 5000 mg (75 mg/kg/day) divided t.i.d. with minor variations and short interruptions throughout the entire treatment duration. Treatment with deferiprone was first interrupted in 1992 due to arthralgia and resumed on 21 OCT 1993 when the patient was enrolled in the LA 03 compassionate use program. Four years later the subject was rolled over into LA 04, an extension of the LA 03 program. A 1997 medical report from his primary care physician indicated that the subject demonstrated a history of excellent compliance with chelation treatment regimen during the LA 03 study. No data are available on subject's compliance during the LA 04 study. The last 3 monthly supply of deferiprone was shipped to the investigator in JUL 2005. As the investigator retired and stopped sending reports, the exact date of the last dose of deferiprone is unknown, but is estimated to be in NOV 2005.

History of the present illness

Liver cirrhosis with marked hemosiderosis was first mentioned in the available medical records on 25 May 1992 (about a year after he started deferiprone) and was noted to be stable between 1992 and 1997. Cirrhosis was largely attributed to iron burden and coincident presence of hepatitis C. In 1997, the subject was treated with interferon; however, therapy was discontinued due to recurrent episodes of hypoglycemia. The second attempt to treat hepatitis C was made in 2002 and resulted in severe hypoglycemic reaction requiring hospitalization.

Chelation treatment with deferiprone was effective as demonstrated by the resolution of symptoms of congestive heart failure and the reduction in iron burden. His liver iron concentration (LIC) reduced from 15.9 mg/g determined by liver biopsy in 1991 to 4.4 mg/g in 1996 (SQUID) and then further reduced to 0.6 mg/g in 1997 (liver biopsy). Serum ferritin was 3424 ug/L in 1991. Mean serum ferritin level dropped from 1915.40 ug/L (1993- 1994) to 721.00 ug/L (1995- 1997). By 2000, ferritin levels were consistently in the 400 to 600 ug/L range. Congestive heart failure was first diagnosed in 1987. The subject became asymptomatic and his systolic function normalized by 1996 (as determined by exercise radionuclide angiogram of 9 OCT 1996). The improvement in cardiac function was attributed to the reduction in cardiac siderosis. However, after 1997 the patient experienced progression of liver fibrosis as well as iron overload. His ferritin levels reached 800 to 1000 ug/L by NOV 2001, and then doubled by NOV 2003 (mean ferritin level in 2003 was 2218.33 ug/L). His liver biopsy in AUG 2006 revealed HCC. The subject received a liver transplant in . His native liver after explantation showed massive iron overload with LIC of over 40 mg/g dry hepatic weight. Two moderately differentiated hepatocellular carcinomas and one dysplastic nodule were noted. The pathologist's report concluded that "iron was a co factor in the development of cirrhosis". During lengthy transplant recovery the subject developed cholestasis and ischemic cholangitis. He was started on a moderate dose of IV deferoxamine shortly after receiving his transplant and did not experience any adverse effects. In early (while still in the hospital) he developed a sudden respiratory collapse that required mechanical ventilation in the intensive care unit. At that time, the subject was also diagnosed with sepsis and multi organ failure.

The subject experienced a cardiac arrest on from which he was successfully resuscitated but his blood pressure remained critically low despite progressive inotropic support.

An echocardiogram obtained on showed moderate left ventricular dysfunction with ejection fraction of 25 %. This was a significant deterioration compared to echocardiogram obtained 29 DEC 2006, which showed normal ventricular function and ejection fraction of >60%. The patient died the next day on .

Previous medical history included diabetes mellitus (1980), hypoparathyroidism (1984), congestive heart failure secondary to cardiac iron overload (1987), hepatitis C (year unknown), splenectomy (1982), osteoporosis (2003), infectious colitis (2006), nephrolithiasis (2006), and bilateral knee arthroplasty (2006). His concomitant medications included insulin since 1985, calcitriol since 1984, Septra (trimethoprim and sulfamethoxazol) since 1980, and testosterone.

A letter from the family physician dated 11 APR 2007 indicated that, although deferiprone may have exacerbated hepatic cirrhosis, too many confounding variables existed to make a definitive causal connection. Numerous other co morbidities were likely unrelated to deferiprone. Complications of cirrhosis were the cause of death.

Subject #207 (Case 2007AP001295)- Acute myelogenous leukemia

Concerns a 74 year old male subject with myelodysplastic syndrome enrolled in Study LA 04 (The Compassionate Use of Deferiprone in Patients with Transfusion-Dependent Anemia and Chronic Iron Overload).

On 21 Jul 2006, the subject started deferiprone at a daily dose of 94 mg/kg/day orally (Lot # HC4084) for the treatment of transfusion-induced iron overload.

On the patient was admitted to hospital for acute myelogenous leukemia. He also presented congestive heart failure on admission. Start dates of the events of acute myelogenous leukemia and congestive heart failure were provided as 12 Jan 2007 and 21 Mar 2007, respectively. A flow cytometry and bone marrow aspiration confirmed acute myelogenous leukemia. Cardiac echography confirmed congestive heart failure. The patient was treated with codeine for cough, and monocor (bisoprolol fumarate) for congestive heart failure. The patient was also treated for concurrent pneumonia with ceftriaxone (intravenously) and azithromycin. Relevant medical history includes refractory anemia and congestive heart failure (secondary to iron overload). On 03 Apr 2007, deferiprone was discontinued and the patient was withdrawn from the compassionate use program. The patient expired on .

The investigator considered the event serious, severe, and not related to the use of deferiprone.

**Multiorgan Failure**

Subject 39 (Case 2002AP000374) — Multiorgan Failure

Case 2002AP000374 concerns an episode of multiorgan failure experienced by a 68-year-old male splenectomized subject with myelofibrosis (Subject 39) enrolled in Study LA-04 (The Compassionate use of Deferiprone in Subjects with Transfusion-Dependent Anemia and Chronic Iron Overload).

On 14 JUL 1997, the subject began deferiprone therapy for the treatment of iron overload at a dose of 75 mg/kg/d orally. The subject was enrolled in the program because of severe multiple ulcerations at the sites of deferoxamine infusion. His serum ferritin at the start of deferiprone was 5,077 µg/L. The subject had a history of neutropenia (ANC of 0.6 to 2.0 $\times 10^9$/L) before initiation of deferiprone therapy. On 15 DEC 1997, he developed a viral infection with ulceration of the mouth, and therapy with deferiprone was interrupted; his ANC was 0.8 $\times 10^9$/L, which was within the range observed during the previous 5 months (0.5 to 1.9 $\times 10^9$/L). The event resolved on 29 DEC 1997 and therapy with deferiprone was restarted. The subject's ANC at that date was 1.20 $\times 10^9$/L. On 09 JAN 1998, the subject developed a severe purulent nasopharyngitis, dysphagia, and hoarseness; deferiprone therapy was interrupted. The event was managed with antibiotics. The ANC value on 06 JAN was 1.94 $\times 10^9$/L. On the subject was hospitalized and treated with multiple antibiotics until . Three weeks later, he developed pneumonia and hepatic and renal failure. The subject died of multiorgan system failure on . Deferiprone therapy had been discontinued for days prior to the subject's death. At the onset of pneumonia, the ANC was 1.29 $\times 10^9$/L, and concomitant medications included Daypro (oxaprozin) 1,200 mg/d, Prinivil (lisinopril) 40 mg/d, Lasix (furosemide) 40 mg/d, Micronase (glyburide) 5 mg/d, and Lanoxin (digoxin) 0.25 mg/d, all taken orally. No autopsy was performed.

