# Proposal for the Inclusion of Deferiprone in the WHO Model List of Essential Medicines for the Treatment of Transfusional Iron Overload in Adult and Paediatric Patients with Thalassaemia Syndromes, Sickle Cell Disease or Other Anaemias

**Report submitted by**

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## Acronyms

| | |
|---|---|
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| aRBX | Automated red blood cell exchange |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area under the curve |
| AYA | Adolescent and Young adult |
| CADTH | Canada's Drug and Health Technology Agency |
| CEA | Cost-effectiveness analysis |
| CI | Confidence interval |
| CrI | Credible intervals |
| CUA | Cost-utility analysis |
| CV | Coefficient of variance |
| DFO | Deferoxamine |
| DFP | Deferiprone |
| DFX | Deferasirox |
| Dw | Dry weight |
| EMA | European Medicines Agency |
| EML | List of essential medicines |
| EMLc | List of essential medicines for children |
| eGFR | Estimated glomerular filtration rate |
| FDA | Food and Drug Administration |
| HCRU | Healthcare resource utilization |
| ICT | Iron chelation therapy |
| ICUR | Incremental cost-utility ratio |
| ITT | Intention-to-treat |
| LIC | Liver iron concentration |
| LVEF | Left ventricular ejection fraction |
| MET | Manual transfusion exchange |

| | |
|---|---|
| MRI | Magnetic resonance imaging |
| NMA | Network meta-analysis |
| NR | Not reported |
| ODD | Orphan drug designation |
| PK | Pharmacokinetics |
| PLN | Polish zlotys |
| QALY | Quality-adjusted life-year |
| RCT | Randomized controlled trial |
| SCD | Sickle cell disease |
| SD | Standard deviation |
| SE | Standard error |
| SF | Serum ferritin |
| SLR | Systematic literature review |
| SOC | Standard of care |
| SPC | Summary of product characteristics |
| SQUID | Superconducting quantum-interference device |
| SUCRA | Surface under the cumulative ranking curve |
| t.i.d | Three times a day |
| TIF | Thalassaemia International Federation |
| ULN | Upper limit of normal |
| WMD | Weighted mean difference |

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# 1. Summary Statement of the Proposal for Inclusion

This application advocates the inclusion of deferiprone in the complementary list of essential medicines (EML) and the list of essential medicines for children (EMLc), for the treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle cell disease or other anaemias.

Sickle cell disease (SCD) and beta-thalassaemia are hereditary blood disorders that require regular blood transfusion as part of their treatment. Patients who receive repeated transfusions are at risk of iron overload, which leads to organ damage, particularly affecting the liver and heart, and eventually, premature death if left untreated. Deferiprone (DFP) is an oral iron chelator for the treatment of transfusional iron overload in adult and paediatric patients with SCD or beta-thalassaemia and is available as an oral solution, immediate-release tablet, or modified-release tablet. DFP is more effective than deferoxamine in reducing cardiac iron and has also been demonstrated to reduce serum ferritin and liver iron, while providing an acceptable safety profile. Moreover, it can be used in combination with another chelating agent. DFP also represents a cost-effective and cost-saving option compared to other ICTs and reduces the economic burden on the healthcare system.

# 2. Consultation with WHO Technical Departments

# 3. Other Organization(s) Consulted and/or Supporting the Submission

**Organization submitting the application:**

Chiesi Farmaceutici S.p.A

**Other organizations supporting the submission:**

Thalassaemia International Federation

*Letter of support included in the appendix*

# 4. Key Information for Deferiprone

## 4.1. International Non-proprietary Name of the Medicine

**International Non-proprietary Name (INN)**

Deferiprone

## 4.2. Anatomical Therapeutic Chemical Code of the Medicine

**Anatomical Therapeutic Chemical (ATC)**

In the ATC classification system, deferiprone is classified as "iron chelating agents" and can be identified by the ATC code: V03AC02 (1).

## 4.3. Dosage Form(s) and Strength(s) Proposed for Inclusion: Including Adult and Age-Appropriate Paediatric Dose Forms/Strengths

DFP is available as an oral solution or as film-coated tablets. Furthermore, it has two different available formulations, immediate release formulations and a modified release formulation. Table 1 shows the presentations and formulations of DFP currently available.

Table 1. Currently available presentations and formulations of DFP

| Pharmaceutical form | Route of administration | Formulation | Strength | Packaging | Content | Package size |
|---|---|---|---|---|---|---|
| Film-coated tablet | Oral use | Immediate release | 500 mg | Bottle | - | 100 tablets |
| Film-coated tablet | Oral use | Immediate release | 1000 mg | Bottle | - | 50 tablets |
| Film-coated tablet | Oral use | Immediate release | 1000 mg | Bottle | - | 100 tablets |
| Film-coated tablet | Oral use | Immediate release | 1000 mg | Blister | - | 50 tablets |
| Film-coated tablet | Oral use | Modified release | 1000 mg | Blister | - | 50 tablets |
| Oral solution | Oral use | Immediate release | 100 mg/ml | Bottle | 250 ml | 1 bottle |
| Oral solution | Oral use | Immediate release | 100 mg/ml | Bottle | 500 ml | 1 bottle |

Note: the table above is based on the available formulations of the originator, Ferriprox® (deferiprone). Generic deferiprone is also available in some countries. The availability of the different formulations or presentation varies by country.

The 1000mg and 500mg immediate-release tablet and 100mg/ml oral solution formulations are administered three times a day (t.i.d), while the 1000mg modified-release tablet formulation allows for a twice a day administration. In single-dose and multiple-dose Pharmacokinetic studies of deferiprone in healthy volunteers, the modified release formulation had equivalent 24-h drug exposure to the original immediate-release tablet administered three times a day (LA45-0116), and exposure was not affected by administration with food (LA53-0116) (2). In a multicentre, open-label, Phase 2 trial, the modified-release formulation also showed a safety and tolerability profile similar to that of the immediate-release formulation with no new safety concerns identified

in patients with transfusion-dependent blood disorders who were already taking deferiprone immediate-release t.i.d. for the treatment of transfusional iron overload (NCT03802916) (2).

In the US, Ferriprox ® (deferiprone) oral solution is indicated in adult and pediatric patients 3 years of age and older with thalassaemia syndromes, sickle cell disease or other anemias. Ferriprox ® (deferiprone) tablets (IR and twice a day) is indicated in adult and pediatric patients 8 years of age and older with thalassaemia syndromes, sickle cell disease or other anemias. Approved patient population may vary slightly depending on national registration process and locally approved indications.
Inclusion of the following deferiprone formulations in the EML and EMLc is proposed:

- EML: immediate release tablets; modified release tablets; oral solution
- EMLc: immediate release tablets from 8 years of age and older; modified release tablets from 8 years of age and older; oral solution from 3 years of age and older

## 4.4. Indication(s)

DFP is indicated for the treatment of iron overload from blood transfusions in patients with thalassaemia syndromes, sickle cell disease or other anaemias. Table 2 shows the different indications according to a selection of regulatory agencies.

Table 2. DFP indications from a selection of regulatory agencies (based on the indication for Ferriprox®(deferiprone) the originator)

| Regulatory agency | DFP indication |
|---|---|
| Food and Drug Administration (FDA) | Deferiprone (Ferriprox®) oral solution is indicated for the treatment of transfusional iron overload in adult and paediatric patients 3 years of age and older with thalassaemia syndromes, sickle cell disease or other anaemias (4)<br><br>Deferiprone (Ferriprox®) tablets is indicated for the treatment of transfusional iron overload in adult and paediatric patients 8 years of age and older with thalassaemia syndromes, sickle cell disease or other anaemias (5)<br><br>*Limitations of use*<br>Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with myelodysplastic syndrome or in patients with Diamond Blackfan anemia |
| Health Canada | Deferiprone (Ferriprox®) is indicated for the treatment of patients with transfusional iron overload due to thalassaemia syndromes when current chelation therapy is inadequate and for the treatment of transfusional iron overload due to sickle cell disease or other anaemias (6)<br><br>*Limitations of use*<br>Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with myelodysplastic syndrome or in patients with Diamond Blackfan anaemia |

| | |
|---|---|
| European Medicines Agency (EMA) | Deferiprone (Ferriprox®) monotherapy is indicated for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate (7)<br><br>Deferiprone (Ferriprox®) in combination with another chelator is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction (7) |

The US SCD indication was granted for the originator, Ferriprox® (deferiprone), based on accelerated approval and study LA38-0411 (FIRST) and its open-label extension, LA38-EXT, were conducted to address one of the post-marketing requirements associated with the accelerated approval of Ferriprox® (deferiprone) in the US. The LA38/LA38-EXT study enrolled both patients with SCD and other anaemias requiring blood transfusion. Twenty percent of the patients enrolled were patients with other anaemias and subgroup analysis suggests that the effect of DFP is similar in this patient population. Safety data of patients with other anaemias from the LA38/LA38-EXT study and post-marketing data also suggest a similar safety profile among all types of patients. "Other anaemias" is approved in the therapeutic indications in those countries in which the treatment of iron overload in SCD is authorized – the US, Canada, Brazil, and Turkey. "Other anaemias" is not included in the therapeutic indication in the countries in which thalassaemia major is authorized but not SCD.

### 4.5. Orphan Drug Designation

In the US, DFP has received an orphan designation for treatment of iron overload in patients with hematologic disorders requiring chronic transfusion therapy, while in Europe DFP has an ODD for treatment of neurodegeneration with brain iron accumulation and treatment of SCD (8,9).

## 5. Proposal for an Individual Medicine or Representative of a Pharmacological Class / Therapeutic Group

This application is for the inclusion of DFP as a therapeutic alternative to an existing representative medicine in subsection 10.3 (other medicines for hemoglobinopathies) of the WHO EML and EMLc. It is proposed that DFP be included as a therapeutic alternative to DFO, which is already present in this subsection as the representative medicine for the relevant indication.

## 6. Information Supporting the Public Health Relevance

### 6.1. Disease Overview

**SCD** and **beta-thalassaemia** are heritable life-threatening hemoglobinopathies that lead to severe anaemia.

**SCD** is a multisystem disorder that affects nearly every organ in the body. It is characterized by the presence of sickle haemoglobin which causes sickle-shaped erythrocytes. SCD is a life-threatening disease that leads to haemolytic anaemia and blockages in small blood vessels, which may potentially lead to ischemia and infarction, and can damage organs (10). SCD is one of the most common hemoglobinopathies worldwide and it is recognized by the WHO as a global public health problem (11). Globally, approximately 605,000 infants are born each year with sickle cell disorders and in 2019 there were estimated to be around 5.69 million people living with SCD (12). The prevalence varies by region and is highest in Africa, the Mediterranean basin, and the Middle East (13,14). Of the individuals living with SCD today, more than half are located in sub-Saharan Africa or India (13).

In **beta-thalassaemia** the reduced or absent production of functional haemoglobin results in severe and life-threatening anaemia. The total annual incidence of symptomatic individuals with beta-thalassaemia is estimated to be 1 in 100,000, though incidence rates vary by region. Approximately 60,000 children are born each year with symptomatic forms of the disease. Prevalence is highest in the Mediterranean region, the Middle East, Central Asia, India, Southern China, and East and Southeast Asia (15).

Blood transfusions are one of the cornerstones of the management of SCD and beta-thalassaemia. However, one of the major causes of morbidity in these patients is **iron overload** due to chronic red blood cell transfusions (16–18). Untreated or inadequately treated iron overload leads to complications such as liver fibrosis and cirrhosis, hepatocellular carcinoma, cardiomyopathy, and endocrine disorders such as hypothyroidism, diabetes, gonadal failure, and growth delay (19–21). Iron chelation with agents such as DFP, deferasirox (DFX), or deferoxamine (DFO), is the main treatment for transfusional iron overload.

## 6.2. Target Population

Adult and paediatric patients with transfusional iron overload associated with thalassaemia syndromes, sickle cell disease, or other anaemias.

## 6.3. Alternative Medicines Currently Included on the Model Lists

At present there are two iron chelators included in the Model Lists:

- **DFO** is currently included in the EML and EMLc in:
    - Section 10.3 (other medicines for hemoglobinopathies) with the indication "other specified sickle cell disorders or other hemoglobinopathies" (ICD11 code: 3A51.Y)
    - Section 4.2 (antidotes and other substances used in poisonings - specific) with the indication "harmful effects of drugs, medicaments or biological substances, not elsewhere classified" (ICD11 code: NE60)
- **DFX** is listed as a therapeutic alternative to DFO in section 10.3

# 7. Treatment Details

## 7.1. Dosage Regimen and Duration of Treatment

The recommended dose of DFP oral solution is 25 mg/kg to 33 mg/kg actual body weight, orally, three times per day, for a total daily dose of 75 mg/kg/day to 99 mg/kg/day. The dose should be rounded to the nearest 2.5ml (4).

DFP tablets are available in three different formulations. Two different 1000 mg formulations (immediate release and modified release), and a 500 mg formulation (immediate release), each of which has its own dosing regimen to achieve the same total daily dose (Table *3*) (5,22).

Table 3. DFP dosing regimens according to its different formulations

| | **DFP tablets 1000 mg twice a day (modified release)** | **DFP tablets 1000 mg three times a day (immediate release)** | **DFP tablets 500 mg three times a day (immediate release)** |
|---|---|---|---|
| **Starting oral dosage** | 75 mg/kg/day (actual body weight) in two divided doses (approx. every 12 hours), with food | 75 mg/kg/day (actual body weight) in three divided doses | 75 mg/kg/day (actual body weight) in three divided doses |
| **Maximum oral dosage** | 99 mg/kg/day (actual body weight) in two divided doses (approx. every 12 hours) with food | 99* mg/kg/day (actual body weight) in three divided doses | 99* mg/kg/day (actual body weight) in three divided doses |
| Source: EMA and FDA<br>* Maximum recommended dose is 99 mg/kg/day in the US and 100 mg/kg/day in the EMA SPC | | | |

For all DFP tablet presentations, dose per kilogram body weight should be calculated to the nearest half tablet.

The recommended dose and dosing regimen of DFP in SCD or other anaemias patients is the same as for patients with thalassaemia syndromes. A study to assess the pharmacokinetic profile of DFP in SCD patients found the profile to be consistent with previous reports in healthy volunteers, which suggests that no special dosing adjustments are required in this population (23).

The dosage regimen and treatment duration described above are based on the prescribing information for Ferriprox®, the originator. Generic deferiprone is also available in many regions, though the formulations and approved indications available in a given country may differ from those described above.

## 7.2. Requirements to Ensure the Appropriate Use of Deferiprone

**Dose adjustments**

The effect of DFP in decreasing body iron is directly influenced by the dose and the degree of iron overload. After starting DFP therapy, it is recommended that serum ferritin concentrations, or other indicators of body iron load, be monitored every two to three months to assess the long-term effectiveness of the chelation regimen in controlling the body iron load. Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). Interruption of therapy with DFP should be considered if serum ferritin falls below 500 µg/l (22).

**Dose adjustments when used with other chelators**

In patients for whom monotherapy is inadequate, DFP may be used with DFO at the standard dose (75 mg/kg/day) but should not exceed 99 mg/kg/day (US label) or 100 mg/kg/day (EU label). In the case of iron-induced heart failure, DFP at 75-100 mg/kg/day should be added to DFO therapy. The product information of DFO should be consulted. Concurrent use of iron chelators is not recommended in patients whose serum ferritin falls below 500 µg/l due to the risk of excessive iron removal (22).

Limited data are available on the combined use of Ferriprox and deferasirox, and caution should be applied when considering the use of such combination (22).

**Monitoring for safety**

Due to the risk of agranulocytosis (ANC<0. $5x10^9$/l), monitoring absolute neutrophil count (ANC) before and during DFP therapy is needed (5). Agranulocytosis (ANC<0. $5x10^9$/l) is a serious and potentially fatal event that can occur with DFP use. Deferiprone can also cause neutropenia (ANC<$1.5x10^9$/l), which may foreshadow agranulocytosis.

ANC must be tested prior to start of DFP therapy and monitored on the following schedule during treatment (*the monitoring regimen may vary by country based on local approved labels and guidelines, which should be followed strictly*) (5):

1. During the first six month of therapy monitor ANC weekly
2. During the next six month of therapy monitor ANC once every two weeks
3. After one year of therapy: monitor ANC every two to four weeks (or at the patient's blood transfusion interval in patients that have not experienced an interruption due to any decrease in ANC)

Reduction in the frequency of ANC monitoring should be considered on an individual patient basis, according to the health care provider's assessment of the patient's understanding of the risk minimization measures required during therapy (5).

In case of neutropenia events (ANC<$1.5x10^9$/l) or agranulocytosis (ANC<$0.5x10^9$/l) instruct the patient to immediately discontinue DFP and all other medicinal products with a potential to cause

neutropenia (5,22). For agranulocytosis (ANC < 0.5 x $10^9$/L), consider hospitalization and other management as clinically appropriate (5).

Advise patients taking deferiprone to immediately interrupt therapy and report to their physician if they experience any symptoms indicative of infection. Interrupt deferiprone if infection develops and monitor the ANC frequently (5).

A plan should be implemented to monitor for and to manage agranulocytosis and neutropenia prior to initiating deferiprone treatment (5).

Do not resume deferiprone in patients who have developed agranulocytosis unless potential benefits outweigh potential risks. Do not rechallenge patients who have developed neutropenia with deferiprone unless potential benefits outweigh potential risks (5).

Deferiprone prescribing information should be consulted for full details, including guidance on patient monitoring and management of neutropenia and agranulocytosis.

Due to the risk of hepatic transaminase elevations, alanine aminotransferase (ALT) should be monitored before and monthly during DFP therapy (5).

Due to the risk of zinc deficiency, zinc levels should be monitored before and regularly during DFP therapy (5).

**Monitoring to assess efficacy**

To assess the effect of DFP on body iron stores serum ferritin concentration should be monitored every two to three months. If the serum ferritin is consistently below 500 mcg/L, consider temporarily interrupting DFP therapy until serum ferritin rises above 500 mcg/L (5).

**Dosage modification for drug interactions**

At least a 4-hour interval should be allowed between administration of d DFP and other drugs or supplements containing polyvalent cations such as iron, aluminium, or zinc (5).

## 7.3. Recommendations in Existing WHO Guidelines

There are no published WHO-specific guidelines regarding the treatment of iron overload due to blood transfusions.

## 7.4. Recommendations in Other Current Clinical Guidelines

The use of iron chelating agents, including DFP, for the treatment of iron overload due to blood transfusions, either for patients with SCD or those with thalassaemia, is recommended by a large number of international and national guidelines (see Table *4*).

Table 4. National and international guidelines that recommend the use of iron chelators for the treatment of transfusional iron overload

| Author/Organization | Country | Title | Date of latest version |
|---|---|---|---|
| Thalassaemia International Federation (TIF) (21) | Worldwide | Guidelines for the management of transfusion dependent thalassaemia (TDT) | 2021 |
| Group of Australian Haematologists (24) | Australia | Australian guidelines for the assessment of iron overload and iron chelation in transfusion-dependent thalassaemia major, sickle cell disease and other congenital anaemias | 2011 |
| Brazilian Thalassemia Association (25) | Brazil | Brazilian Thalassemia Association protocol for iron chelation therapy in patients under regular transfusion | 2013 |
| The Canadian Haemoglobin Association (CanHaem) (26) | Canada | Consensus statement on the care of patients with sickle cell disease in Canada | 2018 |
| La Filière de Santé des Maladies Consitutionnelles Rares du Globule Rouge et de l'Erythropoïèse (MCGRE) (27) | France | Protocole National de Diagnostic et de Soins (PNDS): Syndromes thalassémiques majeurs et intermédiaires | 2021 |
| Italian Society of Hematology (28) | Italy | Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders | 2008 |
| Associazione Italiana Ematologia Oncologia Pediátrica (29) | Italy | Linee-guida per la gestione della malattia drepanocítica in eta' pediátrica in Italia | 2018 |
| National Heart, Lung, and Blood Institute (NIH) (30) | United States | Evidence-based management of sickle cell disease | 2014 |
| American Society of Hematology (31) | United States | American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support | 2020 |
| NHS England Clinical Commissioning Policy (32) | United Kingdom | Clinical Commissioning Policy Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias (all ages) | 2022 |
| British Society for Haematology (33) | United Kingdom | Guidelines for the monitoring and management of iron overload in patients with hemoglobinopathies and rare anaemias | 2021 |
| British Society for Haematology (34) | United Kingdom | Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion | 2017 |

The American Society of Hematology (ASH), Canadian Hemoglobinopathy Association (CanHaem), National Heart, Lung, and Blood Institute (NHLBI), and the British Society for Haematology, among others, have put forward clinical practice guidelines for monitoring and management of transfusional iron load in patients with SCD (26,30,31,34).

For the management of iron overload in thalassaemia syndromes, guidelines include those of the Thalassaemia International Federation (TIF), which are international, as well as national guidelines

such as those of the Brazilian Thalassemia Association, and the Italian Society of Hematology (21,25,28). Some treatment guidelines cover inherited hemoglobinopathies in general and include sections on both SCD and thalassaemia.

The TIF guidelines stress the importance of chelation therapy in those with transfusion-induced iron overload to improve survival, decrease the risk of heart failure, and decrease morbidities, noting that the optimal chelation regime should be tailored to the individual patient and will vary with the patient's current clinical situation (21).

# 8. Review of Benefits: Summary of Evidence of Comparative Effectiveness

A detailed description of key efficacy studies of DFP can be found in Appendix I.

## 8.1. Comparative Effectiveness of Iron Chelation Therapy in Patients with SCD

### 8.1.1. Objective and Rationale

To assess the comparative effectiveness of DFP and DFO, an indirect comparison between DFP, DFX, and DFO in patients with SCD was conducted in January 2022 (unpublished study carried out by Chiesi).

This study utilizes a network meta-analysis (NMA) framework to indirectly compare DFP to DFX and DFO with respect to the following endpoints among patients with SCD who underwent transfusion therapy:

- Change from baseline to 12 months in liver iron concentration (LIC)
- Change from baseline to 12 months in serum ferritin (SF)

### 8.1.2. Methods

Data were obtained from a comprehensive systematic literature review (SLR), conducted with the aim of reviewing the clinical efficacy and safety of DFP and all comparators.

A total of 14 records from 11 primary studies were selected for data extraction in the SLR, as well as three sub-studies.

Out of the 11 primary studies identified from the SLR, studies satisfying the following criteria were included to the NMA:

- Randomized controlled trials (RCTs); and
- Reported at least one of the efficacy endpoints with standard error (SE) or standard deviation (SD). Trials not reporting SE/SD cannot be incorporated into an NMA without making additional assumptions on the variation of the efficacy endpoints. This criterion is to avoid making these assumptions. Mathematically, the reliability weights could not be calculated without a SE or SD, and therefore, could not be included in a NMA model.

Based on the inclusion criteria, two RCTs are included in this NMA, FIRST (NCT02041299) and NCT00067080 (35,36). Both studies reported changes in LIC and in SF (with SE or SD) at 12 months. Table *5* summarizes the key characteristics of the two studies included in the NMA.

Table 5. Studies from the systematic literature review included in the indirect comparison

| Short reference | Trial acronym | Trial arms | Study design | Population | Total N |
|---|---|---|---|---|---|
| Kwiatkowski, 2022 (36) | LA38-0411 (FIRST) | DFP vs DFO | P4, RCT, open label | Patients aged ≥2 years with SCD or transfusion-dependent anaemia | 228 |
| Vichinsky, 2007 (35) | NCT00067080 | DFX vs DFO | P2, RCT, open label | Patients with SCD aged ≥2 with transfusional iron overload | 195 |
| DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; RCT: randomized controlled trial; SCD: sickle cell disease | | | | | |

More details on the systematic review strategy and the study selection, as well as the design, and patient characteristics of the trials included, and quality assessment are explained in Appendix II of the dossier.

### *Network meta-analysis*

#### Base case

The base case analyses utilized the intention-to-treat (ITT) population of two trials: FIRST (LA38-0411) (DFP vs DFO), and NCT00067080 (DFX vs DFO). The NMA was conducted using a Bayesian framework with a non-informative prior. A fixed treatment effect approach was used to accommodate simple networks (only two studies included). An anchored matching-adjusted indirect comparison (MAIC) was considered an alternative approach but was expected to have similar conclusions as the NMA because none of the mutually reported baseline patient characteristics have been identified as potential effect modifiers in a feasibility assessment using the individual patient data of FIRST (LA38-0411). A random effect model was not possible in the absence of an informative prior. Model convergence was assessed using trace plots and Gelman-Rubin-Brooks plots of the potential scale reduction factor with a minimum cut-off below 1.05 by the final iteration. All analyses were performed using R Studio with 5,000 burn-in iterations and 10,000 actual iterations.

The primary NMA assumptions of transitivity were assessed through the comparison of study designs, inclusion/exclusion criteria, and patient characteristics of each trial. While the transitivity assumption appeared reasonable in general, differences were noted with respect to the following:

- Patient characteristics, primarily with respect to race and proportions of patients with SCD (and other anaemias)
- The exclusion criterion of NCT00067080 that excluded patients with baseline serum creatinine above the upper limit of normal (ULN)

Inconsistency was not evaluable because there was no closed loop in the networks. In other words, there was no intervention pair that had direct and indirect evidence available simultaneously. Due to small sample sizes, methods to account for heterogeneity in the populations such as meta-regression and random effects models could not be used. As part of the feasibility analysis of this study, an exploratory study was conducted based on the individual patient data from FIRST (LA38-0411), which identified no effect modifiers for changes from baseline to 12 months in LIC and SF.

The two endpoints to be analysed were changes in LIC and SF from baseline to 12 months. Indirect mean differences with 95% credible intervals (CrI) were reported. As per standard reporting, surface under the cumulative ranking curve (SUCRA) scores and probability of being the best treatment have also been documented (37). Change from baseline to 12 months in cardiac MRI T2* was not considered because it was only reported by FIRST (LA38-0411) and not by NCT00067080 (37).

#### Scenario analyses

Since differences in the proportion of patients with SCD were observed between included trials, an evidence network scenario based on the SCD-only population was analysed. This scenario utilized the SCD subpopulation data of FIRST (LA38-0411).

Since the transitivity assumption may be challenged by the fact that NCT00067080 excluded patients with baseline serum creatinine above the ULN, an evidence network scenario based on the population with baseline serum creatinine below ULN was analysed. This scenario utilized the subpopulation data of FIRST (LA38-0411), which was composed of patients with serum creatinine below ULN.

### 8.1.3. Results

#### Liver iron concentration (LIC) base case – ITT population

Figure *1* presents the evidence network of change in LIC from baseline to 12 months among the treatment arms of FIRST (LA38-0411; DFP vs DFO) and NCT00067080 (DFO vs DFX). The mean changes and mean difference in LIC reported by the two studies are shown in Table *6*.

Figure 1. LIC analysis network

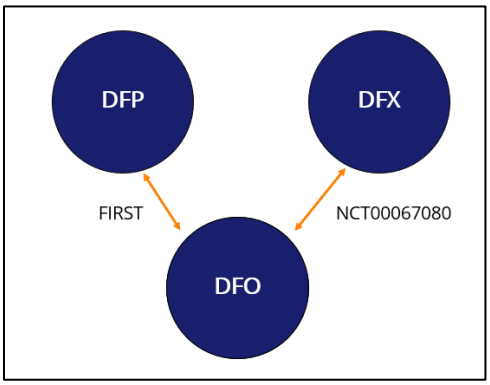



Table 6. Mean changes and mean differences in LIC (ITT population)

| Study | Population | Intervention | N | Mean change mg/dw* (SD) | Mean difference (SE) |
|---|---|---|---|---|---|
| FIRST (LA38-0411) | SCD and other anemias | DFP<br>DFO | 133<br>69 | -2.96 (4.68)<br>-3.39 (4.33) | 0.43 (0.66)<br>Reference |
| NCT00067080† | SCD | DFX<br>DFO | 132<br>63 | -3.00 (6.20)<br>-2.80 (10.40) | -0.20 (1.42)<br>Reference |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; dw: dry weight (gram); LIC: liver iron concentration; SCD: sickle cell disease; SD: standard deviation; SE: standard error; ITT: intention-to-treat
*A negative mean difference indicates a reduction in LIC, which is a positive treatment effect
†Mean and SD reported in NCT00067080 were adjusted for transfusion category (simple, exchange, simple and exchange)

The base case analysis was based on the ITT population. The results of the analysis, in terms of the mean difference in LIC from baseline to 12 months relative to DFP, are reported in Table 7, Table 8 and Figure *2*. Compared to DFP, the mean difference is -0.40 (95% CrI: -1.70, 0.89) for DFO and -0.68 (95% CrI: -3.63, 2.25) for DFX. The results demonstrate that there is no statistically significant difference between DFP and DFO, or DFP and DFX.

