Common Drug Review
Clinical Review Report

March 2016

Drug	deferiprone (Ferriprox)
Indication	The treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Listing request	As per indication
Dosage form(s)	1000 mg tablets and 100 mg/mL oral solution
NOC date	February 13, 2015
Manufacturer	ApoPharma Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

TABLE OF CONTENTS

Tables

Figure

ABBREVIATIONS

AE	adverse event
CI	confidence interval
CIC	cardiac iron concentration
CDR	CADTH Common Drug Review
DFO	deferoxamine
DFP	deferiprone
DFX	deferasirox
dw	dry weight
EF	ejection fraction
ITT	intention-to-treat
LIC	liver iron concentration
LVEF	left ventricular ejection fraction
MCID	minimal clinically important difference
MRI	magnetic resonance imaging
NA	not available
PP	per-protocol (population)
QoL	quality of life
RAND 36	RAND 36-Item Health Survey, Version 1
RCT	randomized controlled trial
SAE	serious adverse event
SF	shortening fraction
SFC	serum ferritin concentration
SQUID	Superconducting Quantum Interference Device
TFC	Thalassemia Foundation of Canada
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Beta thalassemia, also called Mediterranean anemia, is a rare disease typically found in people of Mediterranean, North African, and South Asian descent. It is a hereditary condition that affects the production of the beta globin chains of hemoglobin. Thalassemia patients require lifelong transfusion therapy that can cause iron overload. Iron chelation is the main therapy for the treatment of iron overload. Deferoxamine (DFO) was the first iron chelator available, and is administered over several hours per day by subcutaneous injection. Deferasirox (DFX) was the first oral iron chelator to be approved in Canada. Deferiprone (DFP) is another oral chelating drug indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

Indication under review
Treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Listing criteria requested by sponsor
As per indication

Results and Interpretation

Included Studies

Seven open-label studies were included in this systematic review. Three studies were considered to be pivotal in the manufacturer's submission: a one-year randomized controlled trial (RCT) (LA16)[1] and two five-year observational retrospective studies (LA12[2,3] and Borgna-Pignatti 2006[4]). In addition to these studies, four published RCTs met the inclusion criteria for this review: one two-year Canadian RCT (LA01),[5-7] and three Italian RCTs (Calvaruso 2015,[8] Maggio 2009,[9,10] and Maggio 2002[2,11]). Calvaruso 2015 and Maggio 2009 were five-year RCTs, while Maggio 2002 was a one-year study. Maggio 2009 was the only study that compared DFP with the sequential use of DFP and DFO (DFP-DFO); all other studies compared DFP with DFO alone. None of the included studies compared DFP with DFX, either alone or in combination (as sequential or add-on therapy) with DFO.

The main limitations of these studies were the observational design of the two pivotal studies and the relatively high discontinuation rates in two studies, namely Borgna-Pignatti (39% in the DFP group) and LA01 (40% and 42% in the DFP and DFO groups, respectively).[4,5] It was not clear how these discontinuations were handled in the data analyses. Furthermore, 13% of patients included in the Borgna-Pignatti study were also included in the LA12 study. Small sample size was another limitation, as it meant that studies were powered for the primary outcomes only. All patients were treated with DFO before entry in the included studies; however, whether this chelation therapy was inadequate was clear. The mean age of patients ranged from 17 years to 41 years old; serum ferritin at baseline ranged from 1,122 to 2,795 mcg/L; and dry liver weight ranged from 3.36 mg/g to 9.15 mg/g.

Five studies reported that patients received DFP at a dose of 75 mg/kg/day.[4,5,8,9,11] The average DFP dose in LA16 was 92 mg/kg/day;[1] it ranged from 25 mg/kg/day to 100 mg/kg/day in LA12.[3] DFO dosing was also varied in the included studies, ranging from 20 mg/kg/day to 50 mg/kg/day for four to seven days per week. The clinical expert consulted by CADTH Common Drug Review (CDR) for the purpose of this review stated that these variations in dosing reflect clinical practice.

Efficacy

In one study,[8] mortality was numerically lower in patients treated with DFP compared with those treated with DFO (4% versus 9.8%), while in another study, mortality was numerically higher in patients treated with DFP compared with those treated with DFP-DFO (3.7% versus 1.9%).[9] In one study, treatment failure occurred at a higher rate in the DFP treatment group compared with the DFP-DFO group (7.4% versus 1.9%),[9] while in another study, there was only one treatment failure reported in each of the DFP and DFO treatment groups.[11] For both survival and treatment failure, the differences between DFP and DFO or DFP-DFO were not statistically significant at five years. However, none of the included studies was powered to detect differences in survival or treatment failure. Therefore, the available evidence does not suggest that there is a differential effect on survival for DFP treatment compared with either DFO or sequential therapy with DFO and DFP, nor does the evidence suggest that there is a difference in the likelihood of treatment failure with DFO and DFP.