The subject had a medical history of myelofibrosis, atrial fibrillation, and congestive heart failure.

The treating physician declared the complications of the subject's underlying diseases as the

probable cause of death and did not relate it to treatment with deferiprone.

**Diarrhea**

Subject 107 (Case 2002AP000750)— Diarrhea

Case 2002AP000750 concerns an episode of diarrhea experienced by a 33-year-old splenectomized male β-thalassemia/hemoglobin E subject (Subject 107; height: 155 cm, weight: 41 kg) that was enrolled in Study LA-11 (Efficacy and Safety of Deferiprone in β-Thalassemia/Hemoglobin E Diseases Subjects in Thailand).

The subject began deferiprone treatment on 11 AUG 2000 at a daily dose of 1,000 mg/d (50 mg/kg/d) because of severe iron overload. On 03 JAN 2001, the subject had his regular visit to the thalassemia center. On he experienced hyperpyrexia and acute diarrhea. He was hospitalized for hyperpyrexia and severe acute diarrhea, and treatment with deferiprone was discontinued. On that day, his ANC was $4.48 \times 10^9$/L. He died on because of acute severe diarrhea. Concomitant medication before the onset of the event was folic acid 5 mg/d, orally.

The investigator reported the event as severe with no relationship to deferiprone.

**Trauma/Post-Surgical Complications**

Subject 604 (Case 2002AP000445)— Internal Injury

Case 2002AP000445 concerns an episode of internal injury experienced by a 22-year-old splenectomized male subject (Subject 604; height: 157 cm; weight: 43.2 kg) with thalassemia major and history of positive hepatitis C antibody enrolled in Study LA-06 (Maintenance Trial of Deferiprone) in LA-02 Subjects).

The subject began deferiprone therapy for the treatment of iron overload at a dose of 75 mg/kg/d orally on 24 MAR 1995. He was hospitalized on for severe cranial and abdominal trauma (liver laceration and nephrectomy) caused by a car accident. At the time of the accident, DFP treatment had been interrupted since 23 NOV 1999 for decreased ferritin. On this subject died because of injuries sustained from the accident. The concomitant medications at the onset of the event included Fenospen (phenoxymethylpenicillin) for splenectomy and Cardioaspirina (acetylsalicylic acid) for thrombocytosis.

The investigator considered the event as severe with a doubtful relationship.

Subject 49 (Case 2006AP000365)— Postprocedural complication

Case 2006AP000365 concerns an episode of severe fractures, postsurgical complications experienced by a 45-year-old splenectomized male subject (Subject 49; weight: 63.5 kg, height: 166 cm) with homozygous β-thalassemia major and transfusional hemosiderosis enrolled in Study LA-04 (The Compassionate-use of Deferiprone in Subjects with Transfusion-Dependent Anemia and Chronic Iron Overload). ApoPharma received report of this event on 15 MAY 2006.

Subject originally commenced therapy with deferiprone on 28 DEC 1998, with interruption from 04 SEP 2002 until 04 MAR 2004 because of progressive hearing loss unrelated to deferiprone. He reinitiated therapy with deferiprone on 05 MAR 2004 at a total daily dose of 4,750 mg (75 mg/kg/d). Before the accident, he was taking amiodarone 200 mg/d orally, Coumadin (warfarin) 4 mg/d orally, Synthroid (levothyroxine) 50 µg/d orally, Lantus (insulin) 20 U/d subcutaneously and Lasix (furosemide) 20 mg/d orally.

On the subject fell off a motorbike and broke both humeri and the left femur, for which he was hospitalized. He had irrigation and debridement of an open femur fracture with open reduction and internal fixation of an intercondylar/supracondylar femur fracture. There were no complications during the surgery. However, subsequently the subject became hypotensive, requiring vasopressors. He was treated with broad-spectrum antibiotics throughout the entire course. He was intubated because of respiratory distress and was extubated when improved, but required intubation a second time for mechanical ventilation. Throughout his course, it was never possible to wean him off the pressors.

The patient developed progressive multiorgan failure related to his impaired cardiovascular status with renal and liver failure and passed away on . An autopsy was refused by the family.

The subject had a history of chronic congestive heart failure, pulmonary hypertension, tachyarrhythmia, hyperglycemia, diabetes mellitus, and hypothyroidism. He also had ototoxicity, which was ascribed to dereroxamine, and required a cochlear implant in DEC 2003.

The investigator described the event as severe and not related to the use of deferiprone, which had been discontinued approximately 3 weeks earlier upon his last hospitalization.

Subject ID# LA04-222 (Case ID 2010AP001844) - Intestinal obstruction

Concerns a 53-year-old non- splenectomized female patient with hereditary haemochromatosis and transfusion-induced iron overload.

The subject had a medical history of mitochondrial disease from 20 NOV 2004, mild congestive heart disease from 01 SEP 1990, hypothyroidism from 01 OCT 1990 and hyperaldosteronism from 15 AUG 1998.

On 02 FEB 2009, the subject started deferiprone at a total daily dose of 60 mg/kg/day (3000 mg/day) orally for the treatment of iron overload and on 23 APR 2009, the dose was increased to 75 mg/kg/day (3700 mg/day).

The subject had a history of multiple abdominal adhesions. On an unknown date, the patient was hospitalized for laparoscopic surgery to correct the problem, but post surgery, she experienced abdominal obstruction. On the subject died. During the treatment with deferiprone her neutrophil counts were within the normal range.

Concomitant medications at the time of the onset of the event were not reported.

The investigator considered the event serious, and not related to the use of deferiprone.