Table 7. LIC analysis results (ITT population)

| Treatment | Mean difference (95% CrI) | Probability of being best* | SUCRA* |
|---|---|---|---|
| DFO | -0.40 (-1.70, 0.89) | 30.69% | 57.52% |
| DFP | Reference | 14.13% | 29.59% |
| DFX | -0.68 (-3.63, 2.25) | 55.18% | 62.88% |

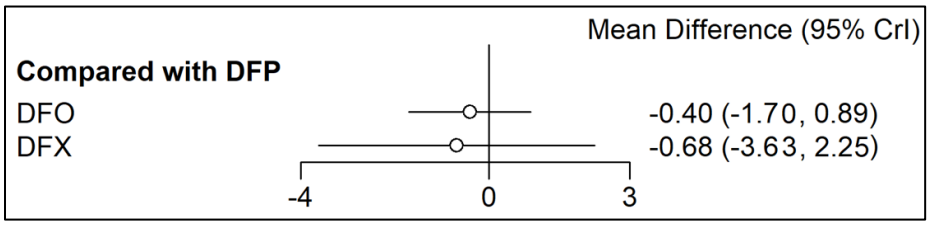
CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; ITT, intention-to-treat; LIC: liver iron concentration; SUCRA: surface under the cumulative ranking curve
*Probability of being the best and SUCRA are reported as part of the NMA, but are not relevant in the context of the following: 1) a non-inferiority trial (FIRST) was included in the NMA, and 2) no significant difference was observed between DFP vs DFO, or DFP vs DFX

Table 8. LIC analysis pairwise comparison matrix (IIT population)

| Treatment* | DFO | DFP | DFX |
|---|---|---|---|
| DFO | DFO | 0.40 (-0.89, 1.70) | -0.29 (-2.92, 2.38) |
| DFP | -0.40 (-1.70, 0.89) | DFP | -0.68 (-3.63, 2.25) |
| DFX | 0.29 (-2.38, 2.92) | 0.68 (-2.25, 3.63) | DFX |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron concentration; ITT, intent-to-treat
*Treatments listed in the first column are the references, treatments listed in the first row were compared to the reference treatments listed in the first column

Figure 2. LIC analysis forest plot (ITT population)




CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; ITT, intent-to-treat; LIC: liver iron concentration

## LIC scenario analysis – SCD subpopulation

Table *9* presents the mean changes and mean differences in LIC for the network scenario examining the SCD subpopulation from FIRST (LA38-0411) (84.7% of ITT population had SCD) and the ITT population from NCT00067080 (100.0% SCD). The evidence network is the same as the base case. The results of the scenario are presented in Table *10*, Table *11*, and Figure *3*. Compared to DFP, the mean difference is -0.58 (95% CrI: -1.83, 0.66) for DFO and -0.84 (95% CrI: -3.84, 2.19) for DFX. The results of this scenario analysis show the same trend as the ITT analysis and that there is no statistically significant difference between DFP and DFX or DFP and DFO.

Table 9. Mean changes and mean differences in LIC (SCD subpopulation)

| Studies | Population | Intervention | N | Mean change mg/dw* (SD) | Mean difference (SE) |
|---|---|---|---|---|---|
| FIRST (LA38-0411) | SCD | DFP<br>DFO | 114<br>57 | -2.49 (4.45)<br>-3.09 (3.59) | 0.60 (0.63)<br>Reference |
| NCT00067080† | SCD | DFX<br>DFO | 132<br>63 | -3.00 (6.20)<br>-2.80 (10.40) | -0.20 (1.42)<br>Reference |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; dw: dry weight (gram); LIC: liver iron concentration; SCD: sickle cell disease; SD: standard deviation; SE: standard error

*A negative mean difference indicates a reduction in LIC, which is a positive treatment effect

†Mean and SD reported in NCT00067080 were adjusted for transfusion category (simple, exchange, simple and exchange)

Table 10. LIC analysis results (SCD subpopulation)

| Treatment | Mean difference (95% CrI) | Probability of being best* | SUCRA* |
|---|---|---|---|
| DFO | -0.58 (-1.83, 0.66) | 35.17% | 62.61% |
| DFP | Reference | 9.15% | 23.18% |
| DFX | -0.84 (-3.84, 2.19) | 55.68% | 64.22% |

CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron concentration; SCD: sickle cell disease; SUCRA: surface under the cumulative ranking curve

*Probability of being the best and SUCRA are reported as part of the NMA, but are not relevant in the context of: 1) a non-inferiority trial (FIRST) was included in the NMA, and 2) no significant difference was observed between DFP vs DFO, or DFP vs DFX

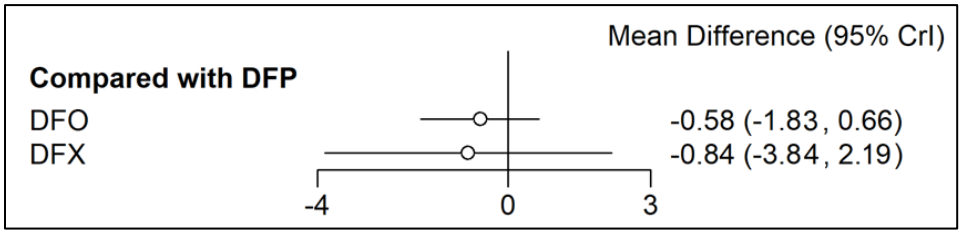
Table 11. LIC analysis pairwise comparison matrix (SCD subpopulation)

| Treatment* | DFO | DFP | DFX |
|---|---|---|---|
| DFO | DFO | 0.58 (-0.66, 1.83) | -0.25 (-2.98, 2.52) |
| DFP | -0.58 (-1.83, 0.66) | DFP | -0.84 (-3.84, 2.19) |
| DFX | 0.25 (-2.52, 2.98) | 0.84 (-2.19, 3.84) | DFX |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron concentration; SCD: sickle cell disease

*Treatments listed in the first column are the references, treatments listed in the first row were compared to the reference treatments listed in the first column

Figure 3. LIC analysis forest plot (SCD subpopulation)




CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron concentration; SCD: sickle cell disease

## LIC scenario analysis – subpopulation with serum creatinine below upper limit of normal (ULN)

Table *13* presents the mean changes and mean differences in LIC for the network scenario examining the subpopulation with serum creatinine below ULN from FIRST (LA38-0411) (97.0% of ITT population were below ULN) and the ITT population from NCT00067080 (100.0% below ULN). The categorization of serum creatinine ULN is presented in Table *12*. The evidence network is the same as the base case. The results of the scenario are presented in Table *14*, Table 15, and Figure 4. Compared to DFP the mean difference is -0.43 (95% CrI: -1.70, 0.85) for DFO and -0.72 (95% CrI: -3.68, 2.25) for DFX. This scenario analysis shows the same trend as the ITT analysis and that there is no statistically significant difference between DFP and DFO or DFP and DFX.

Table 12. Serum creatinine upper limit of normal

| Age (year) | ULN (mg/dL) - male | ULN (mg/dL) - female |
|---|---|---|
| Age < 5 | 0.43 | 0.43 |
| 5 ≤ Age < 12 | 0.61 | 0.61 |
| 12 ≤ Age < 15 | 0.81 | 0.81 |
| 15 ≤ Age < 19 | 1.08 | 0.84 |
| Age ≥ 19 | 1.20 | 1.10 |
| ULN: upper limit of normal | | |

Table 13. Mean changes and mean differences in LIC (serum creatinine below ULN subpopulation)

| Studies | Population | Intervention | N | Mean change mg/dw* (SD) | Mean difference (SE) |
|---|---|---|---|---|---|
| FIRST (LA38-0411) | Serum creatinine below ULN‡ | DFP<br>DFO | 128<br>68 | -3.11 (4.70)<br>-3.56 (4.12) | 0.45 (0.65)<br>Reference |
| NCT00067080† | Serum creatinine below ULN‡ | DFX<br>DFO | 132<br>63 | -3.00 (6.20)<br>-2.80 (10.40) | -0.20 (1.42)<br>Reference |

| Studies | Population | Intervention | N | Mean change mg/dw* (SD) | Mean difference (SE) |
|---|---|---|---|---|---|
| DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; dw: dry weight (gram); LIC: liver iron concentration; ULN: upper limit of normal<br>*A negative mean difference indicates a reduction in LIC, which is a positive treatment effect.<br>†Mean and SD reported in NCT00067080 are adjusted for transfusion category (simple, exchange, simple and exchange)<br>‡Definition of ULN is presented in Table 12 | | | | | |

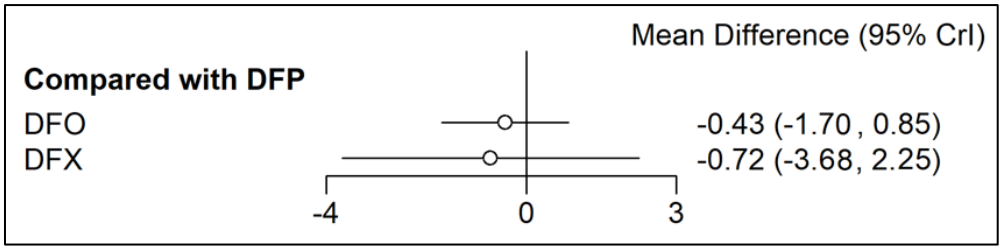
Table 14. LIC analysis results (serum creatinine below ULN subpopulation)

| Treatment | Mean difference (95% CrI) | Probability of being best* | SUCRA* |
|---|---|---|---|
| DFO | -0.43 (-1.70, 0.85) | 30.94% | 58.07% |
| DFP | Reference | 13.53% | 28.76% |
| DFX | -0.72 (-3.68, 2.25) | 55.53% | 63.17% |
| CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron concentration; SUCRA: surface under the cumulative ranking curve; ULN: upper limit of normal<br>*Probability of being the best and SUCRA are reported as part of the NMA but are not relevant in the context of: 1) a non-inferiority trial (FIRST) was included in the NMA, and 2) no significant difference was observed between DFP vs DFO, or DFP vs DFX | | | |

Table 15. LIC analysis pairwise comparison matrix (serum creatinine below ULN subpopulation)

| Treatment* | DFO | DFP | DFX |
|---|---|---|---|
| DFO | DFO | 0.43 (-0.85, 1.70) | -0.29 (-2.97, 2.40) |
| DFP | -0.43 (-1.70, 0.85) | DFP | -0.72 (-3.68, 2.25) |
| DFX | 0.29 (-2.40, 2.97) | 0.72 (-2.25, 3.68) | DFX |
| DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron concentration; ULN: upper limit of normal<br>*Treatments listed in the first column are the references, treatments listed in the first row were compared to the reference treatments listed in the first column | | | |

Figure 4. LIC analysis forest plot (serum creatinine below ULN subpopulation)

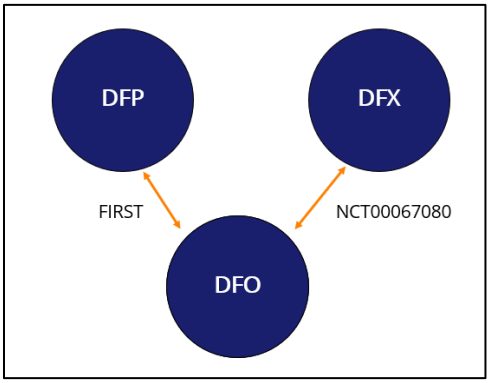



CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron concentration; ULN: upper limit of normal

### Serum ferritin (SF) base case – ITT population

Figure *5* presents the evidence network of change in SF from baseline to 12 months among the treatment arms of FIRST (LA38-0411) (DFP vs DFO) and NCT00067080 (DFO vs DFX). The mean changes and mean differences in SF reported by the two studies are shown in Table *16*.

Figure 5. Serum ferritin analysis network




DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox

Table 16. Mean changes and mean differences in SF (ITT population)

| Studies | Population | Intervention | N | Mean change µg/L* (SD) | Mean difference (SE) |
|---|---|---|---|---|---|
| FIRST (LA38-0411) | SCD and other anemias | DFP<br>DFO | 143<br>74 | 15.70 (2060.00)<br>-352.00 (1270.00) | 367.70 (305.47)<br>Reference |
| NCT00067080[†] | SCD | DFX<br>DFO | 132<br>63 | -183.00 (1651.00)<br>-558.00 (951.00) | 375.00 (187.10)<br>Reference |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; dw: dry weight (gram); ITT, intention-to-treat; SCD: sickle cell disease; SD: standard deviation; SE: standard error; SF: serum ferritin

The base case analysis utilizes the ITT population. The results, in terms of the mean difference in SF from baseline to 12 months relative to DFP, are reported in Table 17, Table 18, and Figure *6*. Compared to DFP, the mean difference is -364.39 (95% CrI: -961.37, 237.22) for DFO and 11.15 (95% CrI: -688.24, 712.52) for DFX. DFO is numerically preferable (mean difference -376.14; 95% CrI: -739.09, -5.29) to DFX. The results demonstrate that there is no statistically significant difference between DFP and DFO, or DFP and DFX.

Table 17. SF analysis results (ITT population)

| Treatment | Mean difference (95% CrI) | Probability of being best* | SUCRA* |
|---|---|---|---|
| DFO | -364.4 39 (-961.37, 237.22) | 86.20% | 92.98% |
| DFP | Reference | 11.63% | 31.44% |
| DFX | 11.15 (-688.24, 712.52) | 2.17% | 25.58% |

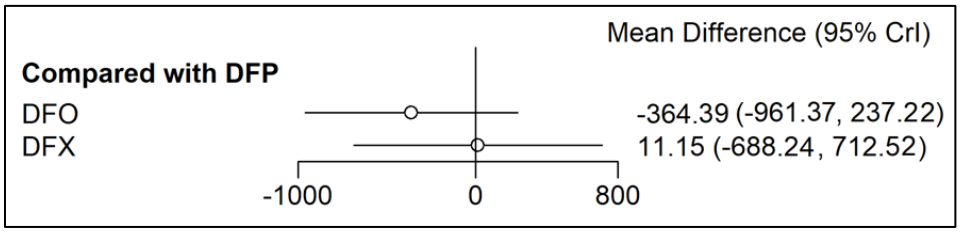
CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; ITT, intention-to-treat; SUCRA: surface under the cumulative ranking curve; SF: serum ferritin
*Probability of being the best and SUCRA are reported as part of the NMA, but are not relevant in the context of: 1) a non-inferiority trial (FIRST) was included in the NMA, and 2) no significant difference was observed between DFP vs DFO, or DFP vs DFX

Table 18. SF analysis pairwise comparison matrix (ITT population)

| Treatment* | DFO | DFP | DFX |
|---|---|---|---|
| DFO | DFO | 364.39 (-237.22, 961.37) | 376.14 (5.29, 739.09) |
| DFP | -364.39 (-961.37, 237.22) | DFP | 11.15 (-688.24, 712.52) |
| DFX | -376.14 (-739.09, -5.29) | -11.15 (-712.52, 688.24) | DFX |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; ITT, intention-to-treat; SF: serum ferritin
*Treatments listed in the first column are the references, treatments listed in the first row were compared to the reference treatments listed in the first column

Figure 6. SF analysis forest plot (ITT population)




CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; ITT, intent-to-treat; SF: serum ferritin

## SF scenario analysis – SCD subpopulation

Table *19* presents the mean changes and mean differences in SF for the network scenario examining the SCD subpopulation from FIRST (LA38-0411) (84.8% of ITT population had SCD) and the ITT population from NCT00067080 (100% of ITT population had SCD). The evidence network is the same as the base case. The results of the scenario are presented in

Table *20*, Table 21, and Figure 7. Compared to DFP, the mean difference is -556.18 (95% CrI: -1217.68, 117.79) for DFO and -182.56 (95% CrI: -942.53, 588.51) for DFX. DFO is numerically preferable (mean difference -374.70; 95% CrI: -738.39, -7.08) to DFX. The results of this scenario analysis show the same trend as the ITT analysis in that there is no statistically significant difference between DFP and DFO, or DFP and DFX.

Table 19. Mean changes and mean differences in SF (SCD subpopulation)

| Studies | Population | Intervention | N | Mean change µg/L* (SD) | Mean difference (SE) |
|---|---|---|---|---|---|
| FIRST (LA38-0411) | SCD | DFP<br>DFO | 122<br>62 | 177.00 (2150.00)<br>-381.00 (2240.00) | 558.00 (344.70)<br>Reference |
| NCT00067080† | SCD | DFX<br>DFO | 132<br>63 | -183.00 (1651.00)<br>-558.00 (951.00) | 375.00 (187.10)<br>Reference |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SCD: sickle cell disease; SD: standard deviation; SE: standard error; SF: serum ferritin

*A negative mean difference indicates a reduction in SF, which is a positive treatment effect

†Mean and SD reported in NCT00067080 were adjusted for transfusion category (simple, exchange, simple and exchange)

Table 20. SF analysis results (SCD subpopulation)

| Treatment | Mean difference (95% CrI) | Probability of being best* | SUCRA* |
|---|---|---|---|
| DFO | -556.18 (-1217.68, 117.79) | 92.66% | 96.28% |
| DFP | Reference | 5.11% | 18.51% |
| DFX | -182.56 (-942.53, 588.51) | 2.23% | 35.22% |

CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SCD: sickle cell disease; SF: serum ferritin; SUCRA: surface under the cumulative ranking curve

*Probability of being the best and SUCRA are reported as part of the NMA, but are not relevant in the context of the following: 1) a non-inferiority trial (FIRST) was included in the NMA, and 2) no significant difference was observed between DFP vs DFO, or DFP vs DFX

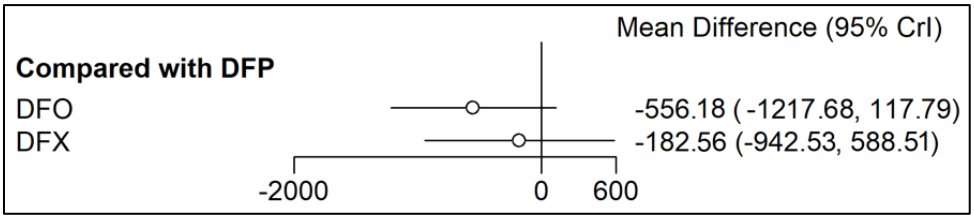
Table 21. SF analysis comparison matrix (SCD subpopulation)

| Treatment* | DFO | DFP | DFX |
|---|---|---|---|
| DFO | DFO | 556.18 (-177.79, 1217.68) | 374.70 (7.08, 738.39) |
| DFP | -556.18 (-1217.68, 117.79) | DFP | -182.56 (-942.53. 588.51) |
| DFX | -374.70 (-738.39, -7.08) | 182.56 (-588.51, 942.53) | DFX |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SCD: sickle cell disease; SF: serum ferritin

*Treatments listed in the first column are the references, treatments listed in the first row were compared to the reference treatments listed in the first column

Figure 7. SF analysis forest plot (SCD subpopulation)




CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SCD: sickle cell disease; SF: serum ferritin

## SF scenario analysis - subpopulation with serum creatinine below upper limit of normal (ULN)

Table *22* presents mean changes and mean differences in SF for the network scenario examining the subpopulation with serum creatinine below ULN from FIRST (LA38-0411) (96.3% of ITT population were below ULN) and the ITT population from NCT00067080 (100% below ULN). The categorization of serum creatinine ULN is presented in Table 12. The evidence network is the same as the base case. The results are reported in Table 23, Table 24, and Figure 8. Compared to DFP, the mean difference is -387.68 (95% CrI: -994.05, 211.54) for DFO and -12.77 (95% CrI: -724.22, 692.78) for DFX. DFO is numerically preferable (mean difference -373.59; 95% CrI: -740.39, -6.34) to DFX. The results of this scenario analysis show the same trend as the ITT analysis in that there is no statistically significant difference between DFP and DFO, or DFP and DFX.

Table 22. Mean changes and mean differences in SF (serum creatinine below ULN subpopulation)

| Studies | Population | Intervention | N | Mean change µg/L* (SD) | Mean difference (SE) |
|---|---|---|---|---|---|
| FIRST (LA38-0411) | Serum creatinine below ULN‡ | DFP<br>DFO | 136<br>73 | 56.70 (2060.00)<br>-330.00 (2180.00) | 386.70 (310.33)<br>Reference |
| NCT00067080† | Serum creatinine below ULN‡ | DFX<br>DFO | 132<br>63 | -183.00 (1651.00)<br>-558.00 (951.00) | 375.00 (187.10)<br>Reference |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SCD: sickle cell disease; SD: standard deviation; SE: standard error; SF: serum ferritin; ULN: upper limit of normal

*A negative mean difference indicates a reduction in SF, which is a positive treatment effect

†Mean and SD reported in NCT00067080 were adjusted for transfusion category (simple, exchange, simple and exchange)

‡Definition of ULN is presented in Table 12

Table 23. SF analysis results (serum creatinine below ULN subpopulation)

| Treatment | Mean difference (95% CrI) | Probability of being best* | SUCRA* |
|---|---|---|---|
| DFO | -387.68 (-994.05, 211.54) | 87.42% | 93.6% |
| DFP | Reference | 10.40% | 29.54% |
| DFX | -12.77 (-724.22, 692.78) | 2.18% | 26.86% |

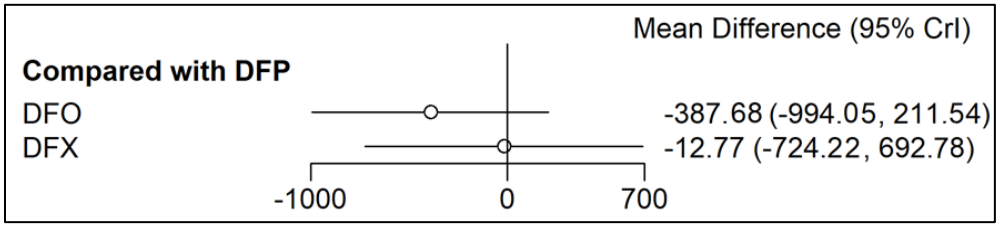
CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SUCRA: surface under the cumulative ranking curve; SF: serum ferritin; ULN: upper limit of normal
*Probability of being the best and SUCRA are reported as part of the NMA, but are not relevant in the context of: 1) a non-inferiority trial (FIRST) was included in the NMA, and 2) no significant difference was observed between DFP vs DFO, or DFP vs DFX

Table 24. SF analysis pairwise comparison matrix (serum creatinine below ULN subpopulation)

| Treatment* | DFO | DFP | DFX |
|---|---|---|---|
| DFO | DFO | 387.68 (-211.54, 994.05) | 373.59 (6.34, 740.39) |
| DFP | -387.68 (-994.05, 211.54) | DFP | -12.77 (-724.22, 692.78) |
| DFX | -373.59 (-740.39, -6.34) | 12.77 (-692.78, 724.22) | DFX |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SF: serum ferritin; ULN: upper limit of normal
*Treatments listed in the first column are the references, treatments listed in the first row were compared to the reference treatments listed in the first column

Figure 8. SF analysis forest plot (serum creatinine below ULN subpopulation)




CrI: credible interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SF: serum ferritin; ULN: upper limit of normal

### 8.1.4. Discussion

This study evaluated the comparative efficacy of DFP, DFO, and DFX based on the endpoints of change in LIC and SF from baseline to 12 months using an NMA framework. The NMA considered two studies: FIRST (LA38-0411) and NCT00067080. The results showed no significant differences in mean reduction of LIC and SF levels from baseline to 12 months between DFP and DFX or DFP and DFO. The results of the base case analysis examining the ITT population were consistent with scenario analyses examining the subpopulation of patients with a diagnosis of SCD and the subpopulation of patients with serum creatinine below ULN.

FIRST (LA38-0411) was a non-inferiority trial in which two approaches were taken to show non-inferiority (36). In the first approach, the effect of the intervention, DFP vs the comparator, DFO, was based on a pre-specified non-inferiority margin; this was applied to evaluate the non-inferiority of DFP vs DFO in LIC reduction. In this approach, if the lower limit (or upper limit depending on the direction) of the CI/CrI is larger than the non-inferiority margin, it provides evidence for statistically significant non-inferiority. The non-inferiority margin in FIRST (LA38-0411) for change in LIC from baseline to 12 months was -2 mg/dw. In the NMA, the comparison of DFP and DFX for the ITT analysis (mean difference -0.68; 95% CrI -3.63, 2.25) showed no significant differences between the two ICTs in terms of reduction of LIC from baseline to 12 months. In the second approach, the non-inferiority of DFP relative to DFO in SF reduction was concluded if the CI contains zero, as would be in a superiority trial. In contrast to this approach, the first approach attempts to prove directly that the difference between the intervention and comparator is smaller than a scientifically meaningful margin and usually requires a large sample size to show non-inferiority. Thus, the second approach can be viewed as less statistically sound for a non-inferiority claim, and its conclusion should be interpreted with caution as failing to prove that there is a difference is not equivalent to proving there is no difference (or that the difference is very small). In the NMA, the non-inferiority of DFP vs DFX in the reduction of SF from baseline to 12 months can be concluded based on the fact that the CrI contains zero. Likewise, the non-inferiority of DFP to DFX can be demonstrated using the second approach.

In addition to the mean differences, probability of being the best and SUCRA are reported as part of the NMA but are not relevant in the context of: 1) a non-inferiority trial (FIRST; LA38-0411) was included in the NMA, and 2) no significant difference was observed between DFP vs DFO, or DFP vs DFX.

In conclusion, the NMA provides a comprehensive assessment of the efficacy of DFP and comparators of DFO and DFX for the treatment of transfusional iron overload in patients with SCD. The results of this NMA, including the base case and scenario analyses, suggest that there is no statistically significant difference between DFP and DFO, or DFP and DFX in the reduction of LIC and SF. Findings should be considered in the context of the study's limitations.

## 8.2. Comparative Effectiveness of Iron Chelation Therapies in Patients with Beta-Thalassaemia

### 8.2.1. Objective and Rationale

Treatment of iron overload in SCD patients is the most recent indication of DFP, however, DFP was originally indicated for the treatment of iron overload in beta-thalassaemia patients. For this reason, we consider it relevant to include in the dossier the results of a comparative assessment between DFP, DFX, and DFO for this indication. The most recent available comparative analysis is one carried out in 2011 (study not published, analysis carried out by Chiesi), which is the one included here, however, it is expected to be updated during 2023.

This study utilizes a pairwise meta-analysis and indirect comparisons to estimate comparative outcomes rather than network meta-analysis since the evidence networks for the different comparisons were sparse (Figure 9, Figure 11, Figure 14, and Figure 15) and loops in the evidence network were observed for only one outcome measure (SF, Figure 11). For such evidence networks, simple indirect comparisons are simpler and more transparent but give the same results as NMA; sensitivity analyses on the analysis of SF also suggested that the use of mixed treatment comparison would have had minimal impact on the results for that comparison.

### 8.2.2. Methodology

A systematic review was conducted to identify relevant clinical data from the published literature regarding the clinical effectiveness of the three iron chelators, DFP, DFO and DFX, for the treatment of chronic iron overload in people with.

Out of the 20 primary studies identified from the SLR, studies satisfying at least one of the following criteria were included to the meta-analysis:

- Reported change from baseline on one of the following outcome measures after one year's treatment:
  - Change from baseline in LIC measured using biopsy or SQUID
  - Change from baseline in serum ferritin levels
  - Change from baseline cardiac MRI T2*
  - Change from baseline in left ventricular ejection fraction (LVEF)
- Studies not reporting at least one measure of variability/precision (SE, SD, 95% CI or CV) for any given endpoint were excluded from meta-analyses on that endpoint.
- Studies not published as full journal articles were excluded as they were unlikely to report sufficient detail in the abstract to assess study inclusion and comparability with other studies or extract the required information for meta-analysis.
- Studies reporting only transformed outcomes or geometric means were excluded from analyses of outcomes in which most studies reported outcomes only on a natural scale (e.g., arithmetic means of untransformed data), and vice-versa.

These criteria were specified to ensure that the meta-analyses included only studies reporting comparable outcomes for comparable patients.