Two observational studies reported that DFP treatment was associated with significantly lower rates of cardiac events than DFO treatment (19% versus 5%,[3] and 15% versus 0%,[4] for DFO and DFP, respectively). However, these findings should be interpreted with caution because the design of these studies potentially introduced bias relative to group classification and outcome assessment. In Borgna-Pignatti, for example,[4] treatment groups were defined for each year based on the treatment the patient was receiving on January 1 of the given year. Therefore, it was possible to be classified as receiving one treatment on January 1, switch to a different treatment during the year, and have a cardiac event at a later date in the year. In this case, the event would be attributed, possibly erroneously, to the treatment assigned on January 1.

Furthermore, findings from the observational studies were not supported by the results of the included RCTs in terms of the effects of chelation on left ventricular ejection fraction (LVEF). Three RCTs reported the mean change from baseline in LVEF between DFP and DFO. At one year, the results were not consistent between LA16 and Maggio 2002 or LA01: Maggio et al. 2002 reported that the mean difference between the two treatments (–1.0%; 95% confidence interval [CI]: –3.3 to 1.3) was not significant; however, at two years, in RCT LA01, there was no significant difference between DFP and DFO in terms of effect on LVEF (mean difference 5.4%; $P = 0.4027$). In LA16, DFP was associated with statistically significant amelioration of LVEF compared with DFO (mean difference 2.8%; 95% CI, 1.0 to 4.6; $P = 0.0034$). Of note, LVEF was not the primary outcome in LA16, LA01, or Maggio 2002, and none of these studies was powered to detect statistical differences for this outcome. Therefore, any statistically significant results should be interpreted with caution. Overall, the available evidence suggests a potentially lower cardiac burden in patients treated with DFP compared with those treated with DFO, although this is highly uncertain.

In general, the included studies showed no significant differences between DFP and DFO in terms of their effects on reducing serum ferritin and liver iron concentrations (LICs). However, the findings were more inconsistent with respect to the effects of these treatments on cardiac iron concentrations. For instance, in study LA16, DFP was associated with statistically significantly higher cardiac iron concentration reduction compared with DFO after one year of treatment (16.5 versus 15.01 mLsec; ratio of geometric mean 112%; $P = 0.0228$),[1] while Maggio et al. 2009 reported no significant difference between these treatments after five years.[9]

Five included studies reported rates of treatment compliance. In four studies, compliance with DFP was significantly better than with DFO (mean difference ranged from 4% to 23%), while the pivotal RCT, LA16, showed similar rates of compliance for DFP and DFO (93.7% versus 93.2%, respectively). Given that the non-RCT studies are more reflective of clinical practice, these data suggest that compliance with DFP may be better than compliance with DFO. Quality of life (QoL) data were reported for study LA16 only (using

the RAND 36 questionnaire), and suggested that DFP is not significantly different from DFO with respect to effects on QoL, except within the emotional role domain. However, the interpretation of this observation is limited by the absence of a valid minimal clinically important difference (MCID) to interpret the score differences.

The results of the two published meta-analyses included as supplementary information support the conclusion that DFP and DFO are not different with respect to their effects on mortality, LVEF, serum ferritin concentrations, and LICs.

Harms

Reporting of safety data was inconsistent across the included studies. Of note, rates of treatment withdrawal due to adverse events (WDAE) were higher in the DFP groups (range: 6.9% to 29.3%) than in the DFO treatment groups (range: 0% to 7%). Adverse events (AEs) reported at higher rates in DFP-treated patients versus DFO included nausea, eructation, increased aspartate aminotransferase, electrocardiogram T-wave inversion, and increased appetite (all > 5% more frequent). In addition, leukopenia, neutropenia, or agranulocytosis occurred at higher rates in DFP-treated patients (2.8% to 15.9%) versus DFO patients (0% to 2.8%), while 23% of patients treated with sequential DFP-DFO reported leukopenia, neutropenia, or agranulocytosis. A total of eight patients treated with DFP and 34 patients treated with DFO died during the included studies. These results are consistent with the conclusions of two published meta-analyses, suggesting that DFP is associated with higher rates of AEs compared with DFO.