# H Pooled Safety Data: Summary of Non Fatal Serious Adverse Events, irrespective of causality, in at least one deferiprone treated patient

| | Total No. of patients exposed (N=642) | |
|---|---|---|
| | Patients | |
| **Body system<br>Preferred term** | **#** | **%*** |
| **Blood and lymphatic system disorders** | **57** | **8.9** |
| Neutropenia | 39 | 6.1 |
| Agranulocytosis | 11 | 1.7 |
| Lymphadenitis | 6 | 0.9 |
| Thrombocytopenia | 2 | 0.3 |
| Lymphadenopathy | 1 | 0.2 |
| **Cardiac disorders** | **13** | **2.0** |
| Cardiac failure congestive | 5 | 0.8 |
| Atrial fibrillation | 4 | 0.6 |
| Atrial flutter | 2 | 0.3 |
| Angina unstable | 1 | 0.2 |
| Cardiac failure | 1 | 0.2 |
| Cor pulmonale | 1 | 0.2 |
| Intracardiac thrombus | 1 | 0.2 |
| Torsade de pointes | 1 | 0.2 |
| **Ear and labyrinth disorders** | **2** | **0.3** |
| Deafness | 1 | 0.2 |
| Vertigo | 1 | 0.2 |
| **Gastrointestinal disorders** | **6** | **0.9** |
| Abdominal pain | 4 | 0.6 |
| Colitis | 1 | 0.2 |
| Pancreatitis | 1 | 0.2 |
| **General disorders and administration site conditions** | **8** | **1.2** |
| Pyrexia | 7 | 1.1 |
| Pain | 1 | 0.2 |

1) Treatment Emergent Adverse Events are coded with MedDRA Dictionary Version 13.0.
2) * Percentage is calculated out of the 642 patients exposed.
3) Data cutoff date: 31AUG2010

| Body system<br>Preferred term | Total No. of patients exposed (N=642)<br>Patients<br># | <br><br>%* |
|---|---|---|
| **Hepatobiliary disorders** | **3** | **0.5** |
| Cholelithiasis | 1 | 0.2 |
| Hepatic congestion | 1 | 0.2 |
| Hepatitis | 1 | 0.2 |
| **Infections and infestations** | **33** | **5.1** |
| Cellulitis | 5 | 0.8 |
| Gastrointestinal infection | 3 | 0.5 |
| Infectious mononucleosis | 3 | 0.5 |
| Device related infection | 2 | 0.3 |
| Device related sepsis | 2 | 0.3 |
| Pharyngotonsillitis | 2 | 0.3 |
| Pneumonia | 2 | 0.3 |
| Sepsis | 2 | 0.3 |
| Urinary tract infection | 2 | 0.3 |
| Acute sinusitis | 1 | 0.2 |
| Bacteraemia | 1 | 0.2 |
| Bacterial infection | 1 | 0.2 |
| Bacterial sepsis | 1 | 0.2 |
| Bronchopneumonia | 1 | 0.2 |
| Corneal abscess | 1 | 0.2 |
| Cytomegalovirus hepatitis | 1 | 0.2 |
| Gastroenteritis viral | 1 | 0.2 |
| Influenza | 1 | 0.2 |
| Meningitis bacterial | 1 | 0.2 |
| Pyelonephritis | 1 | 0.2 |
| Serratia sepsis | 1 | 0.2 |
| Sinusitis | 1 | 0.2 |
| Staphylococcal infection | 1 | 0.2 |
| Tonsillitis | 1 | 0.2 |

1) Treatment Emergent Adverse Events are coded with MedDRA Dictionary Version 13.0.
2) * Percentage is calculated out of the 642 patients exposed.
3) Data cutoff date: 31AUG2010

| | Total No. of patients exposed (N=642) | |
|---|---|---|
| | Patients | |
| **Body system<br>Preferred term** | **#** | **%*** |
| Upper respiratory tract infection | 1 | 0.2 |
| Viral infection | 1 | 0.2 |
| Yersinia infection | 1 | 0.2 |
| **Injury, poisoning and procedural complications** | **11** | **1.7** |
| Femur fracture | 2 | 0.3 |
| Road traffic accident | 2 | 0.3 |
| Transfusion reaction | 2 | 0.3 |
| Femoral neck fracture | 1 | 0.2 |
| Foot fracture | 1 | 0.2 |
| Hip fracture | 1 | 0.2 |
| Sternal fracture | 1 | 0.2 |
| Thoracic vertebral fracture | 1 | 0.2 |
| **Investigations** | **4** | **0.6** |
| Arthroscopy | 2 | 0.3 |
| Blood glucose increased | 2 | 0.3 |
| **Metabolism and nutrition disorders** | **9** | **1.4** |
| Diabetic ketoacidosis | 3 | 0.5 |
| Diabetes mellitus | 2 | 0.3 |
| Hypoglycaemia | 2 | 0.3 |
| Dehydration | 1 | 0.2 |
| Hypocalcaemia | 1 | 0.2 |
| Hypokalaemia | 1 | 0.2 |
| **Musculoskeletal and connective tissue disorders** | **6** | **0.9** |
| Back pain | 2 | 0.3 |
| Bursitis | 1 | 0.2 |
| Intervertebral disc protrusion | 1 | 0.2 |
| Joint effusion | 1 | 0.2 |
| Musculoskeletal pain | 1 | 0.2 |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **1** | **0.2** |

1) Treatment Emergent Adverse Events are coded with MedDRA Dictionary Version 13.0.
2) * Percentage is calculated out of the 642 patients exposed.
3) Data cutoff date: 31AUG2010

| Body system<br>Preferred term | Total No. of patients exposed (N=642)<br>Patients<br># | <br><br>%* |
|---|---|---|
| Leukaemia | 1 | 0.2 |
| **Nervous system disorders** | **1** | **0.2** |
| Encephalitis | 1 | 0.2 |
| **Psychiatric disorders** | **4** | **0.6** |
| Confusional state | 1 | 0.2 |
| Major depression | 1 | 0.2 |
| Oppositional defiant disorder | 1 | 0.2 |
| Self injurious behaviour | 1 | 0.2 |
| Suicidal ideation | 1 | 0.2 |
| **Renal and urinary disorders** | **3** | **0.5** |
| Renal colic | 2 | 0.3 |
| Nephrolithiasis | 1 | 0.2 |
| **Respiratory, thoracic and mediastinal disorders** | **4** | **0.6** |
| Chylothorax | 1 | 0.2 |
| Pulmonary congestion | 1 | 0.2 |
| Pulmonary oedema | 1 | 0.2 |
| Respiratory distress | 1 | 0.2 |
| **Surgical and medical procedures** | **21** | **3.3** |
| Splenectomy | 8 | 1.2 |
| Cholecystectomy | 3 | 0.5 |
| Knee operation | 3 | 0.5 |
| Adenotonsillectomy | 1 | 0.2 |
| Catheterisation venous | 1 | 0.2 |
| Hernia repair | 1 | 0.2 |
| Lithotripsy | 1 | 0.2 |
| Meniscus operation | 1 | 0.2 |
| Nail operation | 1 | 0.2 |
| Tympanoplasty | 1 | 0.2 |
| Ureterolithotomy | 1 | 0.2 |

1) Treatment Emergent Adverse Events are coded with MedDRA Dictionary Version 13.0.
2) * Percentage is calculated out of the 642 patients exposed.
3) Data cutoff date: 31AUG2010

| Body system<br>Preferred term | Total No. of patients exposed (N=642)<br>Patients<br># | <br><br>%* |
|---|---|---|
| Urethral repair | 1 | 0.2 |

1) Treatment Emergent Adverse Events are coded with MedDRA Dictionary Version 13.0.
2) * Percentage is calculated out of the 642 patients exposed.
3) Data cutoff date: 31AUG2010

# I Narratives of fatal agranulocytosis cases from postmarketing

Case 2003AP000129 – Agranulocytosis

Case 2003AP000129 concerns an episode of agranulocytosis in a 60-year-old male patient with hemochromatosis, reported by the German Health Authority. ApoPharma received a report of this event on 10 FEB 2003.