Eleven RCTs comparing the efficacy and safety of DFP, DFO and DFX were identified in the systematic. Of these, six studies were deemed to be suitable for inclusion for meta-analysis Table *25*.

Table 25. Studies included in the meta-analysis

| Short reference | Trial arms | Study design | Population | Total N |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **DFP monotherapy** | | | | |
| Pennell, 2006 (38) | DFP vs DFO | P3, RCT, open-label | Patients with homozygous β-thalassaemia, regularly transfused, chelated with subcutaneous DFO with no symptoms of heart failure prior to screening | 61 |
| Maggio, 2002 (39) | DFP vs DFO | P3, RCT, open-label | Patients with thalassaemia major with serum ferritin between 1,500 and 3,000 ng/mL | 144 |
| **DFP-DFO combination therapy** | | | | |
| Tanner, 2007 (40) | DFP + DFO vs DFO | Double-blind placebo-controlled RCT | Patients with diagnosis of TM, currently maintained on subcutaneous DFO therapy, > 18 yrs with mild to moderate myocardial siderosis | 65 |
| **DFP-DFO sequential therapy** | | | | |
| Maggio, 2008 (41) | Sequential DFP + DFO vs DFP alone | P3, RCT, open-label | Thalassaemia major patients with serum ferritin concentrations between 800 and 3,000 µg/L, over 13 yrs of age | 213 |
| Galanello, 2006 (42) | Sequential DFP + DFO vs DFO | P3, RCT, open-label | Patients ≥10 yrs, most serum ferritin values between 1,000 µg/L and 4,000 µg/L and undergoing chelation therapy | 60 |
| **DFX monotherapy** | | | | |
| Cappellini, 2006 (43) | DFX vs DFO | P3, RCT | Paediatric (at least 2 yrs of age) and adult pts with a diagnosis of β-thalassaemia with chronic iron overload from blood transfusions indicated by an LIC of 2 mg Fe/g dw or greater. Pts need to be receiving at least 8 blood transfusions/yr | 586 |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; dw: dry weight; LIC: Liver iron concentration; P: phase; RCT: randomized controlled trial; yrs: years

### 8.2.3. Results

#### Liver iron concentration (LIC)

Four RCTs reported LIC measured using biopsy or SQUID (38,39,42,43) (Table 26 and Figure 10).

*DFP vs DFO*

Pooled analysis of two RCTs (38,39) comparing DFP and DFO monotherapy demonstrated no significant difference in the effect of the two iron chelators on LIC (weighted mean difference [WMD] in change from baseline: -0.165 mg/g dw [SE 0.627], p=0.793), consistent with the individual results of the two RCTs.

*DFP vs DFX*

The network diagram for indirect comparisons undertaken is shown in Figure 10. An indirect comparison of DFP and DFX, via DFO showed that there was no significant difference in the effect of these two chelators on LIC (p=0.443). The single trial assessing the efficacy of DFX did not meet its primary objective of non-inferiority to DFO across the total study cohort (43). This was considered to result from an imbalance in dosing of DFX and DFO at lower baseline LICs, whereas an analysis of just those patients with baseline LICs ≥ 7 mg/g dw (DFX doses 20 and 30 mg/kg/), showed that the non-inferiority criteria were achieved. The doses of DFX used in these patients

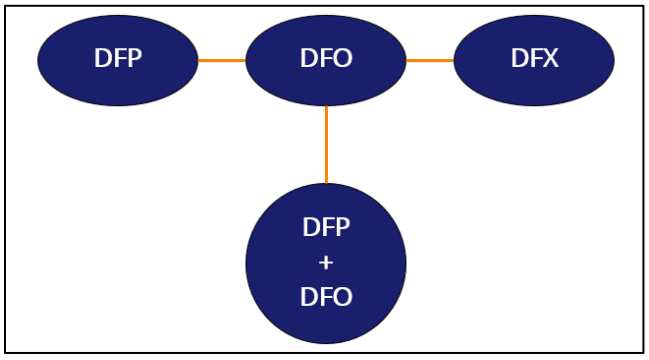
are more reflective of the doses that would generally be used in clinical practice, as highlighted by the summary product characteristics (SPC). We, therefore, conducted a sensitivity analysis excluding the subgroups from the Cappellini study with baseline LIC < 7 mg/g dw. This analysis confirmed the results of the main analysis, showing no statistically significant difference in the effect of DFP and DFX on LIC (p=0.384).

### *DFP-DFO combination therapy*

In a comparison between DFP–DFO sequential therapy (DFP for 5 days/week and DFO for 2 days/week) and DFO monotherapy, a single RCT (42) reported no statistically significant difference in the reduction of LIC (p=0.224), although the effect was numerically larger in the monotherapy arm. An indirect comparison of DFP–DFO sequential therapy with DFP monotherapy, via DFO monotherapy, showed that DFP and DFP–DFO sequential therapy are also comparable in their effect on LIC (WMD [SE]: 0.339 mg/g dw [0.643], p=0.598).

One RCT identified by the systematic review assessed the efficacy of combination therapy (DFP, 75 mg/kg/day, 7 days/week; DFO, 34.9 mg/kg/day, 5 days/week) versus DFO alone (43.4 mg/kg/day, 5 days/week) (40). This study was excluded from the statistical analysis since it reported liver iron measured using liver MRI T2* technology. However, the results of this study are worthy of consideration here, since this demonstrated that improvements in liver T2* were significantly greater for the combination treatment group, compared with DFO monotherapy (between-treatment difference 39%, 95% CI, 20% to 61%, p<0.001).

Figure 9. Network diagram for LIC



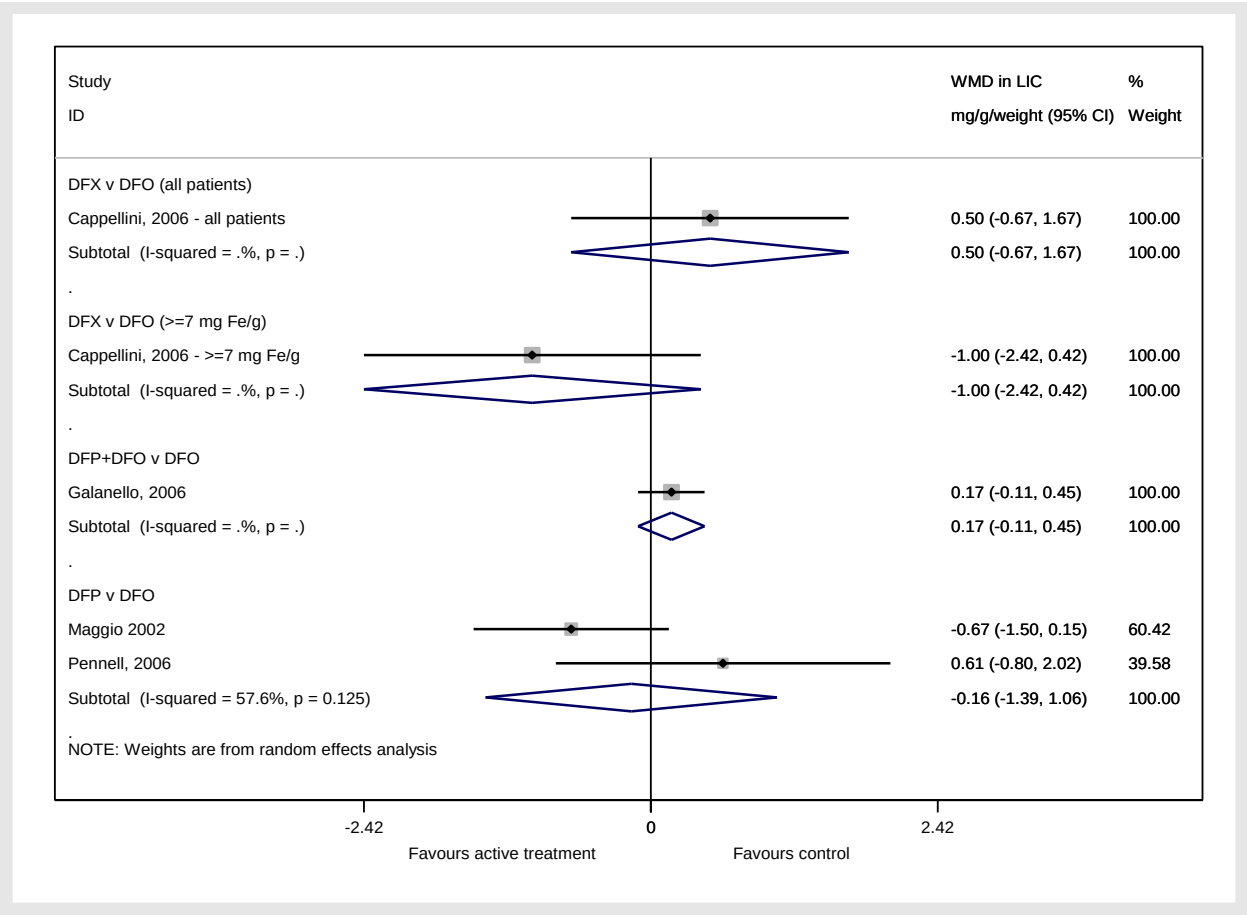

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron concentration

Table 26. Results and data inputs for the meta-analysis and indirect comparisons on liver iron concentration

| Study | Active treatment | Control | No. pts | Change from baseline, mg/g dw | | |
|---|---|---|---|---|---|---|
| | | | | Mean | SE | p value |
| | | | | | | |
| Maggio, 2002 (39) | DFP: 75 mg/kg/d | DFO: 5 d/wk, 50 mg/kg/d | T: 71; C: 73 | -0.672 | 0.421 | 0.111 |
| Pennell, 2006 (38) | DFP: 75 mg/kg/d, increased to target 100 mg/kg/d | DFO: ≥ 5 d/wk, 50 mg/kg/d | T: 27; C: 30 | 0.610 | 0.721 | 0.398 |
| Pooled[†] | DFP | DFO | | -0.165 | 0.627 | 0.793 |
| | | | | | | |
| Galanello, 2006 (42) | DFP + DFO: DFP 5 d/wk, 75 mg/kg/d; DFO for the remaining 2 d/wk, 20 to 60 mg/kg/d | DFO: 5-7 d/wk, 20 to 60 mg/kg/d | T: 29; C: 30 | 0.174 | 0.143 | 0.224 |
| | | | | | | |
| Cappellini, 2006 (43): all patients | DFX: LIC 2-3 mg/Fe g dw, 5 mg/kg/d; LIC >3-7 mg Fe/g dw, 10 mg/kg/d; LIC > 7mg Fe/g dw, 20 mg/kg/d; LIC > 14 mg Fe/g dw, 30mg/kg/d | DFO, 5 d/wk: LIC 2-3 mg/Fe g dw, 20-30 mg/kg/d; LIC >3-7 mg Fe/g dw, 25-35 mg/kg/d; LIC > 7mg Fe/g dw, 35-50 mg/kg/d; LIC > 14 mg Fe/g dw, ≥ 50 mg/kg/d | T: 273; C: 268 | 0.500 | 0.598 | 0.403 |
| Cappellini, 2006 (43): ≥7 mg Fe/g dw | DFX: LIC > 7mg Fe/g dw, 20 mg/kg/d; LIC > 14 mg Fe/g dw, 30 mg/kg/d | DFO, 5 d/wk: LIC > 7mg Fe/g dw, 35-50 mg/kg/d; LIC > 14 mg Fe/g dw, ≥ 50 mg/kg/d | T: 185; C: 186 | -1.000 | 0.726 | 0.168 |
| | | | | | | |
| Indirect comparison | DFP vs DFX (using whole Cappellini trial population) | | | -0.665 | 0.866 | 0.443 |
| | DFP vs DFX (excluding Cappellini low-dose sub-group) | | | 0.835 | 0.959 | 0.384 |
| | DFP + DFO vs DFP | | | 0.339 | 0.643 | 0.598 |

C: control group; d: day; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; dw: dry weight; Fe: iron; IC: indirect comparison; LIC: liver iron concentration; SE: standard error; T: treatment group; wk: week. [†] Random-effects meta-analysis. The analysis suggested that there was no significant heterogeneity (p=0.125), although 57.6% of variability in effects was due to heterogeneity ($I^2$=57.6%)

Figure 10. Forest plot for LIC




CI: confidence interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron concentration; WMD: weighted mean difference. Where only one study was available for pooling, heterogeneity testing was not appropriate and hence these statistics are not shown on the figure.

## Serum ferritin (SF)

Five RCTs meeting the inclusion criteria reported data on untransformed change in SF (38,39,41–43). While these studies reported arithmetic means and SE, Tanner et al. (40) analysed SF on a log-scale to deal with skewed data and reported only geometric means and coefficient of variation; this study was therefore excluded from further statistical analysis. However, this study provides important results for DFP–DFO combination therapy and is considered below as part of the discussion of results.

### *DFP vs DFO*

Meta-analysis of two RCTs (38,39) DFP and DFO monotherapy demonstrated no significant difference in the efficacy of the two iron chelator monotherapies on SF levels (WMD in change from baseline: 92.56 µg/L [SE 126.04], p=0.463), consistent with the individual results of the two RCTs (Table *27* and Figure *12*).

### *DFP vs DFX*

Since the network for this outcome (Figure 11) included one loop, the IC between DFP and DFX can be calculated in one of two ways: either via DFO or via both DFP–DFO sequential therapy and DFO. The more direct route (via DFO only) was used in the base case analysis since it has higher statistical power, although results for both analyses are shown (Table *27* and Figure *12*).

The base case analysis showed DFP to be significantly more effective than DFX (WMD in change from baseline: -429.27 µg/L [SE 143.40], p=0.003), whereas using the DFP–DFO sequential therapy and DFO loop found the difference between DFOP and DFX to be non-significant (WMD in change from baseline: -135.83 µg/L [SE 220.74], p=0.538). However, the results of the two IC were not significantly different (p>0.25) from each other, demonstrating that the evidence network is consistent. Subsequently, use of mixed treatment comparison rather than simple IC would not have changed the conclusions of the analysis, although it is likely that mixed treatment comparison would have estimated the difference between DFP and DFX to be smaller than the base case analysis.

Meta-analyses of the Cappellini study, in which DFX and DFO were compared, showed a high degree of heterogeneity between subgroups with different baseline LIC; smaller differences in effect size were observed between treatments for patients with high baseline LIC than low baseline LIC (Table 27 and Figure 12). To test the effect of this heterogeneity on the IC of DFP and DFX, a sensitivity analysis was conducted including only those patients with baseline LIC ≥ 7 mg Fe/g dw. This analysis suggested that DFP and DFX were equally efficacious in their effect on SF (Table *27*); there was no significant difference between DFP and DFX regardless of the route taken in the IC (p>0.25).

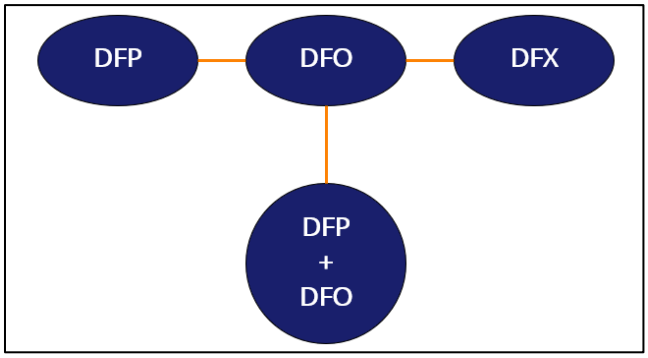
Overall, the analyses conducted demonstrate that DFP is at least as effective as DFX in controlling SF levels.

### *DFP-DFO combination therapy*

No significant difference in effect on SF between sequential DFP-DFO therapy and DFO alone were observed in one RCT ((42). Another study demonstrated greater improvement in SF over 12 months with sequential therapy versus DFP (p=0.008) (41).

As described already for the liver iron outcomes, Tanner et al assessed the efficacy of more intensive combination therapy (DFP, 75 mg/kg/day, 7 days/week; DFO, 34.9 mg/kg/day, 5 days/week) versus DFO alone (43.4 mg/kg/day, 5 days/week) (40). This study was excluded from the statistical analysis since it reported SF on a log-scale. However, the results of this study are worthy of consideration here, since this demonstrated that improvements in SF were significantly greater for the combination treatment group, compared with DFO monotherapy (between-treatment difference −40%; 95% CI, −48% to −28%; p<0.001).

Figure 11. Network diagram for SF




DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SF: serum ferritin

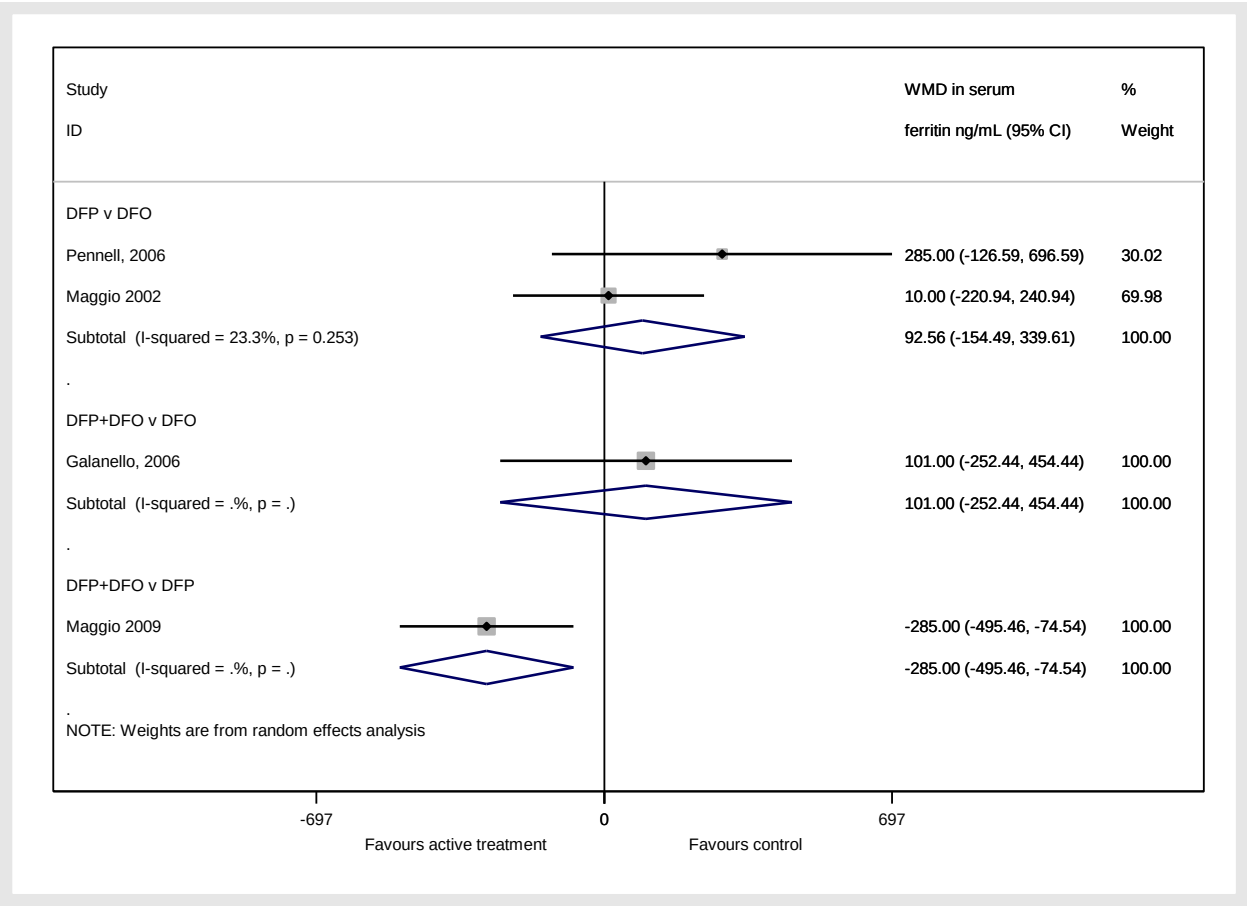
Table 27. Results and data inputs for the meta-analysis and indirect comparisons on SF levels

| Study | Active treatment | Control | No. pts | Change from baseline, µg/L[§] | | |
|---|---|---|---|---|---|---|
| | | | | Mean | SE | p value |
| | | | | | | |
| Pennell, 2006 (38) | DFP: 75 mg/kg/d, increased to target 100 mg/kg/d | DFO: ≥ 5 d/wk, 50 mg/kg/d | T: 27; C: 29 | 285.00 | 210.00 | 0.175 |
| Maggio 2002 (39) | DFP: 75 mg/kg/d | DFO: 5 d/wk, 50 mg/kg/d | T: 71; C: 73 | 10.00 | 117.83 | 0.932 |
| Pooled[†] | DFP | DFO | | 92.56 | 126.04 | 0.463 |
| Galanello, 2006 (42) | DFP+DFO: DFP 5 d/wk, 75 mg/kg/d; DFO for the remaining 2 d/wk, 20 to 60 mg/kg/d | DFO: 5-7 d/wk, 20 to 60 mg/kg/d | T: 29; C: 30 | 101.00 | 180.33 | 0.575 |
| Maggio, 2009 (41) | DFP+DFO: DFP 4 d/wk, 75 mg/kg/d; DFO 3 d/wk, 50 mg/kg/d | DFP: 75 mg/kg/d | T: 105; C: 108 | -285.00 | 107.38 | 0.008* |
| Cappellini, 2006 (43): ≤ 3 mg Fe/g dw | DFX: 5 mg/kg/d; | DFO: 5 d/wk, 20-30 mg/kg/d; | T: 15; C: 13 | 978.00 | 221.07 | 0.000* |
| Cappellini, 2006 (43): > 3-7 mg Fe/g dw | DFX: 10 mg/kg/d | DFO: 5 d/wk, 25-35 mg/kg/d | T: 73; C: 77 | 801.00 | 116.57 | 0.002* |
| Cappellini, 2006 (43): >7-14 mg Fe/g dw | DFX: 20 mg/kg/d | DFO: 5 d/wk, 35-50 mg/kg/d | T: 80; C: 89 | 328.00 | 103.61 | 0.000* |
| Cappellini, 2006 (43): > 14 mg Fe/g dw | DFX: 30mg/kg/d | DFO: 5 d/wk, ≥ 50 mg/kg/d | T: 115; C: 101 | 77.00 | 193.97 | 0.691 |
| Pooled: Cappellini, 2006 (43): all subgroups[‡] | DFX: LIC 2-3 mg/Fe g dw, 5 mg/kg/d; LIC >3-7 mg Fe/g dw, 10 mg/kg/d; LIC > 7mg | DFO, 5 d/wk: LIC 2-3 mg/Fe g dw, 20-30 mg/kg/d; LIC >3-7 mg Fe/g dw, 25-35 mg/kg/d; LIC > 7mg Fe/g dw, 35-50 mg/kg/d; | T: 283; C: 280 | 521.83 | 68.39 | < 0.001 * |

| Study | Active treatment | Control | No. pts | Change from baseline, µg/L[§] | | |
|---|---|---|---|---|---|---|
| | | | | Mean | SE | p value |
| | Fe/g dw, 20 mg/kg/d; LIC > 14 mg Fe/g dw, 30mg/kg/d | LIC > 14 mg Fe/g dw, ≥ 50 mg/kg/d | | | | |
| Pooled: Cappellini, 2006 (43): ≤ 7 mg Fe/g dw[‡] | DFX: LIC 2-3 mg/Fe g dw, 5 mg/kg/d; LIC >3-7 mg Fe/g dw, 10 mg/kg/d | DFO, 5 d/wk: LIC 2-3 mg/Fe g dw, 20-30 mg/kg/d; LIC >3-7 mg Fe/g dw, 25-35 mg/kg/d | T: 88; C: 90 | 839.51 | 103.11 | < 0.001 * |
| Pooled: Cappellini, 2006 (43): > 7 mg Fe/g dw[‡] | DFX: LIC > 7mg Fe/g dw, 20 mg/kg/d; LIC > 14 mg Fe/g dw, 30 mg/kg/d | DFO, 5 d/wk: LIC > 7mg Fe/g dw, 35-50 mg/kg/d; LIC > 14 mg Fe/g dw, ≥ 50 mg/kg/d | T: 195; C: 190 | 272.28 | 91.39 | 0.003* |
| IC (all Cappellini subgroups | DFP V DFX (via DFO) [¶] | | | -429.27 | 143.40 | 0.003* |
| | DFP V DFX (via DFO and DFO+DFP) | | | -135.83 | 220.74 | 0.538 |
| IC (excluding Cappellini low-dose subgroups) | DFP V DFX (via DFO) | | | -179.72 | 155.69 | 0.248 |
| | DFP V DFX (via DFO and DFO+DFP) | | | 113.72 | 228.92 | 0.619 |

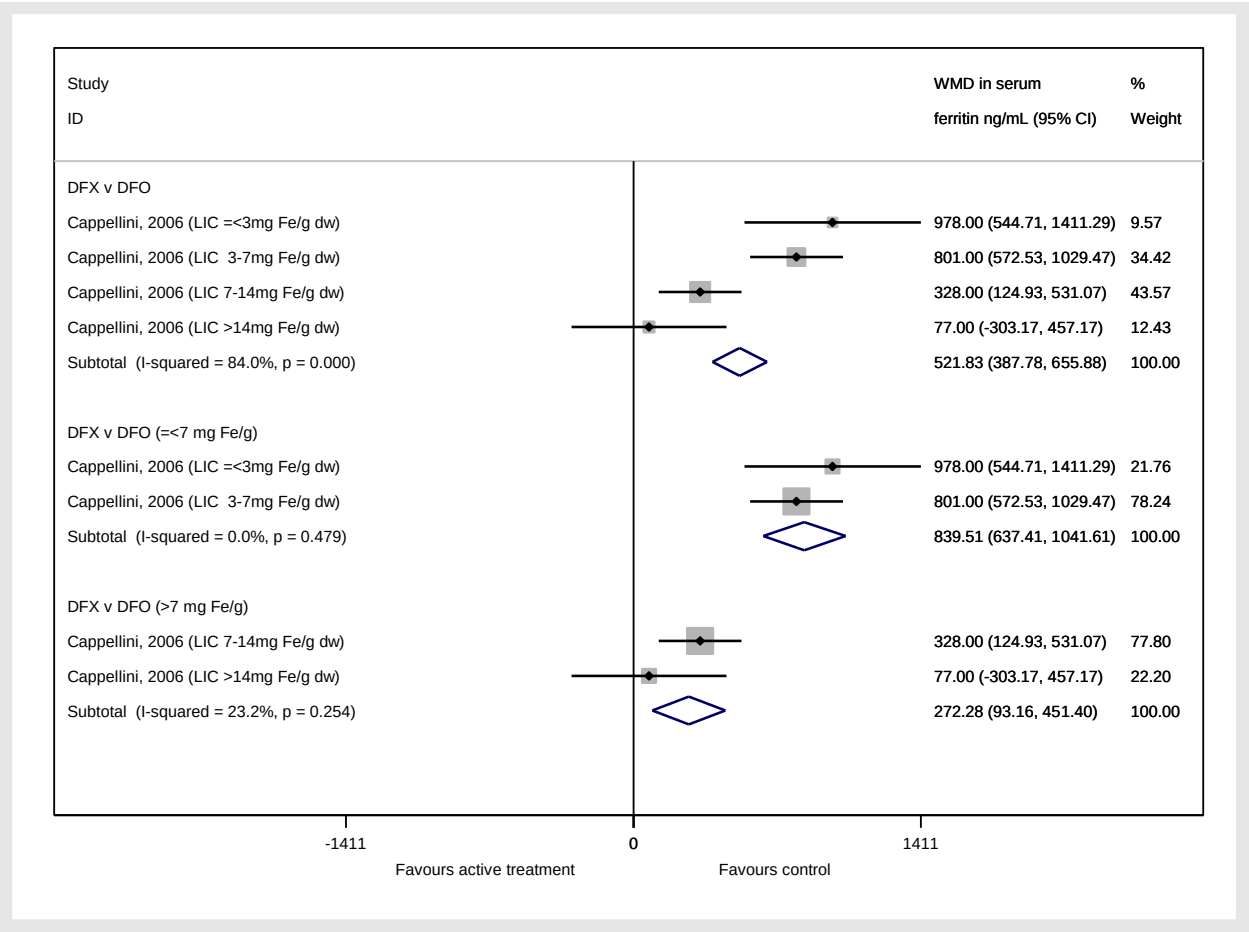
d: day; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; dw: dry weight; Fe: iron; IC: indirect comparison; LIC: liver iron concentration; SE: standard error; wk: week. † Random-effects meta-analysis. The analysis suggested that there was no significant heterogeneity (p=0.253); 23.3% of variability in effects were due to heterogeneity (I2=23.3%); ‡ Fixed-effects meta-analysis; ¶ Base case analysis; § Serum ferritin reported as ng/ml in the Maggio 2002 paper. * Statistically significant (p<0.05)

Figure 12. Forest plot for SF: random-effects meta-analysis




CI: confidence interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SF: serum ferritin; WMD: weighted mean difference. Where only one study was available for pooling, heterogeneity testing was not appropriate and hence these statistics are not shown in the figure

Figure 13. Forest plot for serum ferritin: fixed-effects meta-analyses on Cappellini subgroups




CI: confidence interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; WMD: weighted mean difference

## Cardiac T2*

Two RCTs (38,40) meeting the inclusion criteria reported log-transformed cardiac MRI T2* (Table *28*). Maggio et al. (2009) (41) was excluded from the analysis as it reported arithmetic mean cardiac T2* (rather than ratios of geometric means). In addition, baseline measurements for this study were taken 17-18 months after study initiation rather than at time zero, followed by further measurements 16-14 months later.