Conclusions

Five open-label RCTs and two retrospective observational studies were included in this systematic review. Six studies compared DFP with DFO alone, and one RCT compared DFP with sequential DFP and DFO. Study durations ranged from one to five years. The results of these studies suggest that there is no differential effect on survival for DFP treatment compared with either DFO or sequential DFO and DFP, nor does the evidence suggest there is a difference in the likelihood of treatment failure with DFO and DFP. Similarly, the results of the included studies suggest there is no difference between DFP and DFO in terms of reducing serum ferritin and LICs.

The findings of the included studies were inconsistent with respect to the effects of these treatments on cardiac iron concentrations, and the lower rates of cardiac events reported for some studies suggest that DFP treatment might be associated with a potentially lower cardiac burden compared with DFO treatment. However, this is uncertain due to the absence of any difference between these treatments with respect to LVEF. Moreover, any differences between treatments with respect to cardiac burden were not translated into a survival benefit in the included studies. There is evidence that patients are more likely to adhere to DFP treatment compared with DFO, although there was no evidence of any major differences between the effects of these treatments on QoL. The results of the included studies indicated that compared with DFO, DFP treatment is associated with higher rates of discontinuation due to AEs, and that AEs such as leukopenia, neutropenia, or agranulocytosis occurred more frequently in DFP-treated patients compared with DFO-treated patients. The comparative efficacy and harms of DFP compared with the other oral chelator, DFX, are unclear, because none of the included studies compared DFP with DFX, either alone or in combination with DFO as sequential or add-on therapy.

TABLE 1: SUMMARY OF RESULTS

	LA16[1,12,13]		LA12[3,14]		Borgna-Pignatti[4]		LA01[5-7]		Calvaruso 2015[8]		Maggio 2009[9,10,15]		Maggio 2002[2,11]	
Treatment Group	**DFP N = 29**	**DFO N = 32**	**DFP N = 54**	**DFO N = 75**	**DFP N = 157**	**DFO N = 359**	**DFP N = 35**	**DFO N = 36**	**DFP N = 47**	**DFO N = 41**	**DFP N = 108**	**DFP-DFO N = 105**	**DFP N = 71**	**DFO N = 73**
Study Duration	**1 year**		**5 years**		**5 years**		**2 years**		**5 years**		**5 years**		**1 year**	
Survival	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**n = 47**	**n = 41**	**n = 108**	**n = 105**	**NA**	**NA**
Deaths (%)	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	2 (4%)	4 (9.8%)	4 (3.7%)	2 (1.9%)	**NA**	**NA**
Hazard ratio	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	Not reported		Not reported		**NA**	**NA**
P value	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	0.360		0.32		**NA**	**NA**
Treatment Failure	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**n = 108**	**n =105**	**n = 71**	**n = 73**
Events (%)	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	8 (7.4%)	2 (1.9%)	1 (1.4%)	1 (1.4%)
Hazard ratio	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	Not reported		Not reported	
P value	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	0.088		Not significant	
Cardiac Disease-Free Survival	**NA**	**NA**	**n = 50**	**n = 57**	**n = 157**	**n = 359**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Events (%)	**NA**	**NA**	2 (5%)	8 (19.1%)	0	52	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Hazard ratio	**NA**	**NA**	Not reported		0		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
P value	**NA**	**NA**	0.0033		Not calculated		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Change in LVEF	**n = 28**	**n = 31**	**n = 11**	**n = 10**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**n = 71**	**n = 73**
Mean %	3.07%	0.32%	7.3%	1.9%	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	0%	1%
MD (95% CI)	2.8% (1.0 to 4.6)		5.4%		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	–1% (–3.3 to 1.3)	
P value	0.0034		0.4027		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	Not reported	
Cardiac Iron[a]	**n = 29**	**n = 32**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**n = 34**	**n = 20**	**NA**	**NA**
Mean, mLsec	16.51	15.01	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	Not reported		**NA**	**NA**
MD	Not reported		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**			**NA**	**NA**
P value	0.0228		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	> 0.05		**NA**	**NA**
Liver Iron	**n = 27**	**n = 30**	**n = 21**	**n = 24**	**NA**	**NA**	**n = 13**	**n = 13**	**NA**	**NA**	**NA**	**NA**	**n = 20**	**n = 15**
Mean, mcg/g	–0.93	–1.54	2.8	2.2	**NA**	**NA**	0.36	0.69	**NA**	**NA**	**NA**	**NA**	1.02	0.35
MD	0.61		0.6		**NA**	**NA**	–0.3		**NA**	**NA**	**NA**	**NA**	0.67	
P value	0.3961		0.055		**NA**	**NA**	0.8426		**NA**	**NA**	**NA**	**NA**	> 0.05	
Serum Ferritin	**n = 29**	**n = 32**	**n = 49**	**n = 64**	**n = 157**	**n = 359**	**n = 35**	**n = 36**	**n = 47**	**n = 41**	**n = 26**	**n = 32**	**n = 71**	**n = 73**
Mean, mg/L	–181	–466	2,142[b]	2,143[b]	Not reported		187	2	Not reported		–115	–396	–222	–232
MD	285		Not reported				185 (–270.5 to 640.5)				281 (–215.4 to 77.4)		10 (–22.9 to 240.9)	