The patient had inborn hemochromatosis for which he had been treated with Desferal® since 1995. Desferal® was stopped in 2000 due to allergic side effects.

On 01 AUG 2002, the patient commenced treatment with deferiprone (batch number unknown) at an unknown oral dose. The last blood profile from SEP 2002 was normal. The patient developed flu-like symptoms on 20 OCT 2002 while on vacation. On the patient was prescribed a drug containing paracetamol (750 mg) and chlorpheniramine (chlorfenamin) and an antibiotic because of a high fever. The following day the patient developed multiple painful nodular swellings on the neck. The patient was hospitalized. The blood profile showed severe leucopenia, ANC $0.2 \times 10^9$/L, normal hemoglobin and normal platelet count. Liver and kidney function, as well as electrolytes were normal. The patient developed severe shortness of breath secondary to tracheal compression and that required intubation and mechanical ventilation. Though treated with steroids and antibiotics (Tazobac® and gentamycin) the patient's condition did not improve. Blasts were undetectable in the peripheral blood; bone marrow examination showed a total lack of WBC lines. On the patient was transferred in a hemodynamically stable condition to a clinic by air transport. The lymph nodes decreased and were no longer palpable. The leukopenia persisted despite treatment with granulocyte stimulating factor. A percutaneus dilatation tracheostomy was performed on and antibiotic therapy was changed to Zienam® on 31 OCT 2002 and the following day was extended with Targocid and antifungal therapy. Fluconazole, which was started on 31 OCT 2002, was changed to caspofungin on 05 NOV 2002 under continuous veno-venous hemofiltration. Blood cultures were positive for fungi and mycobacteria. Because of persistent leukopenia the treatment with granulocyte stimulating factor was continued. Subsequent bone marrow biopsy still showed lack of WBC lines. From the patient's condition deteriorated, with pulmonary edema and the development of acute respiratory distress syndrome. In spite of extensive therapeutic steps the loss of pulmonary capacity could not be restored and the patient died on due to septic shock.

An autopsy, performed on indicated a drug-induced agranulocytosis after combination therapy including salicylic acid-containing drugs. This combination has been described in the literature to cause asthma-like conditions, bronchospasms and also agranulocytosis. The autopsy suggested that the cause of death was fungal sepsis with presence of fungi found in all organs: fungal myocarditis, fungal emboli in kidney, spleen, and lungs. Signs of fungal infection were also present in the GI tract with necrosis of mucous membrane of the stomach and necrotizing gastritis with small ulcerations.

Bosselated cirrhosis of the liver with ascites and splenomegaly as well as siderosis of the pancreas were confirmatory for the diagnosis of hemochromatosis.

The reporter states that the drug-induced agranulocytosis is most likely the possible cause of death and the fact cannot be excluded that deferiprone in combination with paracetamol may be responsible for the case. No further information has been received on this event.

ApoPharma commented that agranulocytosis has also been reported with chlorpheniramine use. Concomitant chlorpheniramine use commenced one day prior to the onset of events in this case. In addition, deferiprone® was being used in this patient for the treatment of hemochromatosis, an off-label indication for this product.

ApoPharma has assessed this case as a serious, unexpected ADR possibly related to deferiprone.

Case 2003AP000464 – Agranulocytosis

Case 2003AP000464 concerns a fatal episode of pneumonia and agranulocytosis in a male patient of unknown age with red cell aplasia, reported in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA). ApoPharma initially received a report of this event on 20 NOV 2003.

On 24 APR 2002, the patient commenced treatment with deferiprone (batch number unknown) at an oral daily dose of 1,750 mg for the treatment of iron overload (serum ferritin >4,000 μg/L). The patient refused subcutaneous desferrrioxamine therapy. The patient's medical history included bone marrow depression and resistance to cyclosporin and steroids. On 14 MAY 2002, deferiprone was withdrawn. The patient died from severe pneumonia secondary to agranulocytosis (date of death unknown). Concomitant medications for unknown indications taken prior to the onset of the event included temazepam 10 mg/day, Aspirin 75 mg/day, Frusemide (furosemide) 40 mg/day, and ramipril 2.5 mg twice a day, all since 1999. Additional information was requested through the Medicines and Healthcare products Regulatory Agency. No further information has been provided.

The reporter considered the event to be serious since the patient died due to the reaction, and probably related to the use of deferiprone.

ApoPharma has assessed this case as serious and possibly related to deferiprone.

Case 2003AP000465 – Agranulocytosis

Case 2003AP000465 concerns an episode of agranulocytosis in an 83-year-old female patient with red cell aplasia and myelofibrosis, reported by the MHRA. ApoPharma received a report of this event on 20 NOV 2003.

On 22 OCT 2002 the patient commenced treatment with deferiprone (batch number unknown) at an oral daily dose of 3,750 mg for the treatment of life-threatening iron overload. Before commencement of deferiprone , the patient was on Desferal® 4 g with blood transfusion since 1999; however, the drug was not well tolerated since the patient had experienced two episodes of severe cellulitis at the injection sites. On the patient developed agranulocytosis with septicemia and died as an outcome (date of death unknown). The probable cause of death was reported as agranulocytosis and nonspecific septicemia. Deferiprone was discontinued on . Additional information was requested through the Medicines and Healthcare

products Regulatory Agency, but no further information has been provided.

The reporter described this event as serious and probably related to the use of deferiprone.

ApoPharma has assessed this case as serious and possibly related to the use of deferiprone.

Case 2005AP000076 –Agranulocytosis

Case 2005AP000076 concerns an episode of sepsis and neutropenia in a 21-year-old female patient with beta-thalassemia, reported by a local distributor from the United Arabic Emirates. ApoPharma received a report of this event on 06 FEB 2005.

On 28 AUG 2004, the patient commenced treatment with deferiprone (Batch GL 2669) at a dose of 75 mg/kg/day orally (total daily dose 3,500 mg) for the treatment of iron overload due to regular blood transfusions. During the course of treatment the treating physician received a verbal report of decreased WBC count ($2.0 \times 10^9$/L) based on a blood analysis performed in a private laboratory. The WBC count was repeated on 25 OCT 2004 and 30 OCT 2004, with values at $8.6 \times 10^9$/L with 37% neutrophils and $5.7 \times 10^9$/L with 13% neutrophils, respectively. In the first week of NOV 2004, the patient was hospitalized because of septicemia and neutropenia. The patient died in the same week (exact date of death is unknown). Concomitant medications included Desferal® 3 g, four times per week, vitamin C 100 mg four times per week, folic acid 5 mg/day, and One Alpha® Leo (alfacalcidol) 1.25 mg three times a day. The patient's medical history was significant for beta-thalassemia and hypoparathyroidism.