### *DFP vs DFO*

One RCT by Pennell et al. (38) reported cardiac MRI T2* showing a significant improvement in cardiac iron for patients treated with DFP versus DFO (p=0.02; Table 28).

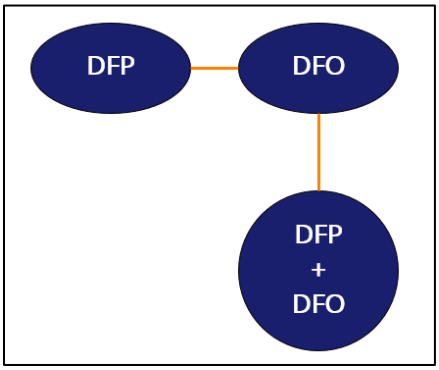
### *DFP vs DFX*

There were no RCTs identified to allow a comparison of DFP with DFX.

### *DFP–DFO combination therapy*

Tanner et al. (40) reported cardiac MRI T2* showing a significant improvement in cardiac iron for patients treated with DFP-DFO therapy versus DFO alone (p=0.02; Table 28). IC of DFP and DFP–DFO combination therapy was conducted via DFO (Figure 14) and showed that there was no significant difference in effect between these two treatments (Table 28).

Figure 14. Network diagram for cardiac MRI T2*




DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; MRI: magnetic resonance imaging

Table 28. Results and data inputs for the meta-analysis and indirect comparisons on cardiac MRI T2*

| Study | Treatment | Comparator | No. pts | Cardiac MRI T2* | | |
|---|---|---|---|---|---|---|
| | | | | Ratio of geometric means | 95% CI | p value |
| Pennell, 2006 (38) | DFP: 75 mg/kg/d, increased to target 100 mg/kg/d | DFO: ≥ 5 d/wk, 50 mg/kg/d | T: 29; C: 31 | 1.1209 | 1.07, 1.17 | 0.02 |
| | | | | | | |
| Tanner, 2007 (40) | DFP+DFO: DFP daily, 75 mg/kg/d; DFO for at least 5 d/wk (mean dose 34.9 mg/kg/d for 5 days) | DFO: 40-50 mg/kg/d for at least 5 d/wk (mean 43.4 mg/kg/d for 5 d) plus placebo | T: 32; C: 33 | 1.1 | 1.02, 1.19 | 0.02 |
| IC | DFP vs. DFP+DFO | | | 0.98 | 0.89, 1.08 | 0.69 |

d: day; DFO: deferoxamine; DFP, deferiprone; IC: indirect comparison; MRI: magnetic resonance imaging; pt: patient; wk: week. * Statistically significant (p<0.05)

## Left ventricular ejection fraction (LVEF)

Three RCTs (38–40) meeting the inclusion criteria reported data on change in LVEF (Table *29* and Figure *15*).

### *DFP vs DFO*

Two RCTs (38,40) reported improvements in LVEF for DFP-treated patients compared with DFO-treated patients. Random-effects meta-analysis confirmed the results of the two RCTs, demonstrating that DFP provides a 2.1% greater absolute improvement in LVEF versus DFO (p=0.019, Table *29* and Figure *16*).

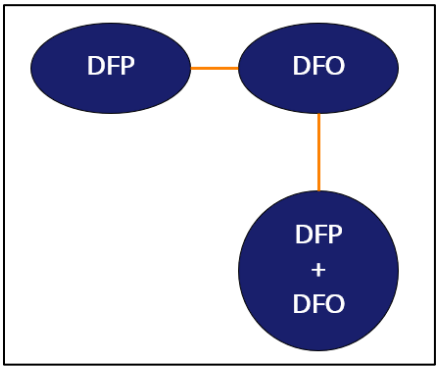
### *DFP vs DFX*

There were no RCTs identified to allow a comparison of DFP with DFX.

### *DFP–DFO combination therapy*

Tanner et al. reported an improvement in LVEF for patients treated with DFP–DFO therapy versus DFO alone that was nearing significance (p=0.051; Table 29 and Figure 16). IC of DFP–DFO combination therapy versus DFP alone was conducted via DFO (Figure 15) and showed that there was no significant difference in effect between these two treatments (Table 29).

Figure 15. Network diagram for LVEF



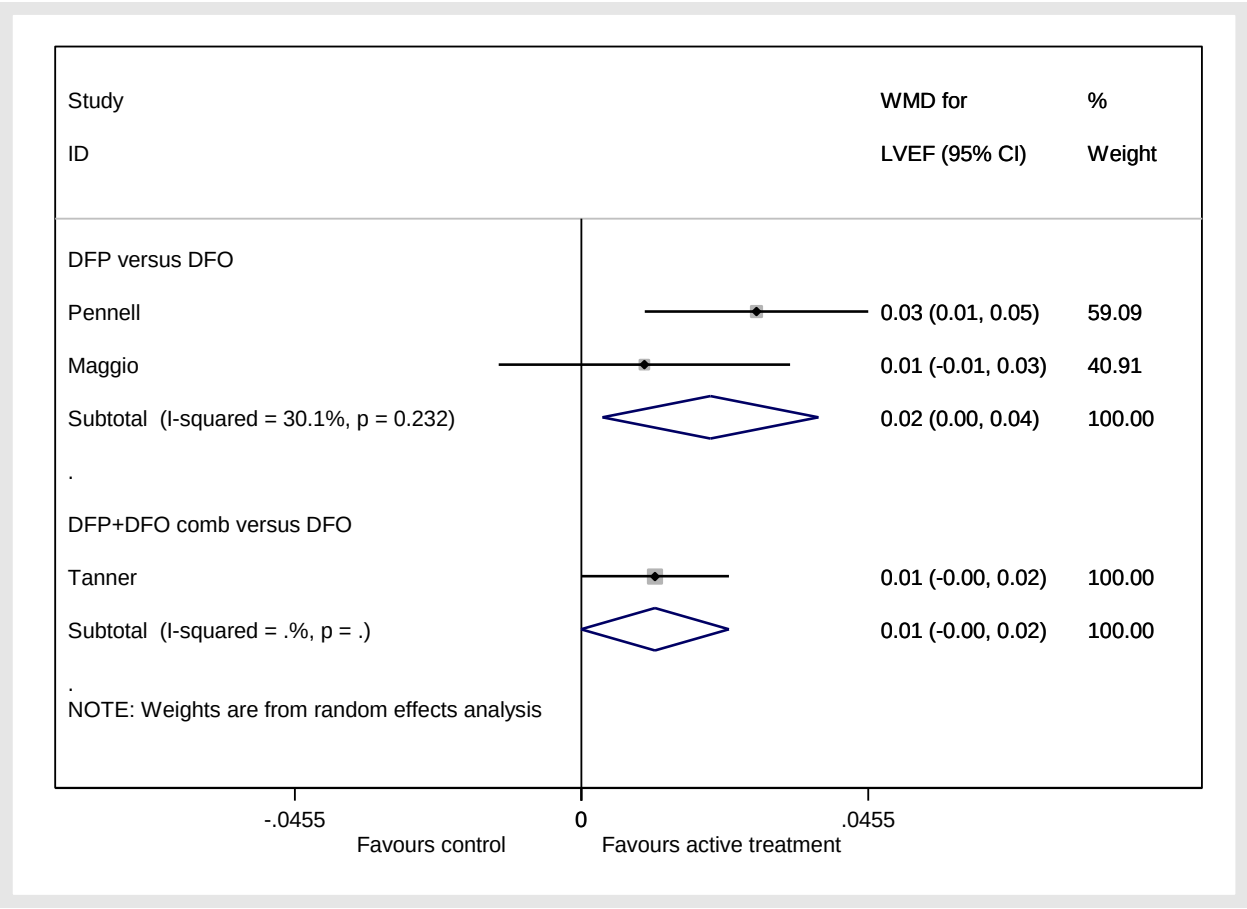

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LVEF: left ventricular ejection fraction

Table 29. Results and data inputs for the meta-analysis and indirect comparisons on LVEF

| Study | Treatment | Comparator | No. pts | Change from baseline, proportion | | |
|---|---|---|---|---|---|---|
| | | | | Mean | SE | p value |
| | | | | | | |
| Pennell, 2006 (38) | DFP: 75 mg/kg/d, increased to target 100 mg/kg/d | DFO: ≥ 5 d/wk, 50 mg/kg/d | T: 29; C: 31 | 0.0278 | 0.0091 | 0.0021* |
| Maggio, 2002 (39) | DFP: 75 mg/kg/d | DFO: 5 d/wk, 50 mg/kg/d | T: 71; C: 73 | 0.0100 | 0.0118 | 0.3971 |
| Pooled† | DFP | DFO | | 0.0210 | 0.0089 | 0.0190* |
| | | | | | | |
| Tanner, 2007 (39) | DFP+DFO: DFP daily, 75 mg/kg/d; DFO for at least 5 d/wk (mean dose 34.9 mg/kg/d for 5 days) | DFO: 40-50 mg/kg/d for at least 5 d/wk (mean 43.4 mg/kg/d for 5 d) plus placebo | T: 32; C: 33 | 0.0117 | 0.0060 | 0.0510 |
| IC | DFP+DFO vs. DFP | | | -0.00930 | 0.0108 | 0.3872 |

d: day; DFO: deferoxamine; DFP: deferiprone; IC: indirect comparison; pt: patient; wk: week. † Random-effects meta-analysis. The analysis suggested that there was no significant heterogeneity (p=0.232); 0.1% of variability in effects were due to heterogeneity (I2=30.1%);* Statistically significant (p<0.05)

Figure 16. Forest plot for LVEF: random-effects meta-analyses




CI: confidence interval; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron concentration; WMD: weighted mean difference. Where only one study was available for pooling, heterogeneity testing was not appropriate and hence these statistics are not shown on the figure

### 8.2.4. Discussion

Meta-analysis and IC of RCT data were conducted, where data allowed, to provide a statistical measure of relative efficacy for those comparisons for which head-to-head RCT data were not available. RCTs identified by the systematic literature review, and meeting additional data reporting criteria, were included in the meta-analysis/IC of efficacy outcomes. The efficacy outcomes considered for this analysis were change in LIC, SF, cardiac MRI T2* and LVEF from baseline to month 12 of iron-chelation treatment. Six RCTs were eligible for meta-analysis; five were DFP monotherapy or DFP–DFO sequential/combination therapy studies; the remaining study compared DFX with DFO and was the pivotal RCT used in the regulatory filing for DFX.

Meta-analysis demonstrates that DFP is equally efficacious to DFO in terms of LIC (n=2, p=0.793) and SF levels (n=2, p=0.463). DFP improves cardiac outcomes compared with DFO; improved

cardiac iron load measured using cardiac MRI T2* (n=1, p=0.02) and improved LVEF (n=2, p=0.019).

In the absence at the time of the study of head-to-head RCTs of DFP and DFX, IC were used to estimate the relative efficacy of these iron chelators. IC via DFO showed that DFP is equally efficacious to DFX in terms of LIC (DFX 20 and 30 mg doses, p=0.384) and SF levels (p=0.248). No RCT data were available relating to cardiac outcomes with DFX treatment. In DEEP-2, a recently published large, randomized trial in children with transfusion-dependent hemoglobinopathies (predominantly beta-thalassaemia), which was not included in the present study as it was not available at the time, non-inferiority of DFP vs DFX was established in the paediatric population. Treatment success was achieved in 55.2% of DFP patients vs 54.8% of DFX patients, and in patients who completed 12 months of treatment, DFP was not inferior to DFX in terms of SF concentration, LIC concentration, or cardiac T2* (44).

DFP–DFO sequential therapy (DFP and DFO given on separate days) is as effective as DFO alone in controlling LIC (n=1, p=0.224) and SF (n=1, p=0.575). For cardiac outcomes, RCT data suitable for meta-analysis were not available. DFP–DFO combination therapy (DFP and DFO can be given on the same day) is more effective than DFO alone in improving cardiac iron burden (cardiac T2*, n=1, p=0.02) and improving function as measured by LVEF (n=1, p= 0.051). For LIC and SF, RCT data suitable for meta-analysis were not available. However, the RCT of Tanner et al. (19) demonstrated that combination therapy provided significant improvements in liver T2* (p<0.001) and SF levels (log-transformed data, p<0.001) compared with DFO alone.

In conclusion, meta-analysis and IC provide a comprehensive assessment of the efficacy of DFP vs comparators (DFO and DFX) for the treatment of transfusional iron overload in patients with thalassaemia. The results of this study suggest that there is no statistically significant difference between DFP and DFO, or DFP and DFX in the reduction of LIC and SF. Furthermore, the study results demonstrated that DFP improves cardiac outcomes compared with DFO, including MRI T2* and LVEF measures.

## 8.3. Comparative Effectiveness of Combination Therapy

DFP is typically administered as a monotherapy but can be given in combination with another approved ICT such as DFO or DFX. Combination therapy is used to increase the effectiveness of ICT in patients who do not adequately respond to monotherapy or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction.

There is extensive evidence regarding the efficacy and safety of DFP combination therapy (40–42,45–47). The use of DFP in combination with other iron chelation agents was approved by the European Medicines Agency (EMA) in 2016. Moreover, the use of combination therapies is recommended for certain patients in several guidelines, such as those of the Thalassaemia International Federation (TIF) and British Society for Haematology (21,22,33).

DFO and DFP have been combined successfully to improve cardiac and hepatic iron clearance. There is evidence of a synergistic shuttle effect between DFP and DFO (48). TIF treatment guidelines state that this combination can be useful for patients in whom monotherapy with either agent has failed to adequately control liver or cardiac iron as well as for patients who are not faring well on DFO monotherapy for compliance reasons, for whom combination therapy can be a means of decreasing the frequency of DFO needed to maintain targets. In addition, TIF notes that for patients with very high levels of cardiac iron (MRI T2* < 8 ms) and/or cardiac dysfunction without frank heart failure, DFO + DFP combination therapy should be strongly considered (21).

There is less evidence regarding the combination of DFP + DFX. In 2021, Piga et al. conducted a systematic literature review to evaluate the efficacy and safety profile of combination chelation therapy with DFP + DFX in patients with transfusion-dependent beta-thalassaemia major (49). The results included a total of seven clinical publications. Of the seven studies, six reported a consistent reduction in at least one of the three studied endpoints (serum ferritin, liver, and cardiac iron) (49). These results suggested that DFP-DFX combination iron chelation therapy could be a highly effective therapeutic option for improving iron overload (49).

### 8.4. Long-Term Effectiveness of Deferiprone Therapy

DFP is associated with a reduction in iron-associated heart disease and/or increased survival compared to treatment with DFO (5).

There is ample evidence available of the long-term effectiveness of DFP, as summarized in the Thalassaemia International Federation treatment guidelines (21) and Berdoukas et al. and demonstrated in studies such as those of Borgna-Pignatti et al. (50) (described in detail in appendix I), Ceci et al. (39), Modell et al. (51), Maggio et al. (39), and Pepe et al. (52) which reported a survival advantage of DFP or DFP + DFO over DFO alone.

## 9. Review of Harms and Toxicity: Summary of Evidence of Comparative Safety

A detailed description of the safety data from key DFP studies can be found in Appendix I.

### 9.1. Patient Exposure

Based on the available information for Ferriprox®, the originator product, it is estimated that DFP has accumulated:

- More than **2,300 subject-years** of exposure from clinical studies
- More than **119,000 patient-years** of exposure in the period from July 2006 through August 2022, of which:
    - Over 66,000 patient-years occurred in the European Union
    - Over 52,000 patient-years occurred outside the European Union

## 9.2. Description of Adverse Events

### 9.2.1. Sickle Cell Disease

According to the prescribing information for DFP (Ferriprox®) in the US, the most common adverse reactions (≥6%) reported during clinical trials in patients with SCD or other anaemias were pyrexia, abdominal pain, bone pain, headache, vomiting, pain in extremity, sickle cell anaemia with crisis, back pain, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, arthralgia, oropharyngeal pain, nasopharyngitis, neutrophil count decreased, cough and nausea (4).

Table 30, drawn from the US product information, lists the adverse reactions (irrespective of a causal assessment; adverse events) of interest that occurred in patients treated with Ferriprox® (deferiprone) in clinical trials in subjects with SCD or other anaemias (4)

Table 30. Adverse reactions occurring in ≥5% of DFP (Ferriprox®)-treated patients with SCD or other anaemias (adapted from the US product information for Ferriprox®)

| Body system & adverse reaction | DFP (Ferriprox®) (N = 152) % patients | DFO (N = 76) % patients |
|---|---|---|
| Blood and lymphatic system disorders | | |
| Sickle cell anaemia with crisis | 17% | 13% |
| Gastrointestinal disorders | | |
| Abdominal pain* | 26% | 13% |
| Vomiting | 19% | 11% |
| Nausea | 7% | 9% |
| Diarrhoea | 5% | 8% |
| General disorders and administration site conditions | | |
| Pyrexia | 28% | 33% |
| Pain | 5% | 4% |
| Infections and infestations | | |
| Nasopharyngitis | 9% | 12% |
| Upper respiratory tract infection | 5% | 3% |
| Investigations | | |
| Alanine aminotransferase increased | 12% | 0% |
| Aspartate aminotransferase increased | 11% | 0% |
| Neutrophil count decreased | 8% | 4% |
| Musculoskeletal and connective tissue disorders | | |
| Bone pain | 25% | 34% |
| Pain in extremity | 18% | 15% |
| Back pain | 13% | 18% |
| Arthralgia | 10% | 8% |
| Nervous system disorders | | |
| Headache | 20% | 13% |
| Respiratory, thoracic, and mediastinal disorders | | |
| Oropharyngeal pain | 10% | 15% |
| Cough | 8% | 15% |

* Grouped term | DFP: deferiprone; SCD: sickle cell disease

Clinically relevant adverse reactions in <5% of patients include neutropenia and agranulocytosis (4).

### 9.2.2. Beta-thalassaemia

The following adverse reaction information represents the pooled data collected from 11 single-arm or active-controlled clinical trials with Ferriprox® (DFP) tablets (three times a day) or Ferriprox® (DFP) oral solution and reported in the US and Canadian product information (4,53). Among 642 patients receiving Ferriprox® (DFP), 492 (76.6%) were exposed for 6 months or longer and 365 (56.9%) were exposed for greater than one year (4,53).

The most common adverse reactions (≥6%) reported during clinical trials were nausea, vomiting, abdominal pain, arthralgia, alanine aminotransferase increased and neutropenia (4,53).

Table 31, drawn from the Canadian prescribing information, lists the adverse drug reactions that occurred in at least 1% of patients treated with Ferriprox® (DFP) in clinical trials in patients with thalassaemia syndromes (4,53).

Table 31. Adverse reactions occurring in ≥ 1% of DFP (Ferriprox®)-treated patients with thalassaemia syndromes (adapted from the Canadian product information for Ferriprox®)

| Body system & adverse reaction | (N = 642)<br>% patients |
|---|---|
| Blood and lymphatic system disorders | |
| Neutropenia | 6.2% |
| Agranulocytosis | 1.7% |
| Gastrointestinal disorders | |
| Nausea | 12.6% |
| Abdominal pain/discomfort | 10.4% |
| Vomiting | 9.8% |
| Diarrhoea | 3.0% |
| Dyspepsia | 2.0% |
| Investigations | |
| Alanine aminotransferase increased | 7.5% |
| Neutrophil count decreased | 7.3% |
| Weight increased | 1.9% |
| Aspartate aminotransferase increased | 1.2% |
| Metabolism and nutrition disorders | |
| Increased appetite | 4.0% |
| Decreased appetite | 1.1% |
| Musculoskeletal and connective tissue disorders | |
| Arthralgia | 9.8% |
| Back pain | 2.0% |
| Pain in extremity | 1.9% |
| Arthropathy | 1.4% |
| Nervous system disorders | |
| Headache | 2.5% |

| | |
|---|---|
| Urinary disorders | |
| Chromaturia | 14.6% |
| DFP: deferiprone | |

The most frequent adverse reactions reported by patients participating in clinical trials were gastrointestinal symptoms such as nausea, vomiting, and abdominal pain, which led to the discontinuation of Ferriprox® (DFP) therapy in 1.6% of patients.

### 9.2.3. Agranulocytosis

Agranulocytosis, a severe form of neutropenia, can occur in patients treated with DFP. A study based on data from clinical trials and post-marketing experience for the period 1999-2014 found 18 episodes of agranulocytosis in 17 (1.5%) of 1,127 clinical trial participants, for a rate of 1.1 per 100 patient-years of drug exposure (total 1653.15 years), and 143 episodes in post-marketing surveillance programs, for a rate of 0.24 per 100 patient-years (during an estimated 58,790 patient-years of post-marketing exposure). Most episodes of agranulocytosis occurred during the first year of treatment: 61% in the first six months and 78% within the first year (54).

## 9.3. Comparative Safety: Sickle Cell Disease

All studies included in the previously described systematic literature review in SCD (section 14.2. in Appendix II) reported safety outcomes. Of patients treated with DFP, from the FIRST (LA38-0411) trial (36), in the ITT population that included SCD and other anaemias, patients treated with DFP were more likely to experience an increase in ALT related to treatment (9.2% vs. 0%) compared to those treated with DFO. In an Italian RCT of DFP versus DFO, 10% of patients on DFP experienced liver damage or an increase in ALT more than twice the normal value, while no patients treated with DFO did (55).

Regarding renal parameters, in the extension of the FIRST (LA38-0411) trial, a decrease of 4.3 µmol/L was observed among patients treated with DFP. In NCT00067080, patients treated with DFX or DFO experienced an increase in serum creatinine of 6.3 µmol/L and 3.06 µmol/L, respectively (56). Among all studies, treatment with DFX increased serum creatinine in 0% to 12.5% of patients and in DFO, 0% to 3.2% of patients. An increase in serum creatinine was often defined as >33% increase relative to baseline on two consecutive measures.

Neutropenia and agranulocytosis were more commonly reported in studies evaluating DFP, with the percentage of patients affected ranging from 5.9% to 9.0% for neutropenia and 0% to 1.5% for agranulocytosis. Neutropenia was less common in patients treated with DFX (0-0.5%) or DFO (2.6%), as was agranulocytosis for those treated with DFO (0% for DFO and no data for DFX) (Table 32).

Table 32. Clinical safety outcomes from studies in the SLR

| Outcome | DFP (n=3) | DFX (n=6) | DFO (n=4) |
|---|---|---|---|
| Any AE, % | 77.6% - 88.2% | 33% - 81.5% | 88.2% - 92.9% |
| Any SAE, % | 26.1% - 27.8% | 0% - 46% | 18.4% - 42.9% |

| | | | |
|---|---|---|---|
| Treatment-related AE, % | 30.6% - 51.5% | 26.7% - 33.5% | 28.6% - 39.5% |
| Treatment-related SAE, % | 5.9% - 9.7% | 4.9% - 46.2% | 3.9% - 39.5% |
| Increased ALT, % | 4.3% - 10% | 1.3% - 6.5% | 0% |
| Increased sCR, % | 0% | 0% - 12.5% | 0% - 3.2% |
| Renal failure, % | - | 0% - 0.5% | - |
| Neutropenia, % | 5.9% - 9.0% | 0% - 0.5% | 2.60% |
| Agranulocytosis, % | 0% - 1.5% | - | 0% |
| SCD crisis, % | 6.7% - 18.7% | 1.1% - 33% | 3.3%- 31.7% |
| Death, % | 1.3% - 6.7% | 0% - 3.2% | 0.5% - 13.3% |
| AE: adverse event; ALT: alanine transaminase; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SAE: serious adverse event; sCR: serum creatinine; SCD: sickle cell disease | | | |

## 9.4. Comparative Safety: Beta-thalassaemia

The SLR of beta-thalassaemia clinical data (section 15.2 of Appendix III) identified 11 RCTs, all but three of which (39,51,57) included data on adverse events. Of the 11 trials, eight reported safety results for one or more treatment arms with DFP, DFO or DFX monotherapy. A full list of the relevant RCTs can be found in Appendix III.

To enable a comparison of adverse event data between different iron chelators, the RCTs identified in the SLR were also assessed for their suitability for statistical analysis. However, it was concluded that a robust statistical analysis could not be performed due to a lack of consistent data reporting; for example, studies did not consistently report on the same AEs and some studies reported AEs in only one study arm. The following tables (Tables 33 and 34) provide a summary of the safety data available from each of the trials included in the SLR.