	LA16[1,12,13]		LA12[3,14]		Borgna-Pignatti[4]		LA01[5-7]		Calvaruso 2015[8]		Maggio 2009[9,10,15]		Maggio 2002[2,11]	
Treatment Group	**DFP N = 29**	**DFO N = 32**	**DFP N = 54**	**DFO N = 75**	**DFP N = 157**	**DFO N = 359**	**DFP N = 35**	**DFO N = 36**	**DFP N = 47**	**DFO N = 41**	**DFP N = 108**	**DFP-DFO N = 105**	**DFP N = 71**	**DFO N = 73**
Study Duration	**1 year**		**5 years**		**5 years**		**2 years**		**5 years**		**5 years**		**1 year**	
P value	0.1598		0.994		< 0.001[c]		Not reported		0.278		Not reported		Not reported	
Mortality	0	0	0	4 (5.3%)	2 (1.3%)	24 (6.7%)	0	0	2 (4.3%)	4 (9.8%)	4 (3.7%)	2 (1.9%)	0	0
AEs	29 (100%)	32 (100%)	Not reported				34 (97%)	35 (97%)	Not reported		59 (56%)	49 (46.7%)	24 (33.8%)	16 (21.9%)
SAEs	2 (6.9%)	0					5 (14.3%)	0	4 (8.6%)	0	Not reported			
WDAEs	2 (6.9%)	2 (6.3%)	Not reported		46 (29.3%)	0	3 (8.6%)	1 (2.8%)	Not reported				5 (7%)	0
Leukopenia, neutropenia, or agranulocytosis	1 (3.4%)	0	Not reported				2 (5.7%)	1 (2.8%)	Not reported		14 (15.9%)	15 (23.1%)	2 (2.8%)	0

AE = adverse event; CI = confidence interval; DFO = deferoxamine; DFP = deferiprone; LVEF = left ventricular ejection fraction; MD = mean difference; MRI = magnetic resonance imaging; NA = not available; SAE = serious adverse events; WDAE = withdrawal due to adverse event.

[a] As measured with T2* MRI.

[b] Mean at the end of period (not the mean change from baseline).

[c] Favouring DFO.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Thalassemia is a rare disease typically found in people of Mediterranean, North African, and South Asian descent. It is a hereditary condition that primarily affects the production of the alpha or beta globin chains of hemoglobin. Beta thalassemia is the prevalent subtype; depending on the severity of the disease, it is classified as major, intermedia, or minor. Severe anemia occurs within the first two years of life in patients with beta thalassemia major, which requires the initiation of lifelong transfusion therapy. Without transfusion therapy, the life expectancy of a beta thalassemia patient is approximately five years.[16] Iron overload is inevitable in these patients due to accumulation from red blood cell transfusions and increased iron absorption secondary to ineffective erythropoiesis. Continued accumulation can lead to iron overload syndrome, or hemosiderosis.[17] If allowed to accumulate, excess iron is deposited in the macrophages of the reticuloendothelial system. When iron stores overwhelm the reticuloendothelial cells, parenchymal iron overload develops and leads to organ dysfunction. This can result in cardiomyopathy, pericarditis, and cardiac arrhythmias; increased susceptibility to infection, liver fibrosis, and cirrhosis; and diseases of the endocrine system, such as diabetes and hypothyroidism.[18] Untreated, the accumulation of iron in various organs will result in death by the second or third decade of life.[19] According to the Thalassemia Foundation of Canada (TFC), there were about 350 cases of transfusion-dependent (meaning more than eight transfusions per year) thalassemia patients in 2006; however, the number of thalassemia patients in Canada continues to grow due to immigration from countries where thalassemia is prevalent.[16] All of these patients will require iron chelation therapy. It is estimated that a large percentage (~70%) of these patients are currently receiving concurrent chelation therapy.[16]