Follow up #1 received on 08 APR 2008:

This Iranian patient was admitted to with pancytopenia. Weight and height were reported as 49.4 kg and 159 cm, respectively.

Agranulocytosis began on 14 OCT 2004. Ferriprox was stopped on admission to hospital on 14 OCT 2004. The patient died three days later on .

Septicemia was ruled out as a possible diagnosis. The patient was reported to have poor compliance with Desferal. Ferritin was reported as 3850 mcg/L. Serological results were negative for hepatitis C virus (HCV).

The treating physician considered the event serious and assessed the event related to the use of Ferriprox. The company assessed the events of agranulocytosis and pancytopenia as serious, severe, and related to Ferriprox.

Follow up #2 received on 25 JUL 2008:

The start date of the event was reported as 03 NOV 2004. On 25 OCT 2004, the patient was stable and the ANC value was 0.7 x10E9 /L. On 31 OCT 2004, Ferriprox therapy was stopped. The patient was admitted to in drowsy state and shock with one day history of sore throat, vomiting, and fever. On on arrival the ANC value was 0.1 x10E9 /L. The patient was treated with triple broad spectrum IV antibiotics. The blood culture revealed pseudomonas. On the treatment with GCSF started as

300 micrograms subcutanoulsy once daily and the patient received activated protein C (Xigris). The serum ferritin was 3150. She was diagnosed with severe neutropenia with septic shock and received Positive Inotrope support as needed but ANC value remained between zero to 0.02 x10E9 /L, but the patient continued to deteriorate developing acute respiratory distress syndrome (ARDS). Patient died on . The company assessment did not change with the follow-up information.

Case 2005AP000519 – Agranulocytosis

Case 2005AP000519 concerns an episode of agranulocytosis in a 20-year-old female patient with beta thalassemia, reported by a local distributor from the United Arabic Emirates. ApoPharma received report of this event on 27 JUN 2005.

On 07 AUG 2004, the patient commenced therapy with deferiprone (batch number unknown) at a dose of 75 mg/kg/day orally for the treatment of beta-thalassemia major. No other medical problems or allergies are known. On 04 JUN 2005, the patient developed neutropenia (ANC = $1.0 \times 10^9$/L). On 11 JUN 2005, the ANC fell to $0.6 \times 10^9$/L and deferiprone was stopped. On 14 JUN 2005, the patient's ANC was $0.0 \times 10^9$/L. Results from the bone marrow aspirate report on 22 JUN 2005 showed markedly reduced granulopoeisis without signs of malignancy. Urine, stool, and blood cultures were negative. Concomitant medications included Zinnat® (cefuroxime) for prophylaxis against infection (dose is unknown), Desferal® , vitamin C and folic acid (doses not provided). The patient died in on . No causality for this event was provided by the reporter. No further information has been provided on this event.

Follow up #1 received on 08 APR 2008:

The patient's date of birth was weight 49.1 kg, height 154cm. The patient received Ferriprox at a daily dose of 3500 mg divided in 3 doses. On the patient was admitted to with a history of chest infection. Lab results on admission revealed agranulocytosis ANC 0.18 x10E9/L. The patient was treated with G-CSF 300 SI s.c. (dates of G-CSF treatment not provided) and antibiotics: Tazocin 4.5 g QID, IV; Flucloxacillin 1 g QID IV; and Teicoplanin 400 mg BD IV.

Medical history included regular blood transfusions (ferritin 2100 mcg/L). Serological results for Hepatitis C Virus (HCV) were negative. Compliance to Desferal was poor. The patient was not splenectomized.

The reporter considered the event to be serious and causally related to Ferriprox. The company considered the event serious, severe, medically confirmed and related to the use of Ferriprox.

Follow up #2 received on 25 JUL 2008:

The start date of the event was 04 JUN 2005 when an ANC value of 0.1 x10E9/L was reported.

On the patient was admitted to with generalized body pain and low grade fever and the ANC value was 0.6 x10E9/L. The patient was under observation for 4 days. She was stable and febrile while treated with oral antibiotics. The ANC value remained

around 0.6 x10E9/L.

On the patient was discharged in good general condition but was re-admitted to with high grade fever, loose stool and right thigh pustular rash on . On 19 JUN 2005 the ANC value was 0.078 x10E9/L. On 20 JUN 2005, the ANC value was 0.186 x10E9/L. The patient was treated with GCSF 300 units subcutaneously daily from 20 JUN 2005 until her death and with three IV antibiotics, namely Tazocin 4.5 g, Flucloxacillin 1 g and Teicoplanin 400 mg.

The ANC value reached zero and never recovered. The patient continued to deteriorate over five days and went into septic shock and acute respiratory distress syndrome (ARDS). Patient died on . The company assessment did not change with follow-up information.

ApoPharma considered this event as serious and probably related to deferiprone.

Case 2005AP001015 – Agranulocytosis

Case 2005AP001015 concerns an episode of agranulocytosis in a 40-year-old male patient with thalassemia major, reported by the regulatory agency in Italy. ApoPharma initially received a report of this event on 16 DEC 2005. Initially, the priority of this report was qualified as periodic; however, the follow-up information received on 28 DEC 2005 changed it into the expedited mode of submission.

On 09 NOV 2005, the patient commenced treatment with deferiprone (Batch GX4489) at a dose of 68 mg/kg/day orally. On the patient experienced agranulocytosis (ANC values were not provided by the reporter) with sepsis, chills and fever, and was hospitalized. Deferiprone was permanently discontinued on 30 NOV 2005. The patient was treated with lenograstim and a therapeutic response was obtained at the increase of the dosage to 10 µg/kg/day when a "normalization of the hemochrome" was noticed by the treating physician.

Follow-up information received on 28 DEC 2005: The patient was treated with lenograstim and a therapeutic response was obtained at the increase of the dosage to 10 µg/kg/day, when a "normalization of the hemochrome" was noticed by the treating physician.

The patient experienced arterial hypertension with massive cerebral hemorrhage followed by coma. The patient died due to cerebral hemorrhage. The reporter considered agranulocytosis as possibly related to deferiprone. Concomitant medications included oral Plavix® (clopidogrel hydrogensulfate), Cardioaspirin® (acetylsalicylic acid), oral Seloken® (metoprolol tartate, 100 mg), oral Androgel® (testosterone, 25 mg), oral Pariet® (rabeprazole sodium, 10 mg), Lantus® (insulin glargine, 100 IU/mL) in injections, Humalog® (insulin lispro) in injections, and Desferal® (500 mg/day).

Additional follow-up information received on 29 DEC 2005 indicated that the patient was treated with deferiprone (batch number GX4489, expiry date 30 JUN 2010). The dose of Cardioaspirin® (acetylsalicylic acid) was also clarified as 100 mg.