Table 33. Summary of adverse events from studies of iron chelating monotherapy included in the SLR

| Short reference | DFP | DFO | DFX |
|---|---|---|---|
| Pennell, 2006 (38) | GI symptoms[1]: 66% (19 pts)<br>Joint problems[2]: 28% (8 pts)<br>Increased appetite: 31% (9 pts) (p<0.001)<br>Neutropenia: 1 episode<br>Agranulocytosis: 0 episodes | Infusion site reaction: 38% (12 pts)<br>Joint problems[2]: 19% (6 pts)<br>Agranulocytosis: 0 episodes | - |
| | No significant differences in: the change or trend over time in ALT level, change in zinc or creatinine level, or ANC or other laboratory data *(Further information on AEs in Appendix I)* | | - |
| Maggio, 2002 (39) | AEs: 24 of 71pts[3]<br>Joint pain: 2 pts<br>Hypertransaminasaemia: 16 pts[4]<br>Increase in fibrosis score: 7 of 21 pts | AEs: 11 of 73 pts[3]<br>Infection: 2 pts<br>Ototoxicity: 2 pts<br>Increase in fibrosis score: 4 of 15 pts | - |
| Modell, 1982 (51) | - | Did not report on AEs | - |
| Cohen, 2008 (57) | - | Did not report on AEs | - |
| Cappellini, 2006 (43) | - | ↑ serum creatinine: 14%<br>Deafness, neurosensory deafness, or hypoacusis: 7 pts, of which 5 (1.7%) related to study drug<br>Cataracts, lenticular opacities: 5 pts, of which 4 (1.4%) related to study drug<br>Agranulocytosis: No drug-related agranulocytosis<br>Cardiac AEs: 6.9%<br>Cardiac SAEs: 1.0% | Most common AEs with relationship to study drug:<br>• Transient GI events[5]: 15.2%<br>• Skin rash: 10.8%<br><br>↑ serum creatinine: 38%<br>Elevated ALT[6]: 2 pts<br>Deafness, neurosensory deafness, or hypoacusis: 8 pts, of which 1 (0.3%) related to study drug<br>Cataracts, lenticular opacities: 2 pts, of which 1 (0.3%) related to study drug<br>Agranulocytosis: No drug-related agranulocytosis<br>Cardiac AEs: 5.1%<br>Cardiac SAEs: 0.7% |
| | | Dose adjustments & interruptions combined were similar in the two groups (36.8% DFX vs 33.1% DFO), as were discontinuations during the study (5.7% DFX vs 4.1% DFO)<br>Zinc and copper levels at the end of the study were comparable between the two groups | |

<table>
<tr>
<td>Piga, 2006 (58)</td>
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<td>
DFO<br>40 mg/kg<br>(n=23)<br>AE: 21 (91.3%)<br>Back pain: 8 (34.8)<br>Cough: 4 (17.4%)<br>Pyrexia: 6 (26.1%)<br>Ab. pain: 8 (34.8%)<br>Rhinitis: 6 (26.1%)<br>Nausea: 2 (8.7%)<br>Vomiting: 2 (8.7%)<br>Asthenia: 4 (17.4%)<br>Headache: 4 (17.4%)<br>Pharyngitis: 8 (34.8%)<br>Diarrhoea: 6 (26.1%)<br>Phar. pain: 6 (26.1%)<br>Influenza: 5 (21.7%)<br>All. conj.: -<br>Dyspepsia: 2 (8.7%)<br>Flu-like ill.: 4 (17.4%)<br>Arthralgia: 3 (13.0%)<br>Vertigo: 3 (13.0%)<br>UTI: 1 (4.3%)<br>Bronchitis: 1 (4.3%)
</td>
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<table>
<tr><td></td><td>DFX<br>10 mg/kg/d<br>(n=24)</td><td>DFX<br>20 mg/kg/d<br>(n=24)</td></tr>
<tr><td>AE:</td><td>24 (100%)</td><td>23 (95.8)</td></tr>
<tr><td>Back pain:</td><td>8 (33.3%)</td><td>10 (41.7)</td></tr>
<tr><td>Cough:</td><td>5 (20.8%)</td><td>10 (41.7)</td></tr>
<tr><td>Pyrexia:</td><td>7 (29.2%)</td><td>10 (41.7)</td></tr>
<tr><td>Ab. pain:</td><td>14 (58.3%)</td><td>9 (37.5)</td></tr>
<tr><td>Rhinitis:</td><td>7 (29.2%)</td><td>9 (37.5)</td></tr>
<tr><td>Nausea</td><td>2 (8.3%)</td><td>8 (33.3)</td></tr>
<tr><td>Vomiting:</td><td>-</td><td>8 (33.3)</td></tr>
<tr><td>Asthenia:</td><td>3 (12.5%)</td><td>7 (29.2)</td></tr>
<tr><td>Headache:</td><td>9 (37.5%)</td><td>7 (29.2)</td></tr>
<tr><td>Pharyngitis:</td><td>10 (41.7%)</td><td>7 (29.2)</td></tr>
<tr><td>Diarrhoea:</td><td>7 (29.2%)</td><td>6 (25.0)</td></tr>
<tr><td>Phar. pain:</td><td>5 (20.8%)</td><td>6 (25.0)</td></tr>
<tr><td>Influenza:</td><td>1 (4.2%)</td><td>5 (20.8)</td></tr>
<tr><td>All. conj.:</td><td>-</td><td>4 (16.7)</td></tr>
<tr><td>Dyspepsia:</td><td>1 (4.2%)</td><td>4 (16.7)</td></tr>
<tr><td>Flu-like ill.:</td><td>7 (29.2%)</td><td>3 (12.5)</td></tr>
<tr><td>Arthralgia:</td><td>4 (16.7%)</td><td>2 (8.3)</td></tr>
<tr><td>Vertigo:</td><td>5 (20.8%)</td><td>2 (8.3)</td></tr>
<tr><td>UTI:</td><td>4 (16.7%)</td><td>1 (4.2)</td></tr>
<tr><td>Bronchitis:</td><td>5 (20.8%)</td><td>-</td></tr>
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Above are AEs reported in four or more patients in any treatment group, irrespective of presumed drug relationship
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<td>AEs with a suspected relationship to the study drug:<br>• No study drug-related nausea<br>• No serious AEs assessed as related to study drug[7]</td>
<td>AEs with a suspected relationship to the study drug:<br>• Nausea in 1 in 6 patients and vomiting in 3 patients in the 20 mg group<br>• No study drug-related arthralgia<br>• No serious AEs assessed as related to study drug[7]</td>
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<td>Serum creatinine above upper limit of normal: 2 pts<br>Neutropenia: No episodes<br>Agranulocytosis: No episodes</td>
<td>Serum creatinine above upper limit of normal: 3 pts in the 10 mg group, 1 in the 20 mg group<br>Neutropenia: No episodes<br>Agranulocytosis: No episodes</td>
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| | | | |
|---|---|---|---|
| | | Thrombocytopenia: No episodes | Thrombocytopenia: No episodes |
| | | Elevations of urinary β-2 microglobulin were detected in all groups but were more frequent in the DFX 20 mg group<br>No patient developed consistent or progressive elevations in transaminase levels<br>Serum copper and zinc levels fluctuated considerably during the study, but no patient developed progressive decreases in these trace elements<br>No retinal findings, lens abnormalities or hearing losses were detected during regular ophthalmological and auditory testing<br>Premature withdrawals: 2 pts in the DFO group (1 suspected to be study-drug related: arthralgia, headache, fever), 2 pts in 20 mg DFX group (1 unsatisfactory therapeutic effect) | |
| Nisbet-Brown, 2003 (59) | - | - | Serious AEs: 9 pts discontinued due to SAEs<br>AEs with a suspected relation to study drug:<br>• 3 serious AEs, all of which were rashes<br>• 3 mild nausea, 1 moderate nausea, 4 mild diarrhoea, 1 abdominal pain [8]<br><br>Transient transaminitis: 5 pts (relation to drug ingestion could not be ruled out)<br><br>No relevant changes between study drug and placebo groups in haematological variables, mean concentrations of serum calcium, phosphorus, magnesium, uric acid, creatinine, urea nitrogen, albumin, creatine kinase, triglycerides, or total cholesterol<br>No abnormalities of renal sediment were noted<br>No relevant changes from baseline in electrocardiographic, audiometric, or ophthalmologic examinations were noted except 1 retinal infarct related to diabetes<br>No significant changes in copper or zinc concentrations |

[1]GI symptoms: nausea, vomiting, or abdominal pain; [2]Joint problems: pain and/or swelling (p=0.30); [3]DFP: temporary dose reduction in 3 (nausea) and temporary treatment withdrawal in 4 (transient hypertranaminsaemia 3, infection 1) and DFO: temporary dose reduction in 6 (because of pain and erythema at the injection site and in one because of transient hypertransaminasaemia) and temporary treatment withdrawal in 4 (infection 2, ototoxicity 2); [4]Five patients were definitively withdrawn from treatment because of recurrence of hypertransaminasaemia (> 2 times the pretreatment values) (n = 3, anti-HCV positive 1) or leukocytopenia (n =

2). Mild hypertransaminasaemia, spontaneously recovering, developed in 10 other patients and mild joint pain in two. 14 of the 16 patients who developed hypertransaminasaemia were anti-HCV positive; [5]Abdominal pain, nausea and vomiting,
diarrhea, and constipation; [6]Greater than twice the ULN; [7]Serious AEs were reported in 12 of 71 pts, with a similar distribution among the treatment groups, but were deemed not to be related to study drugs; [8]18 pts allocated to the study drug, 1 of which did not receive drug
Ab. pain: abdominal pain; AE: adverse event; All. conj,: allergic conjunctivitis; ALT: alanine transaminase; ANC: absolute neutrophil count; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; Flu-like ill.: influenza-like illness; GI: gastrointestinal; HCV: hepatitis C virus; Phar. pain: pharyngolaryngeal pain; pt: patient; ULN: upper limit of normal

Table 34. Summary of adverse events from studies of iron chelating combination or sequential therapy included in the SLR

| Short reference | DFP | DFO | DFP-DFO combination therapy | DFP-DFO sequential therapy |
|---|---|---|---|---|
| Tanner, 2007 (40) | - | GI symptoms[1]: 24%<br>Recurrent GI[2]: 3% | GI symptoms[1]: 38%<br>Recurrent GI[2]: 19% | - |

| | | | | |
|---|---|---|---|---|
| | | Infusion site reaction: 6%<br>Joint problems[3]: 18% | Infusion site reaction: 3%<br>Joint problems[3]: 9%<br>Neutropenia: 2 episodes<br>Agranulocytosis: 1 episode | |
| | | No significant difference between groups in change in creatinine at 12 months<br>Patient withdrawals: 3 in the DFO group (AFib 1, personal reasons 2) and 4 in the combined (agranulocytosis 1, myocardial T2* < 8 ms 1, GI symptoms 1, personal reasons 1) | | |
| Maggio, 2009 (41) | AEs: 59<br>• Agranulocytosis[4]: 3 pts (3.4%)<br>• Neutropenia: 11 (12.5%)<br>• Arthralgia: 6 (6.8%)<br>• GI problems: 16 (18.2%)<br>• ↑ ALT[5]: 23 (26.1%)<br><br>Zinc: No significant difference in change between groups<br><br>Withdrawals: 21 (35%)[6] | - | - | AEs: 49<br>• Agranulocytosis[4]: 0 pts<br>• Neutropenia: 15 (23.1%)<br>• Arthralgia: 5 (7.7%)<br>• GI problems: 7 (10.8%)<br>• ↑ ALT[5]: AEs (33.8%)<br><br>Zinc: No significant difference in change between groups<br><br>Withdrawals: 12 (24%)[6] |
| Maggio, 2009 (45) | Did not report on AEs | Did not report on AEs | Did not report on AEs | Did not report on AEs |
| Galanello, 2006 (42) | - | AEs[7]: 2 pts (7%)<br>Abscess: 1 pt (3%)<br>Allergic reaction: 1 pt (3%)<br>Neutropenia: 2 pts<br>Agranulocytosis: 0 pts<br>Arthropathy: 0 pts | - | AEs[7]: 7 pts (24%)<br>Vomiting: 5 pts (17%)<br>Abdominal pain: 3 pts (10%)<br>Diarrhoea: 1 pt (3%)<br>Agranulocytosis: 0 pts<br>Arthropathy: 0 pts |
| | | No significant change in ALT from baseline in either group or significant difference in trend between the groups<br>Difference in overall frequency of ALT values above 3x upper limit observed for HCV+ patients: 1 of 14 pts in DFO arm and 5/12 in sequential therapy (p=0.06)<br>No significant change in zinc levels from baseline to end of study between the two groups | | |

[1]Nausea, vomiting or abdominal pain, p=0.2; [2] Recurrent: > 2 episodes, p = 0.05; [3]Including pain and/or swelling, p=0.3; [4]Agranulocytosis p = 0.085; [5]Alanine transaminase level increased greater than two-fold; [6]There was no statistically significant difference in temporary or definitive discontinuation of treatment between the two groups, p=0.07; [7]Experienced at least 1 AE, p=0.08

AE: adverse event; AFib: atrial fibrillation; ALT: alanine transaminase; DFO: deferoxamine; DFP: deferiprone; GI: gastrointestinal; HCV: hepatitis C virus; pt: patient

## 9.5. Comparative Safety of Combination Therapy

As described in *section 8.3.*, the use of combination therapies to increase the efficacy of ICT in patients who do not adequately respond to monotherapy, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction, is approved by the EMA and is recommended in many clinical guidelines.

The use of DFP in combination with DFO is widespread, and clinical experience suggests that there are no significant toxicity issues for the combination (48).

Regarding DFP + DFX combination therapy, in the systematic literature review conducted by Piga et al. (49), the adverse events reported with DFP + DFX were consistent with what was previously been reported for DFP or DFX monotherapy; no new adverse events were observed. The most common adverse events across the seven studies included gastrointestinal symptoms, elevation in alanine aminotransferase and/or aspartate aminotransferase, arthralgia, or joint symptoms, an increase in creatinine levels, proteinuria, and red-coloured urine (49). The number of patients reported with neutropenia and thrombocytopenia were low (neutropenia, n=7 patients; thrombocytopenia, n=8 patients); agranulocytosis was not observed. Two studies reported serious adverse events, of which one (acute cholecystitis) was related to treatment (49).

## 9.6. Inappropriate use

The US and European prescribing information for Ferriprox® (DFP) note that no cases of acute overdose have been reported. There is no specific antidote in case of overdose (4,5,22).

Prolonged overdosing, according to the US, European, and Canadian prescribing information, has been reported to be associated with neurological effects such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, abnormal hand movements, and axial hypotonia. These disorders have been observed in children who had been voluntarily prescribed more than 2.5 times the maximum recommended dose. The neurological disorders progressively regressed after DFP discontinuation (4,5,22,53).

## 9.7. Variation in safety

### 9.7.1. Pregnancy and breastfeeding

DFP is contraindicated in pregnancy and in nursing women, according to the European, US, and Canadian prescribing information. No studies in pregnant women have been conducted, and relevant data from clinical use are limited. In animal studies, administration of DFP during the period of organogenesis resulted in embryo-foetal death and malformations at doses lower than equivalent human clinical doses. There is no information regarding the presence of DFP in human milk, the effects on the breastfed child, or the effects on milk production (4,5,22,53).

### 9.7.2. Paediatric use

According to the US prescribing information for Ferriprox® (DFP), the originator, the safety of deferiprone for the treatment of transfusional iron overload in patients with SCD or thalassaemia syndromes has been established in paediatric patients aged three years and older. It notes that the safety of Ferriprox® (deferiprone) has not been established in paediatric patients with chronic iron overload due to blood transfusions who are less than three years old (4).

The information in the Canadian prescribing information for Ferriprox® (DFP) states that it has been studied in 113 paediatric patients with SCD and other anaemias and iron overload who participated in clinical trials, with ages ranging from 3 to 16 years old (66 patients were 3 to <12 years, 47 patients were 12 to 16 years). Of these patients, 77% had SCD. The reported rates of the following adverse events were higher in children than in adults: abdominal pain (41 (36.3%) vs 16 (19.3%), decreased neutrophil count (20 (17.7%) vs 4 (4.8%)), bone pain (41 (36.3%) vs 17 (20.5%)), and oropharyngeal pain (23 (20.4%) vs 8 (9.6%)) (53).

The US prescribing information reports that in a US registry for the period December 2011 to December 2019, which contained 125 SCD patients aged 4 to < 17 years old who had received Ferriprox® (DFP), the adverse reactions, including agranulocytosis, seen in the eight-year period of the registry were similar to those seen in the most recent clinical studies (4). A study of long-term safety in 130 paediatric SCD patients based on data in the same registry but for the period December 2011 to August 2020 similarly found safety results consistent with observations in adult populations and identified no new safety concerns for paediatric patients (36).

In children with thalassaemia syndromes and iron overload, according to the Canadian prescribing information for Ferriprox®, DFP has been studied in 222 paediatric patients who participated in clinical trials, including 61 children < 6 years of age. Higher rates of the following adverse events were reported in those younger than 6 years old than in older patients: decreased neutrophil count (17 (27.9%) vs 40 (6.9%)), neutropenia (7 (11.5%) vs 36 (6.2%)), increased alanine aminotransferase (10 (16.4%) vs 46 (7.9%)), and agranulocytosis (2 (3.3%) vs 9 (1.5%)) (53).

A study conducted in 100 children aged 1-10 years old (mean 5.1 years (±2.4) with transfusion-dependent anaemia (91 thalassaemia major, 8 haemoglobin E-β thalassaemia, 1 SCD) and treated with DFP oral solution found that deferiprone was well tolerated and not associated with new safety concerns. The safety profile of the oral solution was consistent with that demonstrated in earlier studies of DFP tablets in older children and adults (60).

In DEEP-2, a large, multi-centre, randomized trial comparing DFP with DFX in paediatric patients (aged 1 month to 18 years) with transfusion-dependent hemoglobinopathies (90% beta-thalassaemia major, 7% SCD), DFP was found to have an acceptable safety profile. Serious and drug-related adverse events were not significantly different between the DFP and the DFX groups and were similar to those seen in the adult population. The study found no additional safety concerns in very young children (44).

Further information on safety in children from individual clinical trials can be found in the appendix (appendix I, key clinical trials), for the trials for which such information is available.

### 9.7.3. Elderly patients

According to the US prescribing information, clinical studies of DFP did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients (4).

### 9.7.4. Renal impairment

Dose adjustment is not required in patients with mild, moderate, or severe renal impairment, according to the European, US, and Canadian prescribing information for Ferriprox® (DFP). According to the prescribing information, the safety and pharmacokinetics of DFP in patients with end stage renal disease are unknown. LA39-0412 (NCT01770652), an open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired renal function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox® film-coated tablets. Subjects were categorized into 4 groups based on estimated glomerular filtration rate (eGFR): healthy volunteers (eGFR ≥ 90 mL/min/1.73m2), mild renal impairment (eGFR 60-89 mL/min/1.73m2), moderate renal impairment (eGFR 30-59 mL/min/1.73m2), and severe renal impairment (eGFR 15–29 mL/min/1.73m2). Regardless of the degree of renal impairment, the majority of the dose of DFP was excreted in the urine over the first 24 hours as deferiprone 3-O-glucuronide. No significant effect of renal impairment was seen on systemic exposure to DFP. Systemic exposure to the inactive 3-O-glucuronide increased with decreasing eGFR (22,53,61,62).

### 9.7.5. Hepatic impairment

According to the European, US, and Canadian prescribing information for Ferriprox® (DFP), dose adjustment is not required in patients with mildly or moderately impaired hepatic function. The safety and pharmacokinetics of DFP in patients with severe hepatic impairment are unknown. LA40-0412 (NCT01767103), an open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired hepatic function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox® (DFP) film-coated tablets. Subjects were categorized into three groups based on the Child-Pugh classification score: healthy volunteers, mild hepatic impairment (Class A: 5– 6 points), and moderate hepatic impairment (Class B: 7– 9 points). Systemic exposure to DFP and to its metabolite DFP 3-*O*-glucuronide was assessed by the PK parameters $C_{max}$ and AUC. DFP AUCs did not differ between treatment groups, but $C_{max}$ was decreased by 20% in mildly or moderately hepatically impaired subjects compared with healthy volunteers. DFP-3-*O*-glucuronide AUC was decreased by 10% and $C_{max}$ by 20% in mildly and moderately impaired subjects compared with healthy volunteers. A serious adverse event of acute liver and renal injury was seen in one subject with moderate hepatic impairment (22,53)(63).

## 9.8. Warnings and precautions

### 9.8.1. United States

The US prescribing information for Ferriprox® (DFP) includes the following boxed warnings regarding agranulocytosis and neutropenia (4):

- Ferriprox® (DFP) can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis.
- Measure the ANC before starting Ferriprox® (DFP) and monitor regularly while on therapy.
- Interrupt Ferriprox® (DFP) therapy if neutropenia develops.
- Interrupt Ferriprox® (DFP) if infection develops and monitor the ANC more frequently.
- Advise patients taking Ferriprox® (DFP) to report immediately any symptoms indicative of infection.

**Additional warnings and precautions:**

- Liver Enzyme Elevations: Monitor monthly and discontinue for persistent elevations.
- Zinc Deficiency: Monitor during therapy and supplement for deficiency.
- Embryo-Foetal Toxicity: Can cause foetal harm (4).

**Monitoring for safety:**

Due to the risk of agranulocytosis, monitor ANC before and during Ferriprox® (DFP) therapy. Test ANC prior to start of Ferriprox® (DFP) therapy and monitor on the following schedule during treatment:

- First six months of therapy: Monitor ANC weekly
- Next six months of therapy: Monitor ANC once every two weeks
- After one year of therapy: Monitor ANC every two to four weeks (or at the patient's blood transfusion interval in patients that have not experienced an interruption due to any decrease in ANC

Due to the risk of hepatic transaminase elevations, ALT should be monitored before and monthly during Ferriprox® (deferiprone) therapy.

Due to the risk of zinc deficiency, zinc levels should be monitored before and regularly during Ferriprox® (deferiprone) therapy (4).

Please refer to the product label for full product details.

### 9.8.2. Europe

In Europe, the product information for Ferriprox® (DFP) also includes a **boxed warning in reference to neutropenia/agranulocytosis**, as follows (22)**:**

- DFP has been shown to cause **neutropenia,** including agranulocytosis. The patient's ANC should be monitored every week during the first year of therapy. For patients whose Ferriprox® (deferiprone) has not been interrupted during the first year of therapy due to any decrease in the neutrophil count, the frequency of ANC monitoring may be extended to the patient's blood transfusion interval (every 2-4 weeks) after one year of DFP therapy.
- The **change** from weekly **ANC monitoring** to monitoring at the time of transfusion visits after 12 months of Ferriprox® (DFP) therapy, should be considered on an individual patient basis, according to the physician's assessment of the patient's understanding of the risk minimization measures required during therapy.
- In clinical studies, **weekly monitoring of the neutrophil count** has been effective in identifying cases of neutropenia and agranulocytosis. Agranulocytosis and neutropenia usually resolve upon discontinuation of Ferriprox® (DFP), but fatal cases of agranulocytosis have been reported. If the patient develops an infection while on DFP, therapy should be immediately interrupted, and an ANC obtained without delay. The neutrophil count should be then monitored more frequently.
- Patients should be aware to **contact their physician** if they experience **any symptoms** indicative of **infection** (such as fever, sore throat, and flu-like symptoms). Immediately interrupt DFP if the patient experiences infection.

The European prescribing information also includes the following **warnings and precautions** (22):

- **Carcinogenicity/mutagenicity:** In view of the genotoxicity results, a carcinogenic potential of DFP cannot be excluded.
- **Plasma zinc concentration:** Monitoring of plasma Zn2+ concentration, and supplementation in case of a deficiency, is recommended.
- **HIV+ or other immunocompromised patients:** No data are available on the use of DFP in HIV positive or in other immunocompromised patients. Given that DFP can be associated with neutropenia and agranulocytosis, therapy in immunocompromised patients should not be initiated unless potential benefits outweigh potential risks.
- **Renal or hepatic impairment and liver fibrosis:** There are no data available on the use of DFP in patients with end stage renal disease or severe hepatic impairment. Caution must be exercised in patients with end stage renal disease or severe hepatic dysfunction. Renal and hepatic function should be monitored in these patient populations during DFP therapy. If there is a persistent increase in serum ALT, interruption of DFP therapy should be considered. In thalassaemia patients there is an association between liver fibrosis and iron overload and/or hepatitis C. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients careful monitoring of liver histology is recommended.
- **Discoloration of urine:** Patients should be informed that their urine may show a reddish/brown discoloration due to the excretion of the iron-DFP complex.

- **Neurological disorders:** Neurological disorders have been observed in children treated with more than 2.5 times the maximum recommended dose for several years but have also been observed with standard doses of DFP. Prescribers are reminded that the use of doses above 100 mg/kg/day are not recommended. DFP use should be discontinued if neurological disorders are observed.

Please refer to the product label for full product details.

# 10. Summary of Available Data on Comparative Cost and Cost-Effectiveness

## 10.1. Comparative Cost and Cost-effectiveness of Iron Chelation Therapies for the Treatment of Iron Overload in Patients with Beta-Thalassaemia

### 10.1.1. Objective and Rationale

An economic evaluation of iron chelation therapies for the treatment of iron overload in patients with beta-thalassaemia bas been published by Li et al., who conducted a systematic literature review in 2019 with the objective of determining the cost-effectiveness of DFP and its comparators (DFO, DFX, and the combination of DFO + DFP) (64). To supplement the findings of Li et al., a literature review was performed for the purposes of this submission to see if any relevant pharmacoeconomic studies on chelators in beta-thalassaemia patients had been published subsequent to the SLR performed by Li et al. (64).

### 10.1.2. Results

For the comparative evaluation of the cost of chelators in patients with beta-thalassaemia, we included the SLR performed by Li et al. in 2019 (64), which included a total of 8 papers in the final dataset, and a cost-utility analysis in the Chinese context, published by the same author in 2020, which was identified during the supplementary review (65).

The eight papers in the SLR conducted by Li et al. included a total of 19 studies. Of the nineteen studies, DFP was found to be the most cost-effective in: three studies of DFX compared with DFP, three studies of DFP compared with DFO, and one study of DFO + DFP compared with DFP (64).

Moreover, the results of a recent cost-utility analysis of the four chelation regimens (DFP, DFX, DFO, and DFO + DFP) for beta-thalassaemia from the perspective of the Chinese healthcare system showed that DFP was the most cost-effective chelation regimen, followed by DFO, DFX, and DFO + DFP. As a result of this, DFP was demonstrated to have the potential to result in cost-savings and QALY gains for the Chinese healthcare system (65).

### 10.1.3. Discussion

The comparative assessment of the cost of iron chelators for the treatment of iron overload in beta-thalassaemia patients included a systematic review conducted by Li et al. in 2019 (64) and a cost-utility analysis from the Chinese perspective.

The economic SLR included a total of 19 studies and the main conclusion of this SLR was that DFP is the best choice in terms of cost-effectiveness followed by DFO and DFX, when an iron chelator is to be used in monotherapy for beta-thalassaemia major patients. Another major conclusion of this study was that there are substantial differences in costs between countries (regions), as the specific region's legislation had a substantial influence on the economy of drugs. Thus, healthcare experts and clinicians should conduct localized economic research, considering the impact of local economies, price, and other factors to facilitate the choice of the best approach in each specific location (64).

In the study from the Chinese healthcare perspective, the results of the CUA concluded that using DFP as the primary treatment regimen for beta-thalassaemia patients with iron overload has the potential to result in cost-saving and QALY gains for the Chinese healthcare system (65).

The results of the systematic review and the cost-utility study were consistent with each other, showing that DFP is the most cost-effective treatment regimen for beta-thalassaemia iron overload treatment (64,65).

# 11. Regulatory Status, Market Availability and Pharmacopoieal Standards

## 11.1. Regulatory Status and Market Availability of Deferiprone

The regulatory status and market availability of the DFP originator (Ferriprox®), is shown in Table 35.

Table 35. DFP regulatory status and market availability

| Country | Marketing Authorization Status | Registration Year | Marketing Status |
|---|---|---|---|
| **Australia** | Approved | 2003 | Marketed |
| **Bahrain** | Approved | 2006 | Marketed |
| **Brazil** | Approved | 2002 | Marketed |
| **Brunei** | Approved | 2019 | Marketed |
| **Canada** | Approved | 2015 | Marketed |
| **China** | Approved | 2003 | Marketed |
| **Egypt** | Approved | 2006 | Marketed |
| **European Union** | Approved (centralized procedure) | 1999 | Marketed |

| | | | |
|---|---|---|---|
| **Hong Kong** | Approved | 2013 | Marketed |
| **Indonesia** | Approved | 2006 | Marketed |
| **Iraq** | Approved | 2018 | Not marketed |
| **Israel** | Approved | 2008 | Marketed |
| **Jordan** | Approved | 2003 | Marketed |
| **Kuwait** | Approved | 2002 | Marketed |
| **Macao** | Approved | 2012 | Not marketed |
| **Malaysia** | Approved | 2003 | Marketed |
| **Morocco** | Approved | 2008 | Marketed |
| **New Zeeland** | Approved | 2009 | Marketed |
| **Oman** | Approved | 2002 | Marketed |
| **Philippines** | Approved | 2005 | Marketed |
| **Qatar** | Approved | 2002 | Marketed |
| **Saudi Arabia** | Approved | 2005 | Marketed |
| **Singapore** | Approved | 2002 | Marketed |
| **Switzerland** | Approved | 2001 | Marketed |
| **Syria** | Approved | 2004 | Not marketed |
| **Thailand** | Approved | 2004 | Marketed |
| **Trinidad and Tobago** | Approved | 2005 | Not marketed |
| **Tunisia** | Approved | 2003 | Marketed |
| **Turkey (& North Cyprus)** | Approved | 2004 | Marketed |
| **United Arab Emirates** | Approved | 2003 | Marketed |
| **United Kingdom** | Approved | 2021 | Marketed |
| **United States of America** | Approved | 2011 | Marketed |

The table above and the information that follows detail the availability of Ferriprox® (DFP), the originator. Generic DFP is also available in the majority of the European markets, and in Bahrain, Egypt, Indonesia, Malaysia, Oman, Saudi Arabia, Thailand, the United Arab Emirates, Pakistan, and the US.

In all the countries presented in Table 35, DFP is approved for the treatment of transfusional iron overload in patients with thalassaemia major. In the EU it is also approved for use in combination with another chelator for thalassaemia major patients when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction. In the US, Canada, Brazil, and Turkey (and North Cyprus), DFP is also indicated for the treatment of transfusional iron overload in SCD patients.

There are four formulations of the DFP originator (Ferriprox®): 500 mg and 1,000 mg film-coated tablets (immediate release), 1,000 mg tablets (twice-a-day modified release) and 100 mg/mL oral solution. The most recently approved formulation is the 1,000mg twice-a-day that was approved in the US in May 2020. The modified release (twice-a-day oral tablet) is approved and marketed in the US and is also undergoing regulatory submissions in various countries around the world.

In terms of market availability, the DFP originator (Ferriprox®) is available in at least one of its formulations in almost all the countries in which it has a marketing authorization, though the availability of a given formulation varies by country. It should be noted that, as it was approved via the centralized procedure in the European Union, it is marketed in nearly all the European countries, with the exception of: Croatia, Estonia, Hungary, Latvia, Liechtenstein, Lithuania, Malta, Poland, and Slovakia.

## 11.2. Pharmacopeial Standards

European Pharmacopoeia, Edition 11.0:

- Deferiprone, 07/2018:2236
- Deferiprone Oral Solution, 01/2021:2987
- Deferiprone Tablets, 01/2022:2986

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# 13. Appendix I – Deferiprone Key Studies

## 13.1. FIRST (LA38-0411)

LA38-0411, a late-phase (phase IV in the US and phase IIIb in other countries), multicentre, two-arm, randomized, open-label study to assess the efficacy and safety of DFP in the treatment of iron overload in patients with SCD or other anaemias who are receiving chronic transfusion therapy. The primary efficacy endpoint was the change from baseline to month 12 in liver iron concentration (LIC), as measured by R2* MRI. Secondary efficacy endpoints were: the change from baseline to month 12 in cardiac iron (assessed by cardiac T2* MRI), serum ferritin levels, and patient-reported quality of life (36).

A total of 228 patients with a mean age of 16.9 years (range, 3-59), 46.9% of which were female, were randomized in a 2:1 ratio to receive either oral DFP (n = 152) or subcutaneous DFO (n = 76). All 228 received at least one dose of study drug and were included in the safety analysis population, 106while 217 patients (143 DFP, 74 DFO) underwent at least one post-baseline efficacy assessment and were included in the intent-to-treat (ITT) population for the evaluation of the efficacy endpoints. The treatment groups were well-balanced with respect to baseline characteristics and demographics (36).

### Efficacy

An analysis of covariance (ANCOVA) model was used to analyse changes in LIC, cardiac T2* MRI, and serum ferritin levels at 12 months, with treatment as the main factor, and overall average transfusional iron input during the study and the baseline value of the iron load measure as stratification factors (36). Non-inferiority of DFP versus DFO would be shown:

- LIC: If the upper limit of the 96.01% confidence interval (CI) of the difference between treatment groups was ≤ 2 mg/g dw
- Cardiac T2* MRI: If the 96.01% CI contained 0
- Serum ferritin levels: If the 96.01% CI contained 0

For each efficacy measure, in addition to the analyses done on the entire ITT population, separate analyses were also conducted for patients with SCD versus those with other anaemias (36).

**Liver iron concentration:** There was no significant difference in iron reduction between patients treated with DFP versus DFX (36). As shown in Table 36 below, for the overall ITT population, the mean change in LIC (mg/g dw) from baseline was -4.04 mg/g dw for DFP and -4.45 mg/g dw for DFO and the upper limit of the 96.01% CI was 1.57, thereby meeting the noninferiority criterion. In the SCD population the mean change in LIC was –2.60 for DFP and –3.35 for DFO. Noninferiority of DFP was demonstrated for both the SCD and the other anaemias subpopulations (36).

Table 36. Noninferiority analysis of change in LIC (mg/g dw) at month 12 – ITT population and subpopulations (source; Kwiatkowski et al., 2022)

| | N | DFP LS mean (SE) | N | DFO LS mean (SE) | DFP - DFO LS mean (SE) | 96.01% CI* |
|---|---|---|---|---|---|---|
| ITT overall | 133 | -4.04 (0.48) | 69 | -4.45 (0.57) | 0.40 (0.56) | -0.76, 1.57 |
| SCD | 114 | -2.60 (0.43) | 57 | -3.35 (0.56) | 0.74 (0.58) | -0.46, 1.95 |
| Other anaemias | 19 | -6.94 (1.19) | 12 | -5.14 (1.50) | -1.79 (1.81) | -5.67, 2.08 |

* Data were analysed using an ANCOVA model, with treatment as the main factor and covariates including overall average transfusional iron input during the study, baseline LIC, cardiac T2* MRI, or serum ferritin levels, as stratification factors; unless otherwise stated, data are shown as LS mean (SE)
CI: confidence interval; DFP: deferiprone; DFO: deferoxamine; dw: dry weight; LS: least squares; SCD: sickle cell disease; SE: standard error

**Secondary efficacy outcomes:** Analyses of the cardiac iron and serum ferritin also demonstrated the noninferiority of DFP in regard to these outcomes (Table 37) (36).

Table 37. Noninferiority analyses of change in cardiac T2* MRI and serum ferritin levels at month 12 – ITT population and subpopulations (source; Kwiatkowski et al., 2022)

| | N | DFP LS mean (SE) | N | DFO LS mean (SE) | DFP - DFO LS mean (SE) | 96.01% CI† |
|---|---|---|---|---|---|---|
| **Change in log-transformed cardiac T2* MRI, ms** | | | | | | |
| ITT overall | 133 | -0.023 (0.020) | 69 | -0.022 (0.024) | -0.001 (0.024) | -0.051, 0.049 |
| SCD | 114 | -0.003 (0.018) | 57 | 0.013 (0.024) | -0.017 (0.026) | -0.069, 0.036 |
| Other anaemias | 19 | 0.018 (0.050) | 12 | -0.079 (0.063) | 0.097 (0.077) | -0.068, 0.261 |
| **Change in serum ferritin, µg/L** | | | | | | |
| ITT overall | 143 | -414.73 (221.34) | 74 | -749.71 (273.62) | 334.97 (287.75) | -257.63, 927.57 |
| SCD | 122 | 48.16 (229.59) | 62 | -522.57 (298.94) | 570.72 (329.19) | -107.44, 1248.89 |
| Other anaemias | 21 | -983.94 (291.01) | 12 | -180.50 (376.32) | -803.45 (439.65) | -1740.50, 133.61 |

† Data were analysed using an ANCOVA model, with treatment as the main factor and covariates including overall average transfusional iron input during the study, baseline LIC, cardiac T2* MRI, or serum ferritin levels, as stratification factors; unless otherwise stated, data are shown as LS mean (SE)
CI: confidence interval; DFP: deferiprone; DFO: deferoxamine; dw: dry weight; LS: least squares; SCD: sickle cell disease; SE: standard error

**Paediatric population:** A subgroup analysis of paediatric patients was performed to assess whether the efficacy and safety of DFP are comparable to DFO in children with SCD (66). The analysis included children aged 2-16, with 86 in the DFP group and 42 in the DFO group; the majority of children in both groups had a primary diagnosis of SCD. In the efficacy population, after 12 months of treatment, there was no significant difference in the mean (SD) LIC change from baseline in children treated with DFP (n=78) compared to DFO (n=40) (-3.39 ± 4.24 mg/g vs -2.99 ± 3.16 mg/g, respectively; p=0.57) (66).

## Safety

FIRST (LA38-0411) evaluated the safety and tolerability of DFP versus DFO as secondary endpoints. The percentage of patients who experienced at least one AE was 88.2% in both groups and there was no significant difference in the overall rates of SAEs, treatment-related AEs, or AEs leading to withdrawal. A higher percentage of patients in the DFP group reported AEs rated as severe (16.4% vs. 6.6%; p=0.0393). Treatment-related AEs were reported in 51.3% of patients treated with DFP and in 39.5% of the DFO patients (p=0.1215). A total of 12 patients had SAEs that were considered at least possibly related to study treatment: 5.9% (9 patients) in the DFP group and 3.9% (3 patients) in the DFO group (p=0.7550) (Table 38) (36).

Among the AEs that were possibly related to treatment, the most common were: abdominal pain, vomiting, pyrexia, increased alanine transferase (ALT), increased aspartate transferase (AST), and injection site pain (Table *38*). There were some differences between the two groups for treatment-related AEs that are associated with the mode of administration, with abdominal pain and vomiting reported more often in the DFP group and injection-site pain reported solely in the DFO group. Two patients in the DFP group discontinued the study due to these GI events and three in the DFO group due to local-site pain. In terms of laboratory parameters, among patients in the DFP group, 14 (9.2%) had increased ALT and 14 (9.2%) had increased AST levels, while no patients in the DFO group had either (p=0.0059). The increases were small, however, and did not result in any treatment discontinuations (36).

Table 38. Overall summary of AEs and treatment-related AEs – safety population (source; Kwiatkowski et al., 2022)

| Preferred term | DFP n (%) (n=152) | DFO n (%) (n=76) | *p*-value DFP vs DFO (Fisher's exact) |
|---|---|---|---|
| **Overall summary of AEs** | | | |
| AE | 134 (88.2) | 67 (88.2) | 1.0000 |
| Severe AE | 25 (16.4) | 5 (6.6) | .0393 |
| Serious AE (SAE) | 40 (26.3) | 14 (18.4) | .2472 |
| Treatment-related AE* | 78 (51.3) | 30 (39.5) | .1215 |
| Treatment-related SAE* | 9 (5.9) | 3 (3.9) | .7550 |
| Withdrew due to an AE† | 7 (4.6) | 3 (3.9) | 1.0000 |
| **Treatment-related AEs by preferred term occurring in ≥ 5% of patients** | | | |
| Abdominal pain‡ | 26 (17.1) | 3 (3.9) | .0053 |
| Vomiting | 22 (14.5) | 1 (1.3) | .0009 |
| Pyrexia | 14 (9.2) | 7 (9.2) | 1.0000 |
| ALT level increased above normal | 14 (9.2) | 0 (0.0) | .0059 |
| AST level increased above normal | 14 (9.2) | 0 (0.0) | .0059 |
| Neutrophil count decreased | 9 (5.9) | 2 (2.6) | .3441 |
| Nausea | 8 (5.3) | 2 (2.6) | .5024 |
| Chromaturia | 8 (5.3) | 1 (1.3) | .2781 |
| Injection-site pain | 0 (0.0) | 5 (6.6) | .0038 |
| Percentage was calculated based on the number of patients exposed in the study in that treatment group<br>* The causal relationship to study medication was based on the investigator's and sponsor's assessments | | | |

† AEs leading to withdrawal from the study included abdominal pain and vomiting (DFP n = 2), nausea (DFO n = 1), acute chest syndrome (DFP = 1), pneumonia (DFO = 1), car accident (DFP n = 1, DFO n = 1), hepatic and splenic complications (DFP n = 1), neutropenia (DFP n = 1), and agranulocytosis (DFP n = 1)
‡ Includes the preferred terms of abdominal pain and abdominal pain upper
ALT: alanine aminotransferase; AST: aspartate aminotransferase; DFO: deferoxamine; DFP: deferiprone; SAE: serious adverse event

Neutropenia occurred in four patients (2.6%) in the DFP group and there was a single episode of neutropenia, which was deemed not treatment related, in the DFO group. Most neutropenia cases resolved within 4-12 days. There was one case of agranulocytosis in the DFP group, which occurred following 7.5 months of treatment and resolved within one day of treatment discontinuation (36).

Overall, the most commonly reported events in the DFP group were pyrexia, abdominal pain, bone pain, headache, and vomiting, while bone pain, pyrexia, back pain, pain in extremity, oropharyngeal pain, and cough were mostly reported in the DFO group (Table 39) (36).

Table 39. Adverse events by preferred term seen in at least 5% of patients in the safety population (source; Kwiatkowski, 2022)

| Preferred term | DFP n (%) (n=152) | DFO n (%) (n=76) | *p*-value DFP vs DFO (Fisher's exact) |
|---|---|---|---|
| Pyrexia | 43 (28.3) | 25 (32.9) | .5395 |
| Abdominal pain* | 38 (25.0) | 10 (13.2) | .0402 |
| Bone pain | 38 (25.0) | 26 (34.2) | .1609 |
| Headache | 30 (19.7) | 10 (13.2) | .2691 |
| Vomiting | 29 (19.1) | 8 (10.5) | .1273 |
| Pain in extremity | 27 (17.8) | 11 (14.5) | .5771 |
| Sickle cell crisis | 26 (17.1) | 10 (13.2) | .5639 |
| Back pain | 20 (13.2) | 14 (18.4) | .3262 |
| ALT level increased above normal | 18 (11.8) | 0 (0.0) | .0010 |
| AST level increased above normal | 17 (11.2) | 0 (0.0) | .0009 |
| Oropharyngeal pain | 15 (9.9) | 11 (14.5) | .3767 |
| Nasopharyngitis | 14 (9.2) | 9 (11.8) | .6414 |
| Cough | 12 (7.9) | 11 (14.5) | .1604 |
| Arthralgia | 15 (9.9) | 6 (7.9) | .8089 |
| Neutrophil count decreased | 12 (7.9) | 3 (3.9) | .3961 |
| Nausea | 11 (7.2) | 7 (9.2) | .6094 |
| Chromaturia | 9 (5.9) | 2 (2.6) | .3441 |
| Pain | 8 (5.3) | 3 (3.9) | .7556 |
| Diarrhoea | 7 (4.6) | 6 (7.9) | .3670 |
| Chest pain | 5 (3.3) | 4 (5.3) | .4857 |
| Influenza | 5 (3.3) | 5 (6.6) | .3074 |
| Toothache | 3 (2.0) | 5 (6.6) | .1208 |
| Injection-site pain | 0 (0.0) | 5 (6.6) | .0038 |
| Injection-site swelling | 0 (0.0) | 4 (5.3) | .0117 |

Percentage was calculated based on the number of patients exposed in the study in that treatment group
*Includes the preferred terms of abdominal pain and abdominal pain upper
ALT: alanine aminotransferase; AST: aspartate aminotransferase; DFO: deferoxamine; DFP: deferiprone

**Paediatric population:** The previously mentioned subgroup analysis of paediatric patients observed no new safety concerns that had not been previously noted in other populations (66). There were no significant differences between the two groups in overall incidence of AEs (p=0.77) (including neutropenia (p=0.30)), severe AEs (p=0.10), serious AEs (p=0.16), or withdrawals due to an AE (p=0.17), though there was a difference in the overall incidence of nonserious AEs considered at least possibly related to DFP treatment (59.3% vs 33.3%; p=0.01) (66).

Table 40. Summary of AEs in ≥ 5% paediatric patients (2-16 years of age) treated with DFP vs DFO: safety population (source: Hamdy et al., 2021)

| AEs in ≥ 5% paediatric patients | DFP (mg/kg t.i.d) n (%) (n=86*) | DFO (mg/kg/day) n (%) (n=42*) | *p*-value DFP vs DFO |
|---|---|---|---|
| Pyrexia | 29 (33.7) | 15 (35.7) | 0.8449 |
| Bone pain | 27 (31.4) | 16 (38.1) | 0.5504 |
| Abdominal pain/upper | 25 (29.1) | 6 (14.3) | 0.0805 |
| Headache | 17 (19.8) | 6 (14.3) | 0.6245 |
| Vomiting | 17 (19.8) | 4 (9.5) | 0.2040 |
| Back pain | 15 (17.4) | 9 (21.4) | 0.6330 |
| Pain in extremity | 14 (16.3) | 8 (19.0) | 0.8036 |
| Oropharyngeal pain | 12 (14.0) | 9 (21.4) | 0.3148 |
| Neutrophil count decreased | 11 (12.8) | 3 (7.1) | 0.5472 |
| Alanine aminotransferase increased | 9 (10.5) | 0 | 0.0299 |
| Aspartate aminotransferase increased | 9 (10.5) | 0 | 0.0299 |
| Arthralgia | 9 (10.5) | 2 (4.8) | 0.3382 |
| Sickle cell anaemia with crisis | 9 (10.5) | 1 (2.4) | 0.1641 |
| Nasopharyngitis | 9 (10.5) | 4 (9.5) | 1.0000 |
| Cough | 7 (8.1) | 9 (21.4) | 0.0458 |
| Diarrhoea | 5 (5.8) | 4 (9.5) | 0.4742 |
| Nausea | 5 (5.8) | 2 (4.8) | 1.0000 |
| Pharyngitis | 5 (5.8) | 0 | 0.1712 |
| *Percentage was calculated based on the number of patients in the safety population; AEs postexposure are included; DFO: deferoxamine; DFP: deferiprone | | | |

## 13.2. FIRST-EXT (LA38-EXT)

Patients who completed the FIRST (LA38-0411) trial had the option to continue treatment of transfusional iron overload with DFP for up to two years as part of an extension study, FIRST-EXT (LA38-EXT). Patients who had been treated with DFP continued on DFP (DFP-DFP group), whereas those who had received DFO were switched to DFP (DFO-DFP group) (67).

The time points for the efficacy assessments of DFP are defined below. Baseline was defined as the start of DFP treatment, so it differed for the two group, as follows:

- DFP-DFP group: For patients who had received DFP in FIRST (LA38-0411), the start of that study was the baseline, the start of the extension study was year 1 (i.e., the completion of one year of DFP treatment), month 12 of the extension study was year 2, and month 24 of the extension study was year 3.
- DFO-DFP group: For patients who had received DFO in FIRST (LA38-0411), the start of the extension study was baseline, month 12 of the extension study was year 1, and month 24 of the extension study was year 2. There was no year 3.

## Efficacy

Efficacy was assessed by investigating the change in iron load from baseline to year 1 (both groups), from baseline to year 2 (both groups), and from baseline to year 3 (DFP-DFP group only) in LIC (as measured by MRI), in serum ferritin, and in cardiac MRI T2*. Responder analysis was defined as the percentage of patients who showed a ≥20% decline from baseline in LIC or SF or a ≥20% increase from baseline in cardiac MRI T2* at year 1 (both groups), at year 2 (both groups), and at year 3 (DFP-DFP group only) (67).

**Liver iron concentration:** Mean LIC values (mg/g dw) decreased progressively over time, showing that DFP is able to control iron levels for up to three years (Table 41). These decreases were seen in the overall ITT population, as well as in the SCD and other anaemias subpopulations (67).

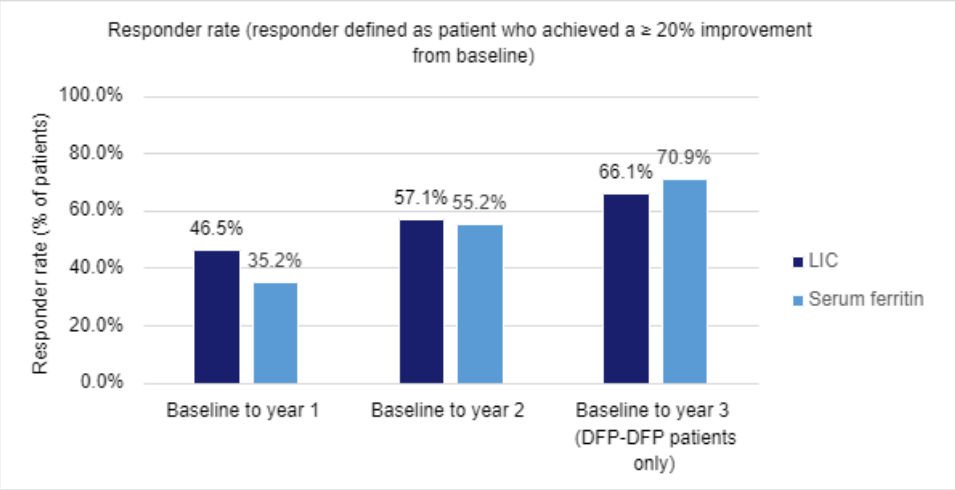
Table 41. Change from baseline LIC (mg/g dw) – ITT population and subpopulations (source: Elalfy et al., 2022)

| Time period | N | DFP<br>mean (SD)<br>[min, max] | p-value* |
|---|---|---|---|
| **Overall ITT population** | | | |
| Baseline to year 1 | 129 | -2.64 (4.64) [-17.50, 8.72] | < 0.0001 |
| Baseline to year 2 | 112 | -3.91 (6.38) [-22.11, 12.28] | < 0.0001 |
| Baseline to year 3<br>(DFP-DFP patients only) | 59 | -6.64 (7.72) [-22.81, 12.58] | < 0.0001 |
| **SCD subpopulation** | | | |
| Baseline to year 1 | 110 | -2.33 (4.41) [-17.50, 8.72] | 0.0000 |
| Baseline to year 2 | 96 | -3.41 (6.04) [-22.11, 12.28] | 0.0000 |
| Baseline to year 3<br>(DFP-DFP patients only) | 50 | -6.05 (7.71) [-22.81, 12.58) | 0.0000 |
| **Other anaemias subpopulation** | | | |
| Baseline to year 1 | 19 | -4.43 (5.62) [-16.31, 6.64] | 0.0030 |
| Baseline to year 2 | 16 | -6.93 (7.68) [-18.38, 7.33] | 0.0026 |
| Baseline to year 3<br>(DFP-DFP patients only) | 9 | -9.96 (7.30) [-17.93, 0.00] | 0.0035 |
| * One-sample t-test<br>DFP: deferiprone; SD: standard deviation | | | |

An additional analysis investigated the rate of responders to DFP treatment, defined as patients who experienced a decline in LIC of at least 20% from baseline. The results showed a progressive

increase in the responder rate over time, from about half of the patients after one year of DFP treatment to around two-thirds after three years (Figure 17) (67).

Figure 17. Responder rate over DFP treatment duration – ITT population (responder defined as patient who achieved a ≥ 20% improvement from baseline) (source: Elalfy et al., 2022)




DFP: deferiprone; ITT: intention to treat; LIC: liver iron concentration

**Serum ferritin:** In the overall ITT population, mean serum ferritin levels did not decrease significantly from baseline during the first year of DFP treatment, but did have significant decreases over the following two years for up to three years (Table 41) (67).

Table 42. Change from baseline in serum ferritin (µg/L) - ITT population and subpopulations (source: Elalfy et al., 2022)

| Time period | N | DFP mean (SD) [min, max] | p-value* |
|---|---|---|---|
| **Overall ITT population** | | | |
| Baseline to year 1 | 125 | -1 (1986) [-6123, 6697] | 0.9952 |
| Baseline to year 2 | 96 | -771 (2171) [-7498, 5569] | 0.0008 |
| Baseline to year 3 (DFP-DFP patients only) | 55 | -1016 (3617) [-7188, 20058] | 0.0420 |
| **SCD subpopulation** | | | |
| Baseline to year 1 | 106 | 130 (2086) [-6123, 6697] | 0.5222 |
| Baseline to year 2 | 81 | -711 (2310) [-7498, 5569] | 0.0070 |
| Baseline to year 3 (DFP-DFP patients only) | 46 | -918 (3926) [-7188, 20058] | 0.1198 |
| **Other anaemias subpopulation** | | | |
| Baseline to year 1 | 19 | -733 (1066) [-2690, 1643] | 0.0078 |
| Baseline to year 2 | 15 | -1095 (1175) [-3285, 854] | 0.0028 |
| Baseline to year 3 (DFP-DFP patients only) | 9 | -1517 (1120) [-3197, 172] | 0.0036 |
| * One-sample t-test<br>DFP: deferiprone; SD: standard deviation | | | |

The responder rate for serum ferritin, defined as an improvement of at least 20% from baseline, also increased over time, from 35% to 71%. (Figure 17) (67).

**Cardiac T2*:** Cardiac T2* MRI values were normal at baseline and remained normal in all patients for the duration of the study (67).

## Safety

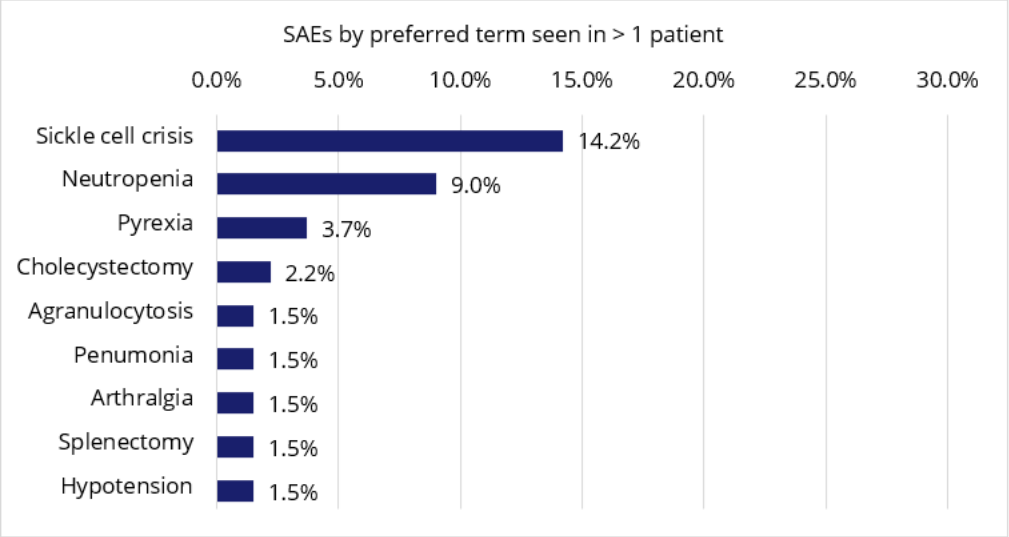
About three-quarters of patients experienced at least one AE of any type; about a quarter of patients experienced at least one serious AE (SAE); about a third experienced an AE that was considered at least possibly related to study product; roughly 10% of patients experienced an SAE that was considered at least possibly related to DFP. In addition, 19 patients (14.2%) had AEs of severe intensity, and two (1.5%) had AEs that led to withdrawal from the study, as shown in Table 43 (67).

Table 43. Overall summary of patients experiencing adverse events – safety population (source: Elalfy et al., 2022)

| **Number of patients with at least one:** | **DFP<br>n (%)<br>n=134** |
|---|---|
| Adverse event (AE) | 104 (77.6) |
| Severe AE | 19 (14.2) |
| Serious AE (SAE) | 35 (26.1) |
| AE at least possibly related to study treatment | 41 (30.6) |
| SAE at least possibly related to study treatment | 13 (9.7) |
| AE leading to withdrawal from the study | 2 (1.5) |

During the two years of the extension study, there were 836 AEs reported, most of which were mild (n=567, 67.8%). The most common AEs reported by individuals were pyrexia, bone pain, abdominal pain, and sickle cell crisis. For SAEs, the most commonly reported were sickle cell crisis, neutropenia, pyrexia, and cholecystectomy (Figure 18) (67).

Figure 18. SAEs by preferred term (source: Elalfy et al., 2022)




The great majority of AEs (n=727, 87.0%) were not considered to be related to the study drug. Of those AEs deemed possibly related to DFP, the most common were neutropenia (12 patients, 9.0%) and abdominal pain (10 patients, 7.5%). Regarding SAEs, 13 patients experienced an SAE considered possibly related to DFP, two of which were agranulocytosis (67).

The long-term safety profile of DFP in patients with SCD or other anaemias observed in the extension trial was acceptable, with most AEs being mild and not considered to be related to DFP (67).

## 13.3. LA16-0102/Pennell 2006

LA16-0102 is a phase III, multi-centre, randomized open-label clinical trial comparing the use of DFP vs the use of DFO over a period of 12 months. The primary objective was to determine whether orally administered DFP exhibits superior efficacy in removing excess iron from the heart compared to that of subcutaneous infusions of DFO, as reflected by MRI T2* assessments of the heart in patients treated with either chelator (38).

The secondary objective was to evaluate the relative efficacy of DFP compared with DFO as assessed by serum ferritin (SF) concentration and liver iron concentration (LIC) (38).

**Patient disposition:** A total of 61 patients were enrolled in the study and randomized in a 1:1 ratio; DFP (n=29), DFO (n=32). Fifty-six patients completed the study, and five patients discontinued prematurely: two taking DFP (one due to cytomegalovirus hepatitis and one due to elevated liver enzymes) and three taking DFO (one due to deterioration of heart function and two due to personal reasons) (38).

**Patient demographics and baseline characteristics:** All patients were Caucasian, of either Greek or Italian ethnicity, with a similar number of male and female patients in the two treatment groups.

Mean patient age was 25.1 and 26.2 years for the DFP and DFO groups, respectively. Treatment groups were well matched at baseline for cardiac T2* (p=0.77), the primary endpoint, as well as for most other baseline measures, including liver iron level and transfusional iron input. However, significant differences were present at baseline for the serum ferritin level (DFP, 1,791±1,029 µg/L; DFO, 2,795±2,441 µg/L; p=0.039), haemoglobin level (DFP, 105±12.0 g/L; DFO, 113±11.9 g/L; p=0.023), and white cell count (DFP, 7.68±2.96x$10^9$/L; DFO, 9.79±4.49x$10^9$/L; p=0.033) (38).