On 30 DEC 2005, the duration of concomitant medications was provided: Plavix® (clopidogrel hydrogensulfate) for 1 month, Seloken® (metoprolol tartate, 100 mg) for 1 month, Androgel®

(testosterone, 25 mg) for 3 months, Pariet® (rabeprazole sodium, 10 mg) for 2 years, Lantus® (insulin glargine, 100 IU/mL) for 15 months, Humalog® (insulin lispro) for 15 months, Desferal® (500 mg) for 6 years, and Cardioaspirin® (acetylsalicylic acid, 100 mg) for 1 month.

ApoPharma has assessed this case as serious and possibly related to deferiprone.

Case 2005AP001024 –Agranulocytosis

Case 2005AP001024 concerns as episode of sepsis and agranulocytosis in a 34-year-old female patient with thalassemia major and a history of hemosiderosis, reported by a health professional in Italy. ApoPharma received a report of this event on 21 DEC 2005.

On 22 SEP 2005, the patient switched to therapy with deferiprone (batch number unknown) at a dose of 72 mg/kg/day orally (total daily dose 4,500 mg), because of intolerance to Desferal (deferoxamine). On an unspecified date the patient was hospitalized for sepsis. Blood analysis on 17 OCT 2005 revealed neutropenia (WBC = $3.14 \times 10^9$/L; ANC = $1.17 \times 10^9$/L and Hb = 69 g/L. On 19 OCT 2005, treatment with deferiprone was withdrawn. Subsequent blood analysis, performed on 24 OCT 2005 showed the following: agranulocytosis and severe anemia (WBC = $1.4 \times 10^9$/L; ANC = $0.05 \times 10^9$/L; platelets = 365 x $10^9$/L; and Hb = 59 g/L). On 24 OCT 2005, the patient underwent a blood transfusion for anemia. No information about concomitant medications was provided by the reporter. The patient died on .

A possible causal relationship with deferiprone was not excluded by the reporter.

ApoPharma considers this event as serious and probably related to deferiprone.

Case 2006AP000007 – Agranulocytosis

Case 2006AP000007 concerns an episode of agranulocytosis in a 17-year-old female patient (weight 50 kg; height 155 cm) with thalassemia major, spontaneously reported by a health professional in Turkey. ApoPharma received a report of this event on 04 JAN 2006.

The patient was receiving blood transfusions in 15-day periods and had been on Desferal® since 5 months of age. On 05 JUL 2005, the patient started combined iron chelation therapy with deferiprone (batch number unknown) at a dose of 60 mg/kg/day orally (total daily dose 3,000 mg) for 5 d/wk and Desferal® for 2 d/wk. WBC counts were performed on blood transfusion days.

On 05 DEC 2005, the patient developed neutropenia (WBC = $1.7 \times 10^9$/L with 60% of neutrophils; Hb = 8.0 g/dL, hematocrit (HCT) = 22.2, PLT = $267.000 \times 10^9$/L). Deferiprone was stopped on the same day. On the patient developed a fever of 39°C and was hospitalized in . On admission, the patient was pale, had hepatomegaly (+3 cm) and minimal splenomegaly; respiratory and cardiovascular systems were normal; no abdominal pain and no meningeal symptoms were found. Blood analysis showed agranulocytosis (WBC = $0.8 \times 10^9$/L with 60% of neutrophils, HCT = 24.2, Hb = 9.0 g/dL). Meropenem® (meropenem trihydrate) and amikacin sulfate were initiated to treat the event, and Targocid® (lyophilised teicoplanin) was later added on 11 DEC 2005. No dosage for these medications was provided by the reporter. On 14 DEC 2005 the therapy was

changed to Tazocin® (piperacillin sodium, tazobactam sodium), amikacin sulfate, and Targocid®. In addition, daily injections of Neupogen® (granulocyte colony stimulating factor) were started on 14 DEC 2005 and continued until 21 DEC 2005. The patient's therapy was changed to the following drugs: vancomycin, Sefagen® (cefotaxime sodium) and amikacin sulfate. On the patient's condition deteriorated. The patient was reported to be icteric, with tachypnea and bilateral rales in lungs; her consciousness became impaired and she developed maculopapular skin rash in the extremities and body. Blood pressure (BP) was 110/65 mm Hg. Laboratory findings were the following: pH = 7.52; $pCO_2$ = 30.2, $HCO_3$ = 25, $pO_2$ was between 93% and 98%; blood glucose = 140 mg/dL. Echocardiography was normal, and ultrasound showed minimal splenomegaly, and Grade I increase in renal parenchymal exogenity. Blood cultures were sterile. Blood analysis performed on confirmed agranulocytosis (WBC = $0.4 \times 10^9$/L, HCT = 21.6, PLT = $331.000 \times 10^9$/L), and the patient was transferred to on the same day. The following therapy was given to the patient: Cipro® 200 mg intravenously twice a day, Ambisome® 50 mg once a day, Zovirax® 250 mg b.i.d., daily s.c. injections of Neupogen® 30 U, Beloc® i.v. b.i.d., Antepsin® b.i.d., daily vitamin K, and Ulcuran® once a day. Blood analysis performed on 19 DEC 2005 showed an increased WBC count ($4.4 \times 10^9$/L); however, on 20 DEC 2005, the WBC was $0.6 \times 10^9$/L. The patient's condition did not improve and she was transferred to where she died on from septic shock. Blood analysis performed on showed WBC = $1.0 \times 10^9$/L. This patient had no significant medical history. Concomitantly the patient was receiving folic acid supplementation with Folbiol®. The treating physician considered the agranulocytosis related to deferiprone. Follow-up information was requested.

Follow-up information received by ApoPharma on 09 FEB 2006 provided an update on the dosage of deferiprone (75 mg/kg), hepatomegaly (the liver extended 3 cm below the right costal margin), pharyngeal hyperemia, icterus, maculopapular rash, splenomegaly of about 1 cm, negative blood cultures, elevated liver enzymes (i.e., serum AST and ALT), findings of miliary tuberculosis (TB)/pneumoconiosis, with pleural effusion and an infarction posterolaterally in the right caudate nucleus. The liver appeared normal (not enlarged) on the CT scan.

The additional information provided was an update of the patient's clinical condition and does not change ApoPharma's assessment as medically confirmed, and serious. The company has assessed this event as probably related to deferiprone. The date of receipt of the original report was 04 JAN 2006 and not 04 JAN 2005.

Case 2006AP000205 – Agranulocytosis

Case 2006AP000205 concerns an episode of agranulocytosis in a 40-year-old male patient with alpha thalassemia, reported by the Australian regulatory authority. ApoPharma received a report of this event on 15 MAR 2006.

The patient commenced treatment with deferiprone (batch number unknown) on an unknown date at a total oral daily dose of 4,500 mg that was stopped on 06 FEB 2006. The patient was admitted to hospital with death as the outcome on due to multiorgan failure from sepsis, and due to agranulocytosis (ANC: $0.01 \times 10^9$/L) with subsequent febrile neutropenia. Deferiprone® administration was stopped and G-CSF injections and unspecified antibiotics were used to treat the patient. Further follow-up information was requested.