DFP therapy was initiated at 75 mg/kg/day and increased to the target of 100 mg/kg/day, equating to an actual prescribed dose over 12 months of 92 mg/kg/day. For DFO, the target dose was 50 mg/kg/day for at least 5 days/week; the actual dose prescribed was 43 mg/kg for 5.7 days/week, equating to 35 mg/kg for 7 days/week (38).

## Efficacy

**Cardiac iron (primary efficacy outcome):** DFP significantly reduced the myocardial iron concentration compared to chelation with DFO, as evidenced by increases in cardiac MRI T2* measurements; T2* rose with DFP to a greater extent than with DFO (Table 44), with the difference in the change between drugs being significant at 6 months (ratio of geometric means, 1.09; p=0.040) and at 12 months (ratio, 1.12; p=0.023) (38).

The potential effects of significant differences between treatment arms in SF, haemoglobin and white cell count at baseline, were explored in additional analyses of cardiac T2*. Differences in haemoglobin and white cell counts at baseline appeared to be due to a difference in the number of splenectomised patients in the two treatment arms (DFP 14% vs DFO 34%). The difference in T2* favouring DFP remained significant (p=0.002) after controlling for baseline SF and splenectomy status. Because the DFO group had more splenectomised patients than the DFP group, the mean transfusional iron load required to maintain the target haemoglobin would have been greater in the DFP-treated patients. Therefore, had the number of splenectomised patients been equal, an even greater difference in T2* in favour of DFP would have been expected (38).

An improvement in both T2* and LVEF was seen in 19 (66%) DFP-treated patients and 14 (45%) DFO-treated patients (38).

Table 44. Cardiac MRI T2* (log transformed) (source: Pennell et al., 2006)

| | Baseline | | 6 months | | 12 months | |
|---|---|---|---|---|---|---|
| | DFP (n=29) | DFO (n=32) | DFP (n=29) | DFO (n=31[††]) | DFP (n=29) | DFO (n=31[††]) |
| Geometric mean[†], milliseconds (CV, %)[‡] | 13.0 (32) | 13.3 (30) | 15.4 (38) | 14.4 (37) | 16.5 (38) | 15.0 (39) |

| | | | | | | |
|---|---|---|---|---|---|---|
| % change from baseline | - | - | 18% | 9% | 27% | 13% |
| Ratio of geometric means | - | | 1.09 | | 1.12 | |
| p value§ | 0.77 | | 0.040 | | 0.023 | |

CV: coefficient of variation; DFO: deferoxamine; DFP: deferiprone | †Geometric mean defined as antilog of the mean of the log data; ‡CV defined as $\sqrt{[e^{MSE}-1]}$, where MSE is the mean square error (equivalent to the variance of the mean in log scale); §Log (T2*) between the two treatment arms was compared by the two-sample t-test; ††One patient had a baseline T2* level value only and was not eligible to be included in the ITT population

### *Secondary efficacy outcomes*

**Other cardiac outcomes:** LVEF improved significantly more in the DFP-treated group after 12 months (DFP: 3.1% improvement versus DFO: 0.32% improvement, p=0.003). A trend to improvement in LVEF appeared in DFP-treated patients within 6 months (p=0.074), but not for DFO (38).

There was also a significant difference at 12 months favouring DFP for the reduction in end-systolic volume (-6.4±6.8 ml vs. -0.6±7.9 ml; p=0.004) and the reduction of end-diastolic volume approached significance (-7.8±13 ml vs. -1.2±13 ml; p=0.060) (38).

**Liver iron concentration and serum ferritin:** Both DFP and DFO led to a reduction in liver iron and serum ferritin, and these changes were not significantly different between the two treatment groups at 12 months (p=0.40 and p=0.16, respectively). After 12 months, there was a decline in LIC with DFP by 0.93 mg/g dry weight (-10.1%; p=0.11) compared with a decrease of 1.54 mg/g dry weight (-24.4%; p=0.002) for DFO. Serum ferritin was reduced by 181 µg/L (-10.1%) in DFP-treated patients and by 466 µg/L (-16.7%) in DFO-treated patients (38).

These results suggest that the two treatments have similar efficacy in controlling non-cardiac iron load at the doses employed (38).

## Safety

Patients were monitored weekly for absolute neutrophil count (ANC) as well as for any adverse events, while serum alanine transaminase (ALT) levels were measured quarterly, and serum creatinine levels were measured at baseline and at 12 months (38).

In the DFP group, the most frequent adverse events were gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain, which occurred in 20 patients (69%), and which were typically mild to moderate and resolved within a median of 3 days (range, 1-17 days) without discontinuation or reduction of dose. In addition, joint problems (pain and/or swelling) were reported in eight patients (28%) and increased appetite in nine (31%) (38,53).

For the DFO group, infusion site reactions were the most common adverse events, occurring in 38% (12 patients) (38). Joint problems were reported in 13% (4 patients) (53).

Table 45. Adverse events reported in ≥10% in either the DFP or DFO arms (source: adapted from the Canadian product information)

| System organ class & preferred term | DFP (N = 29) N subjects (%) | DFO (N = 32) N subjects (%) |
|---|---|---|
| Eye disorders | 3 (10) | 4 (13) |
| Conjunctivitis | 3 (10) | 4 (13) |
| Gastrointestinal disorders | 20 (69) | 14 (44) |
| Nausea | 11 (38) | 0 (0) |
| Abdominal pain upper | 9 (31) | 3 (9) |
| Vomiting | 9 (31) | 5 (16) |
| Diarrhoea | 7 (24) | 2 (6) |
| Abdominal discomfort | 4 (14) | 1 (3) |
| Abdominal pain | 4 (14) | 4 (13) |
| Epigastric discomfort | 4 (14) | 3 (9) |
| Eructation | 4 (14) | 0 (0) |
| Toothache | 3 (10) | 4 (13) |
| General disorders and administration site conditions | 5 (17) | 4 (13) |
| Asthenia | 3 (10) | 4 (13) |
| Chest pain | 3 (10) | 0 (0) |
| Infections and infestations | 19 (66) | 22 (69) |
| Pharyngitis | 7 (24) | 12 (38) |
| Rhinitis | 6 (21) | 5 (16) |
| Viral infection | 6 (21) | 9 (28) |
| Gastroenteritis | 3 (10) | 5 (16) |
| Tooth abscess | 3 (10) | 2 (6) |
| Vaginal infection | 3 (10) | 2 (6) |
| Nasopharyngitis | 2 (7) | 7 (22) |
| Injury, poisoning and procedural complications | 4 (14) | 7 (22) |
| Transfusion reaction | 4 (14) | 4 (13) |
| Allergic transfusion reaction | 0 (0) | 4 (13) |
| Investigations | 21 (72) | 16 (50) |
| Weight increased | 12 (41) | 6 (19) |
| Alanine aminotransferase increased | 11 (38) | 5 (16) |
| Aspartate aminotransferase increased | 6 (21) | 1 (3) |
| Electrocardiogram t wave inversion | 6 (21) | 0 (0) |
| White blood cell count decreased | 5 (17) | 6 (19) |
| Gamma-glutamyltransferase increased | 4 (14) | 2 (6) |
| Electrocardiogram repolarization abnormality | 3 (10) | 0 (0) |
| Neutrophil count decreased | 1 (3) | 4 (13) |
| Weight decreased | 1 (3) | 9 (28) |
| Metabolism and nutrition disorders | 9 (31) | 0 (0) |
| Increased appetite | 9 (31) | 0 (0) |
| Musculoskeletal and connective tissue disorders | 16 (55) | 17 (53) |
| Back pain | 12 (41) | 15 (47) |

| | | |
|---|---|---|
| Arthralgia | 8 (28) | 4 (13) |
| Myalgia | 3 (10) | 2 (6) |
| Nervous system disorders | 15 (52) | 16 (50) |
| Headache | 14 (48) | 16 (50) |
| Dizziness | 2 (7) | 4 (13) |
| Reproductive system and breast disorders | 3 (10) | 3 (9) |
| Dysmenorrhea | 3 (10) | 3 (9) |
| Respiratory, thoracic and mediastinal disorders | 0 (0) | 6 (19) |
| Cough | 0 (0) | 6 (19) |
| Skin and subcutaneous tissue disorders | 5 (17) | 3 (9) |
| Dermatitis contact | 3 (10) | 1 (3) |
| Urticaria | 3 (10) | 2 (6) |

There were no significant differences in ANC between the group treated with DFP and that treated with DFO. There was one episode of neutropenia in the DFP group and there were no episodes of agranulocytosis in either group (38).

At 12 months, the difference in ALT levels between patients treated with DFP and those treated with DFO was not significant (22.9 ± 48.6 U/L vs 4.7 ± 38.2 U/L; p=0.11) and there was no significant difference between the two groups in trend of the ALT level over time (p=0.32). Nor was there a significant difference in the percentage of patients with ALT greater than twice the upper limit, neither at baseline nor at 12 months (38).

Regarding the change in creatinine levels at 12 months, there was no significant difference between the two groups (3.24 ± 10.5 µM vs 0.06 ±12.7 µM; p=0.29). The difference between groups in the change of zinc level at 12 months was also not significant (-0.80 ± 2.8 µM vs 0.23 ± 2.3 µM; p=0.12) (38).

## 13.4. LA12-9907/Piga 2003

LA12-9907 is an open-label, controlled, parallel, longitudinal, retrospective study assessing the occurrence of cardiac disease and survival in patients with thalassaemia major treated for at least four years with DFP or DFO (68).

**Patient disposition & demographics and baseline characteristics**

Fifty-four patients were analysed in the DFP group and 75 patients in the DFO group. At the time of study initiation both groups were similar for gender distribution (DFP: 44% female, DFO: 49% female, p=0.583) and the mean transfusional iron input received during the prior two years (DFP: 0.464±0.085 mg Fe/kg/day; DFO: 0.432±0.110 mg Fe/kg/day, p=0.102). However, patients whose therapy was switched to DFP were younger at baseline than those in the DFO group: the mean age was 17.1±4.1 years compared with 19.4±6.9 years for the DFO group (p=0.018). Also, patients who switched to DFP had initiated chelation therapy with DFO at an earlier age (4.5±2.7 years) than patients who were maintained on DFO (6.8±4.7 years) (p=0.002) (68).

## Results

The average dose of DFP during the study period was 73.7±11.2 mg/kg/day, while the average dose of DFO was 39.2±4.7 mg/kg/infusion, administered an average of 6±1 days/week (68).

**Cardiac disease:** At the first cardiac assessment, abnormal cardiac function was detected in 7 patients in the DFP group and 12 in the DFO group, with the overall prevalence of cardiac disease being similar between the two groups (p=0.606) (68).

- NYHA Class I in 13 patients (n=6 DFP; n=7 DFO)
- NYHA Class II in 3 patients (all DFO)
- NYHA Class III in 2 patients (n=1 DFP; n=1 DFO)
- NYHA Class I in 1 patient (DFO)

None of the patients treated with DFP had worsening of their cardiac function, while 33% (n=4) of the patients treated with DFO did. NYHA cardiac disease class improved in 43% (3/7) of DFP-treated patients and 25% (3/12) of DFO-treated patients (p=0.617) who had been diagnosed with cardiac disease at their first assessment (68).

Among the DFP-treated patients, newly diagnosed cardiac disease occurred in 4% (2/47), while it occurred in 21% (13/63) of the DFO-treated patients who initially free of cardiac disease (68):

- NYHA Class I in 13 patients
- NYHA Class II in one DFO patient
- NYHA Class I worsening to Class III, in one DFO patient

Two patients (4%) in the DFP group and 15 (20%) in the DFO group were diagnosed with cardiac dysfunction (defined as worsening of pre-existing cardiac abnormality or development of new cardiac disease) from the first to the last measurement (p=0.007) (68).

In terms of survival free of heart disease, the Kaplan-Meier analysis over the 5-year period was significantly more favourable in the DFP group (p=0.003). Similar results in favour of DFP were obtained in a sub-group analysis of patients who were matched for age at the start of chelation therapy (p=0.017) (68).

**Deaths:** In the DFP group, none of the 54 died during the study period, compared with 4/75 of those treated with DFO. Of the four who died, three had been found to have cardiac disease at the first assessment of the study period and died as a result of irreversible worsening of their cardiac condition. The fourth patient had a history of drug addiction (and was without signs of cardiac disease) and was not included among the deaths in the survival analysis (68).

**Body iron load and serum ferritin:** The mean overall transfusional iron load was greater in DFP-treated patients throughout the study (0.432±0.076 mg Fe/kg/day with DFP vs 0.408±0.085 mg Fe/kg/day with DFO), although this did not reach statistical significance (p=0.111). The proportion of patients whose SF levels were over 2,500 µg/L in more than 50% measurements rose from 24% to 35% in DFP–treated patients and from 15% to 20% in DFO–treated patients. However, the

between–group difference was not significant (p=0.053), nor was the difference in mean serum ferritin level at the end of the study (2,142±957 vs 2,143±1,481 µg/L; p=0.994) (68).

**Compliance:** In the DFP group, the weighted mean compliance was 89% (range 66-98%) versus 85% (range 54-99%) with DFO (p=0.011) (68).

In conclusion, the analysis suggests that the cardioprotective effect of long-term therapy with DFP is greater than that of DFO in thalassaemia major patients (68).

## 13.5. Borgna-Pignatti 2006

This was an observational study on cardiac morbidity and mortality in patients with thalassaemia major treated with either DFP or DFP (50). The aim was to compare the occurrence of cardiac disease in patients treated with DFO alone and those who were switched from DFO to DFP. Patients had not experienced a cardiac event prior to the start of the study. Of the patients included in this study, 13% (68 of 516) were included in the previous analysis by Piga et al. described in section 13.4 (50)

**Patient disposition:** A total of 516 patients were included, of whom 157 received DFP at some point during the review period and 359 stayed on DFO. Two patients were lost to follow-up. All other patients were followed for the entire study duration of almost 9 years (50)

**Patient demographics and baseline characteristics:** Patient characteristics were similar between the two groups, with the exception of median serum ferritin at time zero. Ferritin was significantly higher in those patients who later switched to DFP, compared with those who stayed on DFO (1,870 µg/L compared with 1,461 µg/L, p< 0.001). Median age at study entry was 17.4 (1.58–25.1) and 17.5 (2.45–24.9) years for DFO and DFP, respectively) (50)

### Results

The median duration of DFP treatment was 4.3 years (range, 0.02–8.9 years); a total of 750 patient-years. The median time on DFO (before switching to DFP) from time zero was 2.0 years (range, 0.06–8.7 years) (50)

**Incidence of cardiac events:** A total of 52 cardiac events occurred during the observation period (Table 46). All patients experiencing a cardiac event were being treated with DFO at the time of the event; 46 patients had only ever been treated with DFO; 6 patients had previously received DFP but were again being treated with DFO at the time of the cardiac event. In patients who had been treated with DFP and who had switched back to DFO, the time between stopping DFP and the cardiac event ranged from 1 year, 8 months to 5 years, 4 months. The yearly incidence of cardiac events in DFO-treated patients ranged from 0.6% to 3.4% (with CIs no wider than 4%) (Table 46) (50)

Table 46. Incidence of cardiac events by calendar year (source: Borgna-Pignatti et al., 2006)

| | DFO | | DFP | |
|---|---|---|---|---|
| Year[†] | No. patients at risk | No. cardiac events (% [95%CI]) | No. patients at risk | No. cardiac events (% [95%CI])[‡] |
| 1995 | 516 | 3 (0.58 [0.12 to 1.69]) | 0 | 0 (NA) |
| 1996 | 444 | 11 (2.48 [1.24 to 4.39]) | 63 | 0 (0 [0 to 5.69]) |
| 1997 | 420 | 4 (0.95 [0.26 to 2.42]) | 75 | 0 (0 [0 to 4.80]) |
| 1998 | 398 | 5 (1.26 [0.41 to 2.91]) | 93 | 0 (0 [0 to 3.85]) |
| 1999 | 396 | 3 (0.76 [0.16 to 2.20]) | 89 | 0 (0 [0 to 4.06]) |
| 2000 | 393 | 4 (1.02 [0.28 to 2.59]) | 87 | 0 (0 [0 to 4.15]) |
| 2001 | 387 | 6 (1.55 [0.57 to 3.34]) | 89 | 0 (0 [0 to 4.06]) |
| 2002 | 374 | 4 (1.07 [0.29 to 2.72]) | 88 | 0 (0 [0 to 4.30]) |
| 2003 | 358 | 12 (3.35 [1.74 to 5.78]) | 92 | 0 (0 [0 to 3.93]) |

CI: confidence interval; NA: not applicable | [†] Each subject is included once in each year, based on the treatment received on January 31st of that year; [‡] One-sided 97.5% confidence interval

Of note, 9 patients (8 on DFO and 1 on DFP) underwent bone marrow transplantation during the observation period and were censored at the time of the procedure. A total of 46 patients switched to DFX starting in July 2001 (29 on DFO, 17 on DFP), and these patients were also censored on initiating DFX therapy. However, none of these patients had experienced a cardiac event up to the end of the observation period (31st December 2003) (50)

**Odds ratio/hazard ratio for cardiac events:** For DFO vs DFP, the odds ratio of experiencing a cardiac event was estimated to be infinite (as there were no events on DFP), with a lower 95% confidence bound of 2.75 (50)

In Cox regression analysis, the hazard of a cardiac event could not be estimated, as all cardiac events occurred in the DFO group. In order to estimate the significance of the protective effect of DFP, it was assumed that one cardiac event had occurred in a low-risk long-term DFP–exposure patient, thus maximizing the impact of an event. This analysis produced a hazard ratio for cardiac events on DFP compared with DFO of 0.09 (95% CI 0.012 to 0.66; p=0.017) (50)

During the study some patients switched back from DFP to DFO. Further regression analysis conservatively assumed that a lack of cardiac protection from DFP may extend up to 2 years beyond the end of DFP treatment. In this analysis one of the six cardiac events that occurred after switching (20 months after treatment switch) was therefore attributed to DFP, resulting in a hazard ratio for cardiac events on DFP compared with DFO of 0.08 (95% CI 0.011 to 0.57; p=0.012). When the known risk factors of sex, age, and serum ferritin level at baseline were taken into account, the hazard ratio was 0.075 (95% CI 0.010 to 0.55; p=0.011) (50)

**Deaths:** There were 26 (5%) deaths during the study: 24 (6.7%) in the DFO group and two (1.3%) in the DFP group. Neither of the DFP deaths were cardiac-related. There were 15 cardiac-related deaths in the DFO group; 10 were classed as cardiac deaths, while a further five patients died of cardiac disease within 4 to 47 months of the first cardiac event (50)

Using the Cox regression model with a time-varying covariate gave a hazard ratio of 0.38 (CI 0.9 to 1.6; p=0.19) of death on DFP, although the analysis is limited by the fact that the number of events was small (50)

## 13.6. LA36-0310

Note: This study is unpublished; the following information is taken directly from the Canadian and US prescribing information, which include descriptions of the study and its results (5,53).

LA36-0310 is a prospective, planned, pooled analysis of transfusion-dependent iron-overloaded patients (nearly all with thalassaemia) that assessed the efficacy of DFP was assessed in transfusion-dependent iron overload patients in whom previous iron chelation therapy (DFO or DFX; mostly DFO) had failed or was considered inadequate due to poor tolerance (5,53).

Data from 747 patients who had received DFP therapy were analysed for study eligibility. Criteria for chelation failure were defined by one or more measures of iron accumulation above a boundary level associated with an increased risk of organ damage, as follows: SF > 2,500 µg/L before treatment with DFP (main criterion); or LIC of > 7 mg/g dw; or excess cardiac iron stores as demonstrated by a cardiac MRI T2* < 20 ms. Results from patients who received DFP in combination with other chelation therapy are excluded from the presented analysis (53).

Analysis criteria were met for SF, LIC, and cardiac MRI T2* for 236 patients (224 with thalassaemia), 87 patients, and 31 patients, respectively. Most (29/31 (93.5%)) of the patients evaluated for the cardiac MRI T2* criterion were from LA16-0102 (53). Data from a total of 236 patients were analysed. Of the 224 patients with thalassaemia who received DFP monotherapy and were eligible for SF analysis, 105 (47%) were male and 119 (53%) were female. The mean age of these patients was 18.2 years (range 2 to 62; 91 patients were <17) (5).

### Efficacy

DFP therapy was considered successful in individual patients who experienced a reduction in SF of ≥20% from baseline within one year of starting therapy (primary efficacy endpoint). Other success criteria (secondary efficacy endpoints) were a decline in LIC of ≥20% from baseline within one year of starting therapy or a decline in cardiac iron overload, defined as an increase in cardiac MRI T2* ≥20% from baseline within one year of starting therapy. Overall success rates were calculated as the proportion of patients with a successful outcome. In order to consider DFP therapy as successful for a particular measure, the lower limit of the 95% confidence interval (CI) for that efficacy measure had to be greater than 20% (53).

The dose of DFP ranged from 35-100 mg/kg/day, administered orally in either tablet or solution form. The majority (77%) of patients eligible for assessment for the primary efficacy endpoint were

administered a dose of 75 mg/kg/day; 18% received a dose of 100 mg/kg/day and 5% received a dose of ≤ 50 mg/kg/day (53).

The success rate for serum ferritin for patients on DFP monotherapy was 50% (95% CI: 43% to 57%). Mean SF decreased by 940 µg/L within one year of therapy (p=0.0001), i.e., from 4,444 µg/L at baseline to 3,503 µg/L at the last observation. The overall success rate for LIC was 38% (95% CI: 28% to 49%). For LIC, the mean decreased by 1.4 mg/g dw within one year of therapy (p=0.09), from 16.4 mg/g dw at baseline to 15.0 mg/g dw at the last observation. The overall success rate for cardiac MRI T2* was 65% (95% CI: 45% to 81%). For cardiac MRI T2* the mean increased by 3.9 ms within one year of therapy (p=0.0001), from 13.3 ms at baseline to 17.2 ms at the last observation (53).

Subgroup analyses were consistent with the primary analysis in that the lower limit of the 95% CI was greater than 20% for all subsets involved in analyses examining the impact of age, gender, and region (53).

#### Safety

A safety evaluation was not included in the LA36-0310 analysis.

# 14. Appendix II - Methodology of the Network Meta-Analysis for Comparative Effectiveness of Iron Chelation Agents for the Treatment of SCD

## 14.1. Systematic Literature Review Methodology

Data were obtained from a comprehensive systematic literature review (SLR), conducted with the aim of reviewing the clinical efficacy and safety of DFP and all comparators. The methodology of the SLR implements the principles outlined in Cochrane Handbook for Systematic Reviews of Interventions, Centre for Reviews and Dissemination Guidance for Undertaking Reviews in Healthcare, and Methods for the Development of NICE Public Health Guidance.

The SLR of English-language publications was conducted in the databases below. The Ovid platform was used to conduct searches for all literature databases.

- MEDLINE and MEDLINE In-process
- Embase and Embase In-process
- EBM Reviews: Cochrane Central Register of Controlled Trials
- EBM Reviews: CDSR
- EBM Reviews: Cochrane Methodology Register
- EBM Reviews: Health Technology Assessments
- EBM Reviews: DARE

The above databases are in accordance with the list of databases suggested by the HTA organizations, such as the National Institute for Clinical Excellence (NICE), Institute for Clinical and

Economic Review (ICER), Canadian Agency for Drugs and Technologies in Health (CADTH), the Pharmaceutical Benefits Advisory Committee (PBAC), and the Scottish Medicines Consortium (SMC).

The scope of the SLR was defined in terms of the Patient population, the Intervention, the Comparators, the Outcomes measures, and the Study design (PICOS). The PICOS is presented in Table *47*, as well as rationale for each inclusion criterion.

Table 47. Systematic literature review PICO

| PICOS | Inclusion | Rationale |
|---|---|---|
| **Population** | Patients with sickle cell disease and iron overload | The target patient population included in SLR searches consists of patients with SCD that have transfusional iron overload |
| **Intervention/ Comparators** | DFX (Exjade®, Jadenu®) | Interventions included the approved iron chelators DFP (Ferriprox®), DFX (Exjade®/Jadenu®) and DFO (Desferal®) as well as any other iron chelation treatments reported in the literature |
| | DFO (Desferal®) | |
| | DFP (Ferriprox®) | |
| | Iron chelators | |
| **Outcomes** | Serum ferritin levels (SF) | Clinical and RWE outcomes focused on studies in patients with SCD experiencing iron overload and receiving approved/recommended pharmacologic treatments (in any combination) as well as emerging treatments (treatments in development). There were no limitations on outcomes |
| | Liver iron concentration (LIC) | |
| | Cardiac MRI T2* | |
| | Treatment response | |
| | Adherence/discontinuation | |
| | Safety | |
| | Other relevant outcomes | |
| **Study design** | Randomized-controlled clinical trials (Phase 2, Phase 3, Phase 4), including crossover studies and open-label studies | Relevant study designs included clinical trials, single-arm studies, and real-world evidence including prospective observational studies, retrospective studies, and cross-sectional studies. All case reports, case series or reviews were excluded. |
| | RCT sub-studies if they report an additional outcome of interest or long-term follow-up data | |
| | Single-arm studies | |
| | Systematic reviews and meta-analyses (to check the bibliography for relevant RCTs) | |
| **Restrictions** | English Language | Only studies published in English were included |
| | 2001 – current | Given the regulatory approvals for DFX (Exjade®, 2006) and DFO (Desferal®, 1972), data published in the last 20 years were included for the SLR to capture key clinical trials and the most up-to-date information on the current use of these iron chelators |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron concentration; RWE: real world evidence; SCD: sickle cell disease; SF: serum ferritin; SLR: systematic literature review; MRI: magnetic resonance imaging; RCT: randomized controlled trial

## 14.2. Systematic Literature Review Findings

In the SLR, a total of 1800 records were identified using the Ovid platform, of which 1180 were included for title/abstract review. After the addition of abstracts identified in the congress review and bibliographic references, 77 records were selected for full-text review. Following full-text review, a total of 14 records from 11 primary studies were selected for data extraction in the SLR, as well as three substudies. Details of the included and excluded studies in SLR searches are presented in the PRISMA flow diagram in Figure 19.

Out of the 11 primary studies identified from the SLR, studies satisfying the following criteria were included to the NMA:

- Randomized controlled trials (RCTs);
- Reported at least one of the efficacy endpoints with standard error (SE) or standard deviation (SD). Trials not reporting SE/SD cannot be incorporate into an NMA without making additional assumptions on the variation of the efficacy endpoints. This criterion is to avoid making these assumptions. Mathematically, the reliability weights could not be calculated without a SE or SD, and therefore, could not be included in a NMA model.

Figure 20 and Table 48 summarizes studies identified by the SLR which were subsequently considered for the NMA, and the study selection process. Based on the inclusion criteria, two RCTs are included in this NMA, FIRST (NCT02041299) and NCT00067080 (36,56). Both studies reported changes in LIC and in SF (with SE or SD) at 12 months. The references for the nine studies excluded are listed in Table 48.