Follow-up information received on 20 MAR 2006 from the Australian regulatory authority provided the indication as alpha thalassemia. ApoPharma has assessed this case as medically confirmed, serious, unlisted and related to deferiprone.

Case 2006AP000252 – Agranulocytosis

Case 2006AP000252 concerns an episode of fatal agranulocytosis in a 71-year-old female patient, reported by the French regulatory authority. ApoPharma received report of this event on 05 APR 2006.

The patient was diagnosed with hemochromatosis about a year preceding the event and was started on deferiprone (batch number unknown) of which the exact date and dose was not known at the time of the initial report. On 07 APR 2006, the company was advised that deferiprone was started in the summer of 2005.

On 11 SEP 2005, the patient experienced fever (41°C) with odynophagia, parotid pain, cervical pain, photophobia and thrush. Treatment with Funzigone® (amphotericin B) - oral suspension, was initiated. On the patient presented perineal swelling that was diagnosed as a furuncle on the labium majora and initiated therapy with Rovamycine® (spiramycyn). Later that day, the patient suffered from loss of consciousness and was admitted to hospital, where she was diagnosed with hypotension, atrial tachycardia with atrial fibrillation, thrush, fever, diarrhea, agranulocytosis (ANC: $0.01 \times 10^9$/L), thrombocytopenia (PLT: $23 \times 10^9$/L) and anemia (hemoglobin = 9.6 g/L). Bone marrow aspirate was compatible with drug-induced agranulocytosis. Despite treatment with Tazocilline® (piperacillin and tazobactam), Amiklin® (amikacin), Perfalgan® (paracetamol), and Neupogen® (G-CSF), the patient's condition deteriorated and she died on .

The patient had a history of a lower urinary tract infection with right renal lithiasis since early SEP 2005 for which Clamoxil® (amoxicillin) and Oflocet® (ofloxacin) were used from 01 SEP 2005 to 06 SEP 2005. The patient's history also included paroxysmal cardiac rhythm troubles and dyslipemia. The patient was nonsplenectomized and hepatitis C negative according to the follow-up information received on 07 APR 2006.

Further follow-up information has been requested from the French regulatory authority.

The company notes that this is an off label use of deferiprone and does not have any information on whether the patient's WBC count was monitored regularly. ApoPharma has assessed this case as medically confirmed, serious and unlisted, and probably related to deferiprone.

Case 2006AP000322 – Agranulocytosis

Case 2006AP000322 concerns an episode of fatal agranulocytosis in a 10-year-old female patient with Blackfan-Diamond anemia, reported by a physician in Sweden. ApoPharma received a report of this event on 28 APR 2006.

On 14 FEB 2006, the patient commenced treatment with deferiprone (batch number unknown) at a dose of 45 mg/kg/day (total daily dose 1,000 mg). Before starting deferiprone the patient's ANC was $2.61 \times 10^9$/L. The blood counts, checked weekly, dropped markedly between weeks

8 and 9; the patient experienced high fever and agranulocytosis (ANC: $<0.1 \times 10^9$/L). The platelet count on that day was $90 \times 10^9$/L. Deferiprone was discontinued promptly. The patient was admitted to the hospital and blood and urinary cultures indicated Staphylococcus aureus and Escherichia coli urinary tract infection, respectively. Intravenous broad spectrum antibiotic therapy was initiated promptly. Pulmonary CT reported 10-15 rounded infiltrates consistent with septic embolies. Blood and urinary cultures revealed Staphylococcus aureus and Escherichia coli respectively. There was no evidence of endocarditis on ECG or echocardiogram. She was started on imepenem, gentamicin and G-CSF (10 mcg/kg/day). The dose of G-CSF was increased to 20 mcg/kg/day according to information received on 29 APR 2006. Her ANC count was < 0.1 x 10E9/L on 28 APR 2006, and 0.2 x 10E9/L on 29 APR 2006.

The company has assessed the primary event of agranulocytosis as medically serious, confirmed, listed and related. The other events are medically confirmed, serious, related and unlisted.

Follow-up information received on 02 MAY 2006 reported that the patient's ANC was less than $0.1 \times 10^9$/L on that day. On the patient was in good condition and was discharged from the hospital but continued therapy with G-CSF for persistent agranulocytosis and with parenteral antibiotics. Follow-up information received on 11 MAY 2006 reported that the thrombocytopenia resolved after 6 days.

On the company was informed that the patient's ANC remained less than $0.1 \times 10^9$/L and that she has been transferred to another hospital for a bone marrow transplant. Follow-up information received on reports that the patient passed away on . The reason was reported as circulatory collapse and probably pulmonary embolism.

Case 2007AP001306 – Agranulocytosis

Case 2007AP001306 concerns a fatal case of infection experienced by a 19 year- old female non-splenectomized patient with thalassemia major followed at the . The following narrative summarizes the information provided by the reporter.

The patient started taking deferiprone on 18 Mar 2007, at a dose of 75 mg/kg/day. At the end of October 2007 (but also referred to as 16 Oct 2007), the patient developed sore throat and stopped taking deferiprone. As the thalassemia center was closed over the weekend, the patient went to a private hospital where a physician who was not familiar with the use of iron chelation therapy considered the event as a common cold and prescribed symptomatic therapy. The patient's condition did not improve and she was hospitalized in that private clinic on (dates of hospitalization provided also as ). Lab results on admission were not available. The patient was treated with IV antibiotics as well as unspecified treatment for heart failure. There are no references to treatment with granulocyte-colony stimulating factors. The patient died on . The preliminary cause of death was septic shock. The lowest reported ANC was 0.1 $x10^9$/L. The company's view is that the event is serious, medically confirmed and possibly related to deferiprone.

Case 2008AP000847 – Agranulocytosis

Case ID 2008AP000847 was reported by a physician from Sweden via the local distributor (Swedish Orphan International) of deferiprone. It concerns a 12 years old non-splenectomized female patient with thalassemia and severe iron overload who died while receiving combination therapy with deferiprone and Desferal (deferoxamine).

In Sep 2007 the patient had her dose of deferoxamine increased from 30-45 mg/kg, 6 hours infusion, 5 times/week to 46 mg/kg, 12 hours infusion, 6 times/week. Also deferiprone was initiated at a low dose of 500 mg/d, or 1/3 tablet three times a day. In December 2007, the dose of deferiprone was increased to 500 mg three times a day (which according to the reporter was not a full dose, based on the patient's weight of 39 kg). During this time, her WBC and granulocytes were normal. Relevant medical history included a failed bone marrow transplant.