Figure 19. PRISMA flow diagram for systematic literature review

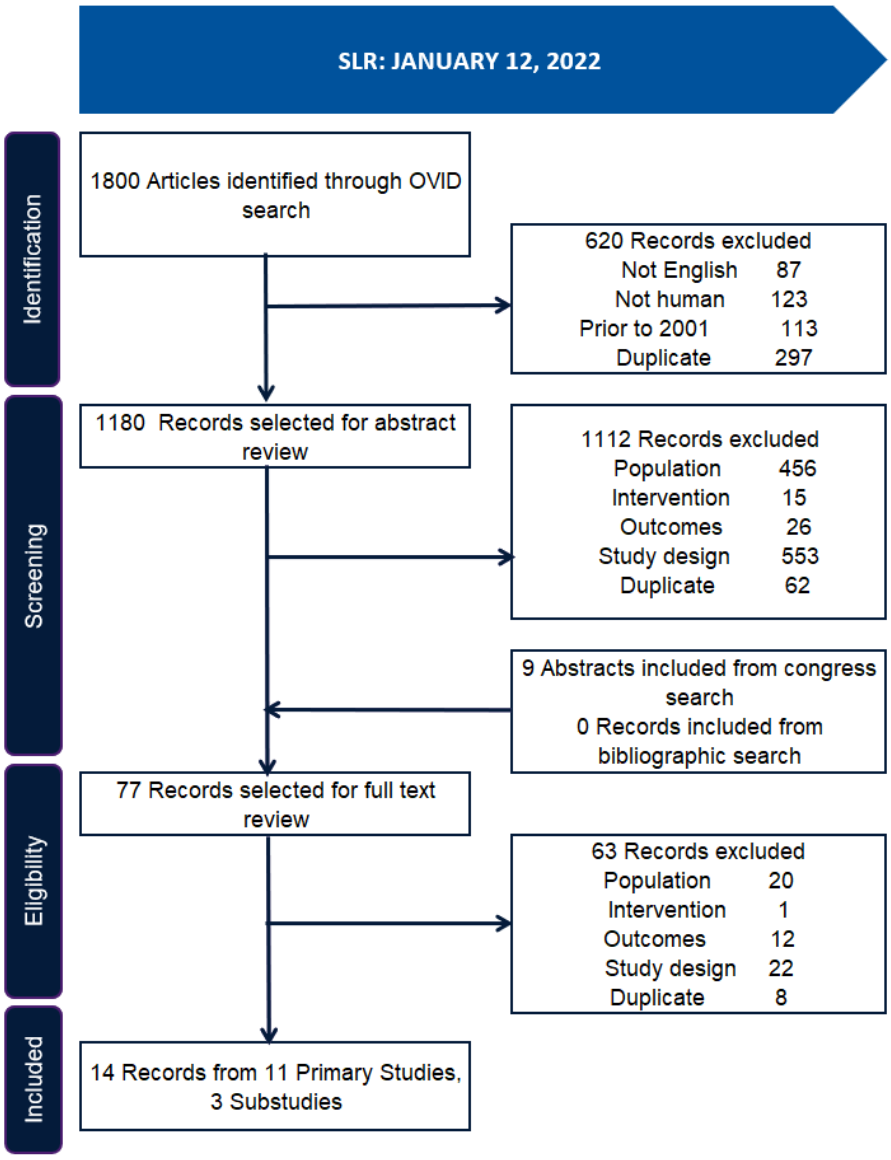
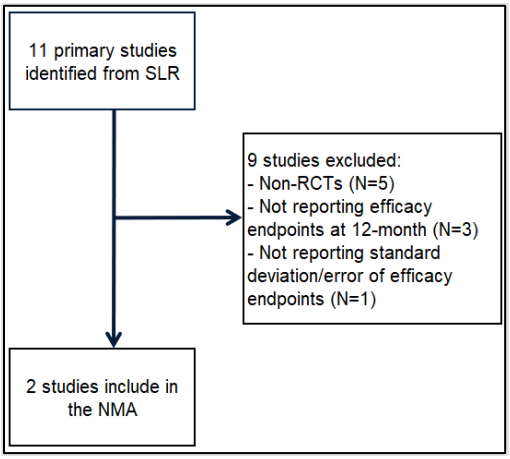


Table 48. Study selection for network meta-analysis

| Study | Trial acronym | Sample size | RCTs | Reporting at 12 months | Change in LIC | Change in SF | Change in Cardiac MRI T2* |
|---|---|---|---|---|---|---|---|
| **Kwiatkowski_Blood_2022*** | **FIRST (NCT02041299)** | **228** | ✓ | ✓ | ✓ | ✓ | ✓ |
| Elalfy_ASPHO_2021a (abstract) | FIRST-EXT | 134 | × | ✓ | ✓ | ✓ | ✓ |
| Calvaruso_BCMD_2014 | Calvaruso_BCMD_2014 | 60 | ✓ | ✓ | × | ■ | × |
| **Vichinsky_BJHaem_2007*** | **NCT00067080** | 195 | ✓ | ✓ | ✓ | ✓ | × |
| Vichinsky_BJH_2011 | NCT01090323 | 185 | × | × | × | × | × |
| Vichinsky_AJH_2013 | CICL670A2201 (NCT00110617) | 203 | ✓ | × | × | × | × |
| Cappellini_Haematologica_2010; Porter_EJH_2015 | EPIC (NCT01250951) | 80 | × | ✓ | ■ | × | × |
| Cancado_AH_2012 | Cancado_AH_2012 | 31 | × | ✓ | ■ | ■ | ■ |
| Tarawah_EHA_2014 (abstract) | Tarawah_EHA_2014 (abstract) | 18 | × | ✓ | × | ■ | × |
| Ware_Lancet_2016 | TWiTCH (NCT01425307) | 121 | ✓ | × | ✓ | ✓ | × |
| Ware_Blood_2012; Alvarez_AJH_2013 | SWiTCH (NCT00122980) | 133 | ✓ | × | × | × | × |

SF: serum ferritin; SLR: systematic literature review; MRI: magnetic resonance imaging; RCT: randomized controlled trial
*Studies highlighted were selected for the NMA based on the inclusion criteria.
■ Mean/median was reported but standard error / standard deviation of mean/median was not. Mathematically, the reliability weights could not be calculated without a standard error / standard deviation (unless additional assumption was made), and therefore, could not be included in the network meta-analysis model

Figure 20. Study selection flow diagram for network meta-analysis




NMA: network meta-analysis; RCT: randomized controlled trial; SLR: systematic literature review

## 14.3. Design and Patient Characteristics of the Trials

Table 49 and Table 50 summarize the trial design, inclusion/exclusion criteria, and population characteristics in each trial selected for the NMA. Out of the 11 studies identified for full extraction,

only two identified by the SLR were consistent with respect to trial design and inclusion/exclusion criteria. However, differences were noted in the patient characteristics of the included trials. The FIRST trial included patients who had other types of anaemia that were not SCD, while all patients in NCT00067080 had SCD. Furthermore, the majority of the study population in the FIRST trial were Caucasian, in contrast to the Black majority in NCT00067080 trial.

Table 49. Studies of the systematic literature review included in the indirect comparison

| Short reference | Trial Acronym | Trial Arms | Study Design | Population | Total N |
|---|---|---|---|---|---|
| Kwiatkowski_Blood_2022 (36) | LA38-0411 (FIRST) | DFP vs DFO | P4, RCT, open label | Patients aged ≥2 years with SCD or transfusion-dependent anaemia | 228 |
| Vichinsky_BJHaem_2007 (35) | NCT00067080 | DFX vs DFO | P2, RCT, open label | Patients with SCD aged ≥2 with transfusional iron overload | 195 |
| DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; RCT: randomized controlled trial; SCD: sickle cell disease | | | | | |

Table 50. Patient characteristics of the included studies

| Study | FIRST (NCT02041299) | | NCT00067080 | |
|---|---|---|---|---|
| Intervention | DFP | DFO | DFX | DFO |
| Sample size, N | 152 | 76 | 132 | 63 |
| Age<br>mean (SD)<br>median [range] | <br>16.9 (10.2)<br>15 [3, 59] | <br>16.9 (8.5)<br>15 [4, 40] | <br><br>15 [3-54] | <br><br>16 [3-51] |
| Male, n (%) | 83 (54.6%) | 38 (50.0%) | 52 (39.4%) | 28 (44.4%) |
| Race, n (%)<br>Caucasian<br>Black<br>Multi-racial<br>Other | <br>120 (78.9%)<br>23 (15.1%)<br>9 (5.9%) | <br>56 (73.7%)<br>14 (18.4%)<br>6 (7.9%) | <br>8 (6.1%)<br>118 (89.4%)<br><br>6 (4.5%) | <br>3 (4.8%)<br>59 (93.7%)<br><br>1 (1.6%) |
| SCD, n (%) | 126 (82.9%) | 63 (82.9%) | 132 (100%) | 63 (100%) |
| Baseline SF (µg/L)<br>n<br>mean (SD)<br>median [range] | <br>143<br>4114.5 (2385.7)<br>3523.7 [564.1-12630.0] | <br>74<br>4136.9 (2649.1)<br>3610.5 [392.5-13048.0] | <br>132<br><br>3460.0 [1082.0–12901.0] | <br>63<br><br>2834.0 [1015.0–15578.0] |
| Baseline LIC (mg/g dw), n (%)*<br>n<br>≤3 | <br>133 | <br>69 | <br>132<br>4 (3.0%) | <br>63<br>6 (9.5%) |

| | | | | |
|---|---|---|---|---|
| >3 to 7 | 1 (0.8%) | | 64 (48.5%) | 21 (33.3%) |
| >7 to 14 | 61 (45.9%) | 37 (53.6%) | 46 (34.8%) | 20 (31.7%) |
| >14 | 71 (53.4%) | 32 (46.4%) | 18 (13.6%) | 16 (25.4%) |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SCD: sickle cell disease; SD: standard deviation; SF: serum ferritin; LIC: liver iron concentration
* The baseline LIC categories were based on the categories reported in the NCT00067080 trial. Categorized LIC data for the FIRST trial was derived from the individual patient data of the trial

## 14.4. Quality Assessment of Trials

The Cochrane ROB2 tool was used to assess bias among randomized controlled trials. Table 51 reports the results of the quality assessment. The assessment revealed low risk of bias for the two studies included for NMA.

Table 51. ROB2 assessment for randomized controlled trials

| Study | Experimental | Comparator | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|---|---|
| FIRST (NCT02041299) | DFP | DFO | + | ! | + | + | + | + |
| NCT00067080 | DFX | DFO | + | ! | + | + | + | + |

*Legend:* + Low risk; ! Some concerns; - High risk; D1: randomisation process; D2: deviations from the intended interventions; D3: missing outcome data; D4: measurement of the outcome; D5: selection of the reported result; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox

# 15. Appendix III - Methodology of the Network Meta-analysis for Comparative Effectiveness of iron Chelation Agents for the Treatment of Beta-thalassaemia

## 15.1. Systematic Literature Review Methodology

A systematic review was conducted to identify relevant clinical data from the published literature regarding the clinical effectiveness of the three iron chelators, DFP, DFO and DFX, for the treatment of chronic iron overload in people with thalassaemia.

The objectives of the review were two-fold:

- To identify RCT and non-RCT evidence for the efficacy and safety of DFP. Non-RCT studies were considered important to provide supporting evidence, particularly where these studies provide data on a large number of patients and the use of DFP in clinical practice.
- To identify RCT evidence of the relative efficacy and safety of the three iron chelators, and where data gaps existed to inform an indirect comparison.

Searches were conducted in The Cochrane Library, OVID MEDLINE (including MEDLINE In-process) and OVID Embase, with no restrictions on date. Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for the condition, the treatments and the outcomes of interest.

This was supplemented by hand searching of conference proceedings via the internet, from the years 2008 to 2010. The following conference proceedings were searched: the American Society for Haematology; the European Haematology Association Congress; the UK Thalassaemia Society; the Thalassaemia International Conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting.

Identified studies were independently assessed by two reviewers in order to confirm that they met the pre-defined inclusion/exclusion criteria (Table 52) and any discrepancies were resolved by a third party. These documents were checked by a second reviewer to ensure quality and any inconsistencies were resolved through discussion.

Table 52. Eligibility criteria in search strategy

| | Description |
|---|---|
| **Inclusion criteria** | |

| | Description |
|---|---|
| **Population** | Thalassaemia patients with chronic iron overload requiring blood transfusions |
| **Interventions** | DFP or combination therapy of DFP and DFO |
| | DFX |
| | DFO |
| **Outcomes** | Liver iron concentration assessed by MRI T2*, liver biopsy, or superconducting quantum-interference device (SQUID) |
| | Cardiac iron concentration assessed by MRI T2* |
| | Cardiac function assessed by left ventricular ejection fraction (LVEF) or end diastolic volume |
| | Total body iron excretion |
| | Maintenance of iron balance as measured by serum ferritin levels |
| | Induction of negative iron balance as measured by serum ferritin levels |
| | Mortality rates |
| | Adverse effects of treatment |
| **Study design** | Randomized controlled trials (RCTs), prospective controlled and uncontrolled trials, observational studies (prospective and retrospective cohort studies) |
| **Language restrictions** | English language only |
| **Exclusion criteria** | |
| **Population** | Patients with a haemoglobinopathy other than thalassaemia |
| | Patients not requiring blood transfusions |
| **Interventions** | DFO monotherapy single-arm study |
| | DFX monotherapy single-arm study |
| | Non-Ferriprox® DFP |
| | Conference proceedings were excluded if they did not include a DFP monotherapy arm |
| **Outcomes** | Outcomes not listed in the inclusion criteria above |
| **Study design** | Case series and case studies. Any non-RCTs with < 100 participants. |
| | Product and disease reviews |
| | Editorials |
| | Short surveys |
| | Letters |
| **Language restrictions** | Non-English language papers |

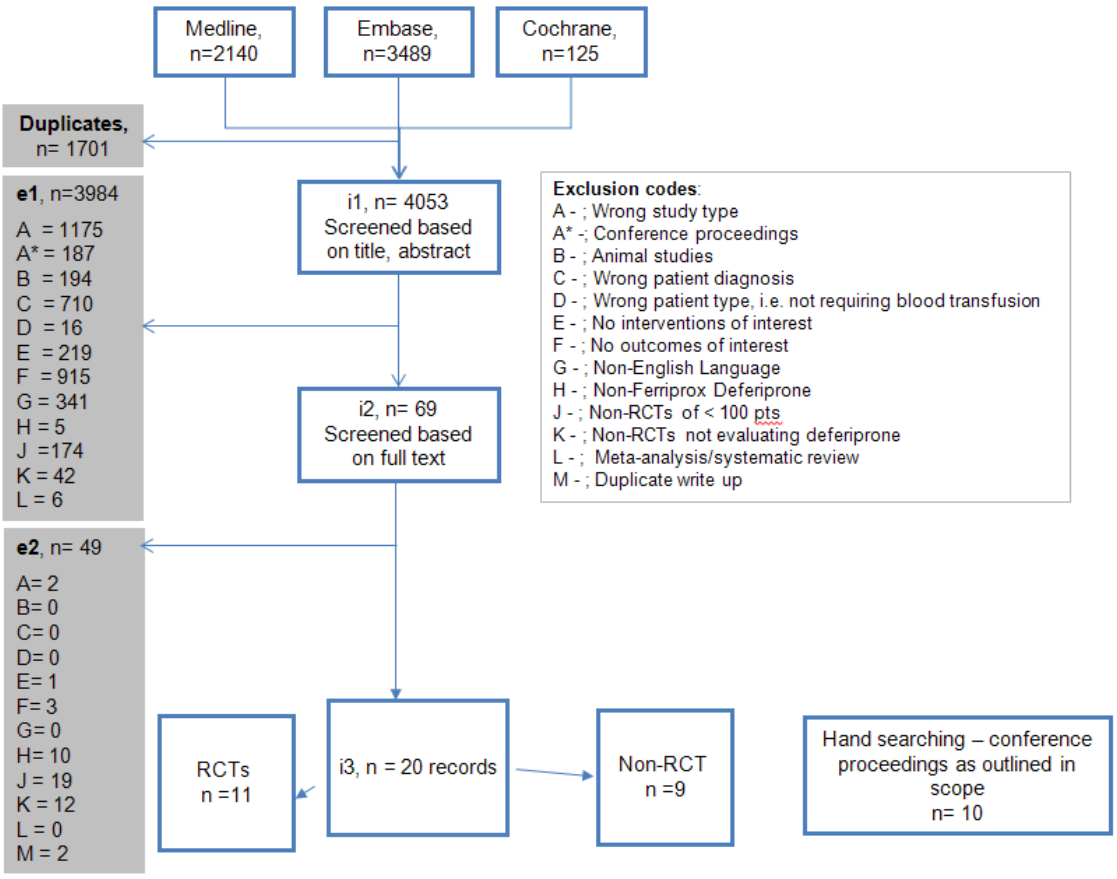
## 15.2. Systematic Literature Review Findings

Following assessment and exclusion of studies based on title, abstract and full text, 20 studies were included in the final data set (11 RCT and 9 non-RCT) (3, 5-9, 11, 13, 18, 19, 21, 22, 76-83).

A further five non-RCT studies (12, 14, 20, 24, 86) that did not meet the inclusion criteria relating either to patient sample size (< 100 patients) or study design (letters), were deemed to provide important additional information (not reported in flow-diagram) (Figure 21).

Conference proceedings that were found in the main searches were excluded at 1st pass. However, as a source of supplementary evidence separate hand searching for conference proceedings was conducted for specific conferences between 2008 and 2010. Ten conferences proceedings relevant to the study population were found.

Figure 21. Schematic for the systematic review




Details of the 11 RCTs included are reported below in Table 53.

Table 53. List of the relevant RCTs

| Short reference | Trial Arms | Study Design | Population | Total N |
|---|---|---|---|---|
| **DFP monotherapy** | | | | |
| Pennell, 2006 (38) | DFP vs DFO | P3, multi-centre, open-label RCT | Patients with homozygous beta-thalassaemia, regularly transfused, chelated with subcutaneous DFO with no symptoms of heart failure prior to screening | 61 |
| Maggio, 2002 (39) | DFP vs DFO | P3, multi-centre, open-label RCT | Patients with thalassaemia major with serum ferritin between 1,500 and 3,000 ng/mL | 144 |
| **DFP-DFO combination therapy** | | | | |
| Tanner, 2007 (40) | DFP + DFO vs DFO | Double-blind placebo-controlled RCT | Patients with diagnosis of TM, currently maintained on subcutaneous DFO therapy, > 18 yrs with mild to moderate myocardial siderosis | 65 |
| **DFP-DFO sequential therapy** | | | | |
| Maggio, 2008 (41) | Sequential DFP + DFO vs DFP alone | P3, RCT, open-label | Thalassaemia major patients with serum ferritin concentrations between 800 and 3,000 µg/L, over 13 yrs of age | 213 |
| Maggio, 2009 (45) | Sequential DFP + DFO vs DFP + DFO vs DFP alone vs DFO alone | Multi-centre, open-label RCT with prospective survival analysis | Patients over 13 yrs of age | 265 |
| Galanello, 2006 (42) | Sequential DFP + DFO vs DFO | P3, RCT, open-label | Patients ≥10 yrs, most serum ferritin values between 1,000 µg/L and 4,000 µg/L and undergoing chelation therapy | 60 |
| **DFO monotherapy** | | | | |
| Modell, 1982 (51) | DFO vs placebo | Randomized controlled trial | Thalassaemia major patients | 19 |
| **DFX monotherapy** | | | | |
| Cohen, 2008 (57) | DFX vs DFO | P3, multi-centre, open-label RCT | Patients at least 2 yrs old with TM and transfusional iron overload (indicated by LIC ≥ 2 mg Fe/g dw. Analysis limited to 541 pts with paired results for LIC | 586 |
| Cappellini, 2006 (43) | DFX vs DFO | P3, RCT | Paediatric (at least 2 yrs of age) and adult patients with a diagnosis of β-thalassaemia with chronic iron overload from blood transfusions indicated by an LIC of 2 mg Fe/g dw or greater. Pts need to be receiving at least 8 blood transfusions/yr | 586 |
| Piga, 2006 (58) | DFX vs DFO | Multi-centre, open-label RCT | Adults with beta-thalassaemia with transfusional hemosiderosis | 71 |
| Nisbet-Brown, 2003 (59) | DFX vs DFX | Double-blind, placebo controlled, dose | Patients with β-thalassaemia with transfusional iron overload, aged 16 yrs and older with serum ferritin values between 1,000 and 8,000 ng//mL and with liver | 24 |
| d: day; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; dw: dry weight; P: phase; RCT: randomized controlled trial; TM: thalassaemia major; wk: week; yrs: years | | | | |

## 15.3. Studies Included in the Meta-analysis and Indirect Comparisons

Studies meeting the inclusion criteria for the systematic review described in Table 53 were included in the meta-analysis if they met at least one of the following additional criteria:

- Reported change from baseline on one of the following outcome measures after one year's treatment:
  - Change from baseline in LIC measured using biopsy or SQUID
  - Change from baseline in serum ferritin levels
  - Change from baseline cardiac MRI T2*
  - Change from baseline in LVEF
- Studies not reporting at least one measure of variability/precision (SE, SD, 95% CI or CV) for any given endpoint were excluded from meta-analyses on that endpoint.
- Studies not published as full journal articles were excluded as they were unlikely to report sufficient detail in the abstract to assess study inclusion and comparability with other studies or extract the required information for meta-analysis.
- Studies reporting only transformed outcomes or geometric means were excluded from analyses of outcomes in which most studies reported outcomes only on a natural scale (e.g., arithmetic means of untransformed data), and vice-versa.

These criteria were specified to ensure that meta-analyses included only studies reporting comparable outcomes for comparable patients.

Eleven RCTs comparing the efficacy and safety of DFP, DFO, and DFX were identified in the systematic literature review. Of these, six studies were deemed to be suitable for inclusion for meta-analysis Table 54.

Table 54. Studies included in the meta-analysis

| Short reference | Trial Arms | Study Design | Population | Total N |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **DFP monotherapy** | | | | |
| Pennell, 2006 (38) | DFP vs DFO | P3, RCT, open-label | Patients with homozygous β-thalassaemia, regularly transfused, chelated with subcutaneous DFO with no symptoms of heart failure prior to screening | 61 |
| Maggio, 2002 (39) | DFP vs DFO | P3, RCT, open-label | Patients with thalassaemia major with serum ferritin between 1,500 and 3,000 ng/mL | 144 |
| **DFP-DFO combination therapy** | | | | |
| Tanner, 2007 (40) | DFP + DFO vs DFO | Double-blind placebo-controlled RCT | Patients with diagnosis of TM, currently maintained on subcutaneous DFO therapy, > 18 yrs with mild to moderate myocardial siderosis | 65 |
| **DFP-DFO sequential therapy** | | | | |
| Maggio, 2009 (41) | Sequential DFP + DFO vs DFP alone | P3, RCT, open-label | Thalassaemia major patients with serum ferritin concentrations between 800 and 3,000 µg/L, over 13 yrs of age | 213 |
| Galanello, 2006 (42) | Sequential DFP + DFO vs DFO | P3, RCT, open-label | Patients ≥10 yrs, most serum ferritin values between 1,000 µg/L and 4,000 µg/L and undergoing chelation therapy | 60 |
| **DFX monotherapy** | | | | |
| Cappellini, 2006 (43) | DFX vs DFO | P3, RCT | Paediatric (at least 2 yrs of age) and adult pts with a diagnosis of β-thalassaemia with chronic iron overload from blood transfusions indicated by an LIC of 2 mg Fe/g dw or greater. Pts need to be receiving at least 8 blood transfusions/yr | 586 |

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; dw: dry weight; LIC: Liver iron concentration; RCT: randomized controlled trial; yrs: years

# 16. Appendix IV: Letter of Support from the Thalassaemia International Federation

**THALASSAEMIA INTERNATIONAL FEDERATION**
In official relations with the World Health Organization

**HEADQUARTERS**
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16 December 2022

To whom it may concern

## LETTER OF SUPPORT

for the ***"Proposal for the Inclusion of Deferiprone in the WHO Model List of Essential Medicines for the Treatment of Transfusional Iron Overload in Adult and Pediatric Patients with Thalassemia Syndromes, Sickle Cell Disease or Other Anemias"***

submitted by Chiesi Farmaceutici S.p.A
to the Expert Committee on Selection and Use of Essential Medicines
of the World Health Organization

Dear Sirs,

In view of the huge unmet needs of transfusion-dependent patients with thalassaemia and other haemoglobin disorders, including sickle cell disease, **the Thalassaemia International Federation is hereby firmly supporting the inclusion of Deferiprone (DFP) in the Essential Medicines List (EML) of the World Health Organization**.

Chelation drugs are an integral part of the clinical management protocols of transfusion-dependent thalassaemias (TDT) but also, in more recent years, of non-transfusion-dependent thalassaemias (NTDT) and sickle cell disease (SCD), affecting an increasing number of patients globally. As proven by clinical studies and practice in the last 30 years, chelation therapy and regular blood transfusion are the cornerstones of the management of haemoglobin disorders, securing the very survival of patients by preventing and treating complications that can lead to high rates of morbidity and premature mortality (e.g. cardiac, hepatic complications, etc.).

The vast genetic heterogeneity, leading to the even greater clinical heterogeneity of people affected with haemoglobin disorders and other transfusion-dependent anaemias, require an individualised, tailor-made treatment approach, involving all three authorised chelators *[i.e. 1) deferoxamine (DFO); 2) deferiprone (DFP); iii) deferasirox (DFX)]*, as some patients are not always tolerant or, even more importantly, responsive to a single drug but need to have access to a particular one or to a combination regimen with at least two of the three authorised chelators. Adverse reactions (v. side effects) of all chelators have been documented and are widely known to physicians through published literature and the marketing authorization applications submitted to regulatory bodies (e.g. FDA, EMA). Deferiprone has presented through the years, further to its effectiveness in reducing iron load in these conditions, an excellent safety profile, which has been described comprehensively by the manufacturing company in the said Proposal.

The contribution of DFP to the reduction of iron load-related complications has been immense, and as a patient-oriented organisation, safeguarding the rights of patients for equal access to quality health and other care, we strongly support its availability and accessibility. Given that **DFP is the only chelation drug alarmingly missing from the WHO EML**, which is used by all countries of the world for the development and updating of national essential medicines lists, we strongly recommend its urgent addition thereto. This is especially important for countries of the developing world, where the 80% of the patient population lives, as they always consult the EML for their national inventories.

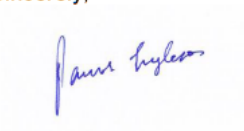
In light of the above, it is the firm position of our Federation[ii] that **all available chelation options must be available and accessible to the treating physicians for the benefit of all patients globally**.

## EXPRESSION OF SUPPORT

The Thalassaemia International Federation (TIF) strongly supports this Proposal as a key step to improve healthcare services and safeguard the right of patients to a decent life, which lies at the heart of the goals of the United Nations 2030 Agenda for Sustainable Development.

We sincerely thank the Applicant for this great effort and hope that the Expert Committee on Selection and Use of Essential Medicines of the World Health Organization will recognise the added value of Deferiprone (DFP).

Sincerely,



Panos Englezos

President,
Thalassaemia International Federation
Honorary President, Pancyprian Thalassaemia Association

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Thalassaemia International Federation

[ii] **ABOUT THE THALASSAEMIA INTERNATIONAL FEDERATION**

The Thalassaemia International Federation (TIF) is a patient-orientated, non-profit, non-governmental umbrella federation, established in 1986 with Headquarters in Nicosia, Cyprus.

**MISSION**: To develop and establish National Control Programmes for the prevention and management of haemoglobinopathies in all affected countries.
**VISION**: To help ensure equal access to quality health care for every patient with thalassemia and other haemoglobin disorders around the world.
**OVERALL PURPOSE**: To act as the global united voice of patients with haemoglobinopathies and particularly for patients with thalassemia.
**VALUES**: (i) Transparency, ethos, accountability, independence and patient centeredness. Objectives, decisions, activities, actions including policy development, communication, and financial issues are governed by the above values, with the patients' benefit being the driving force. (ii) Health and social equity: Fight for securing patients' rights for equal access to quality health and social services regardless of age, gender, ethnicity, political belief or cultural and religious convictions. The disparities and challenges existing within and across countries in all regions of the world including the EU countries with regards to thalassaemia are many. (iii) Improving knowledge and competence: Creation of strong, united, competent patients' associations' to support disease education and establish strong voice for achieving meaningful involvement at a national, European, and International level.

**MEMBERSHIP**: To-date membership boasts 232 members from 64 countries across the globe, including 24 members in 15 EU Member States.

**COLLABORATIONS**: TIF works in official relations with the World Health Organization (WHO) since 1996 and enjoys active consultative status with the United Nations Economic and Social Council (ECOSOC) since 2017. Moreover, it is an Official Partner of the European Commission in the field of Health since 2018 and a member of the Patients and Consumers Working Party (PCWP) of the European Medicines Agency (EMA) since 2010. TIF obtained in 2019 a participatory status at the Council of Europe, as a Member of the Conference of International NGOs. Most remarkably, TIF has been awarded, in the context of the 68th World Health Assembly in May 2015, the 'Dr Lee Jong-wook Memorial Prize' for the Federation's outstanding contribution to public health.

**ACTIVITIES**: Each year TIF undertakes, with the support of its International Scientific Advisory Committee and Patient Advocates Panel, a plethora of activities globally for (i) the empowerment of the patients/parents' community, (ii) the life-long learning of medical professionals working in the field and (iii) the adoption of national health authorities for the adoption of appropriate policies for thalassaemia control.