In Mar 2008, the patient's ferritin value was 2900 ug/L. On 17 Mar 2008, the WBC value was 5.5 x $10^9$/L with ANC 2.1 x $10^9$/L and platelet count 255 x $10^9$/L. On the WBC value was 4.4 x $10^9$/L and no differential count was provided. On her ANC value was 0.1 x $10^9$/L at her local hospital and she had fever for 2 days. Lab results at the time of the event were as follows: ferritin 5785 µg/L, ANC <0.1 x $10^9$/L, thrombocyte counts 70 x $10^9$/L, and C-reactive protein (CRP) 250 mg/L. Blood and throat cultures were positive for E-coli and beta-streptococci, respectively. Deferiprone was discontinued on that day. On the patient was admitted to the pediatric clinic at her local hospital. The patient was treated with Penicillin G (benzylpenicillin). She was in a very good general condition despite her fever. The patient was treated with Neupogen (filgrastim). On the patient had abdominal pain and suspicion of appendicitis. The patient started treatment with broad spectrum antibiotics and she was transferred to the for appendectomy and surgical consultation. However, she was admitted to the ICU due to worsening of her general condition. On the patient died of sudden cardiac arrest. The reporter concluded that the iron overload in her heart, liver and perhaps adrenal glands may have contributed to the fatal outcome of the septicemia. The company considered the event serious, severe, medically confirmed and related to the use of deferiprone.

# J.1 Fatal cases of agranulocytosis in the ApoPharma Safety Database

| | Primary Diagnosis | Therapy | GCSF | Infection reported | Cause of death reported | Onset of agranulocytosis (days) | Duration from onset of agranulocytosis to death date (days) |
|---|---|---|---|---|---|---|---|
| 1. | Thalassemia major | DFP/ DFO | Y | pseudomonas (septic shock) | septic shock; acute respiratory distress syndrome | 67 | 11 |
| 2. | Thalassemia major | DFP/ DFO | Y | chest infection | septic shock; acute respiratory distress syndrome | 301 | 22 |
| 3. | Thalassemia major | DFP/ DFO | Y | Sepsis | massive cerebral haemorrhage | 21 | UNK |
| 4. | Thalassemia major | DFP | UNK | Sepsis | not reported | 23* | 14 |
| 5. | Thalassemia major | DFP/ DFO | Y | sepsis indicated as cause of death, but cultures sterile | septic shock | 153 | 17 |
| 6. | Thalassemia major | DFP | N | unspecified infection | septicemia | 231 | 2 |
| 7. | Thalassemia major | DFP/ DFO | Y | staphylococcus/ Escherichia coli; sepsis | sudden cardiac arrest | 195 | 4 |
| 8. | Red cell aplasia | DFP | UNK | Pneumonia | pneumonia | 20 | UNK |
| 9. | Myelofibrosis/red cell aplasia | DFP | UNK | nonspecific septicemia | agranulocytosis and nonspecific septicemia | 50 | UNK |
| 10. | Haemochromatosis | DFP | Y | fungal sepsis | fungal sepsis | 83 | 16 |
| 11. | Haemochromatosis | DFP | Y | furuncle on the labium majora ; high fever | not reported | 64 | 4 |
| 12. | Diamond-Blackfan anemia | DFP/ DFO | Y | staphylococcus/ escherichia coli | circulatory collapse and probably pulmonary embolism | 70 | 42 |
| 13. | Alpha Thalassemia | DFP | Y | Sepsis | multi-organ failure due to sepsis | UNK | 20 |

1) GCF=Granulocyte Colony Stimulating Factor, or other colony stimulating factor (e.g. filgrastim, lenograstim)
2) Onset of agranulocytosis days is calculated as (Date of AE onset-First date of exposure), where available. Start date of agranulocytosis not provided; one lab test date provided with ANC $<0.5x10^9$/L (onset assumed to be 15$^{th}$ day of same month as lab test).
3) Data cut off: 31 Aug 2010

# J.2 Agranulocytosis episodes with fatal outcome reported Post-Marketing or from literature

| Definition | Total | Thalassemia Major | Non Thalassemia Major |
|---|---|---|---|
| No. of Agranulocytosis Events | 13 | 7 | 6 |
| No. of Subjects with Agranulocytosis | 13 | 7 | 6 |
| Median Age of Subjects reporting Agranulocytosis | 28 (n = 12) | 20 (n = 7) | 60 (n = 5) |
| Standard Deviation of Age of Subjects reporting Agranulocytosis | 24.12 | 9.93 | 28.68 |
| Age (Min / Max) yrs of Subjects reporting Agranulocytosis | 10 / 83 | 12 / 40 | 10 / 83 |
| Sex of Subjects reporting Agranulocytosis - Male / Female / Unknown | 4 / 9 / 0 | 1 / 6 / 0 | 3 / 3 / 0 |
| Median Duration of DFP Exposure for Subjects reporting Agranulocytosis (days) | 67.5 (n = 12) | 154 (n = 7) | 65 (n = 5) |
| Standard Deviation of Duration of DFP Exposure for Subjects reporting Agranulocytosis (days) | 91.948 | 108.28 | 23.636 |
| Range of Duration of DFP Exposure for Subjects reporting Agranulocytosis (days) | 21 / 304 | 22 / 304 | 21 / 84 |
| Median Duration of Agranulocytosis Events (days) | 15 (n = 10) | 12.5 (n = 6) | 18 (n = 4) |
| Standard Deviation of Agranulocytosis Events (days) | 11.72 | 7.66 | 15.86 |
| Duration of Agranulocytosis Events (Min / Max) days | 2 / 42 | 2 / 22 | 4 / 42 |
| Median Time to First Agranulocytosis (days) | 68.5 (n = 12) | 153 (n = 7) | 64 (n = 5) |
| Standard Deviation of Time to First Agranulocytosis (days) | 92.21 | 108.44 | 24.04 |
| Time to First Agranulocytosis (Min / Max) days | 20 / 301 | 21 / 301 | 20 / 83 |
| Dose mg/kg/d (Min / Max) of Subjects reporting Agranulocytosis | 23.65 / 78.70 | 35.71 / 76.90 | 23.65 / 78.70 |
| G-CSF of Agranulocytosis Events - Yes / No / Unknown | 9 / 1 / 3 | 5 / 1 / 1 | 4 / 0 / 2 |
| Hepatitis C Agranulocytosis Events - Yes / No / Unknown | 2 / 3 / 8 | 2 / 2 / 3 | 0 / 1 / 5 |
| Splenectomy of Agranulocytosis Events - Yes / No / Unknown | 0 / 5 / 8 | 0 / 4 / 3 | 0 / 1 / 5 |

1) Days of Exposure is calculated as (End Date of Exposure - First date of Exposure +1), where available.
2) Duration (days) of an Event is calculated as (AE Resolution Date - AE Onset Date +1), where available.
3) For adults, if doses were provided in units other than mg/kg/day, the Subject's weight was used, if this was not available, a weight of 60 kg was assumed. If weight was not provided for children, the dose in mg/kg/day was calculated based on the age and sex of the Subject according to the chart developed by the National Center of Health Statistics in collaboration with the National Center for Chronic Disease prevention and Health promotion.
4) Data cutoff date: 31 Aug 2010