1.2 Standards of Therapy

Iron chelation is the mainstream therapy for iron overload. The initiation of concomitant iron chelation therapy in patients receiving transfusions is dependent on the frequency and volume of transfusions required. In patients with beta thalassemia, major iron overload is inevitable. The typical thalassemic child receiving a hypertransfusion regimen has an intake of 8 mg to 16 mg of elemental iron per day. This is in contrast to an intake of 1 mg to 2 mg per day in the normal population. The institution of concomitant chelation therapy in patients with beta thalassemia major has increased the overall survival of patients to the age of 30 to 55% from 25% in this patient population.[17] For this reason, iron chelation therapy is usually instituted in these patients within a year of the initiation of transfusion therapy. Deferoxamine (DFO) was the first iron chelator available in Canada (2000), and deferasirox (DFX) was the first oral iron chelator to be approved in Canada (2006). A summary of key characteristics of DFO and DFX is provided in Table 2.

According to a guideline published by the Thalassemia Foundation in 2009,[16] DFO is a first-line iron chelator given as 1 g to 2 g by overnight subcutaneous infusion five to seven nights weekly.[16] An alternate form of administration has been the use of 1 g to 2 g twice daily as a subcutaneous bolus administration. Due to the short half-life of DFO, intravenous bolus administration is generally not useful for chronic iron overload. Serum ferritin is monitored regularly with the aim of decreasing ferritin levels to < 1,000 mcg/L. DFX is also recommended in this guideline for patients who are intolerant, non-compliant, or ineffectively chelated with DFO.[16] In Canada, DFX is indicated for the management of chronic iron overload in patients with transfusion-dependent anemias aged six years or older, and for the management of chronic iron overload in patients with transfusion-dependent anemias aged two to five who cannot be adequately treated with DFO.[20] DFO has a varying reimbursement listing: full benefit

in seven provinces and territories (British Columbia, Alberta, Manitoba, New Brunswick, Nova Scotia, Newfoundland, and Yukon); restricted benefit in Saskatchewan; and not listed in Ontario. DFX has a restricted benefit listing in all Canadian provinces and territories except Manitoba and Yukon, where it is not listed.

Hives or local irritation at the injection site have been associated with DFO injections, but are usually controlled by reducing the dose or rate of infusion. DFO is well tolerated by most patients; however, chronic administration has been associated with visual loss and decreases in auditory acuity, although these side effects appear to be reversible upon discontinuation of DFO. The most serious adverse event (SAE) associated with DFO is increased infection with mucormycosis and yersinia.[17] A more critical issue surrounding DFO administration is compliance. This is a particular issue with beta thalassemia major patients as they reach adolescence. Long-term studies in the UK and Italy have indicated that only 50% to 60% of patients are fully compliant with iron chelation DFO therapy, and that this lack of compliance is associated with reduced survival.[17]

In Canada, DFX is indicated in the management of chronic iron overload in patients with transfusion-dependent anemias aged six years or older and in patients aged two to five years who cannot be adequately treated with DFO.[20] The therapeutic dose can range from 10 mg/kg/day to 30 mg/kg/day based on the patient's transfusion rate and trend of iron load.[16] The most frequently occurring adverse events (AEs) in the DFX clinical trials were diarrhea, vomiting, nausea, headache, constipation, dyspepsia, abdominal pain, pyrexia, cough, proteinuria, increases in serum creatinine and transaminases, pruritus, and skin rash.[20]

1.3 Drug

Deferiprone (DFP) is an oral chelating drug with an affinity for ferric ions, binding them in neutral 3:1 (deferiprone:iron) complexes. DFP first became available globally around 1975, and was approved in Canada in May 2015. It is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.[21] The recommended dose is 25 mg/kg to 33 mg/kg body weight orally, three times a day, for a total daily dose of 75 mg/kg to 100 mg/kg body weight.

DFP is available only through a controlled distribution program called Ferriprox Assist. Under this program, only physicians and pharmacists registered with the program are able to prescribe and dispense the product. In addition, DFP can be dispensed only to patients who are registered with and meet the conditions of the Ferriprox Assist program.[21]

Indication under review
Treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
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TABLE 2: KEY CHARACTERISTICS OF DEFEROXAMINE, DEFERIPRONE, AND DEFERASIROX

	Deferoxamine	Deferiprone	Deferasirox
Year of Approval	1982 in US	1999 in Europe and 2011 in US	2005 in US and 2006 in Europe
Year of Approval in Canada	2000	2015	2006
Mechanism of Action	Binds ferric ions in a 1:1 ratio	Binds ferric ions in a 3:1 ratio	Binds ferric ions in a 2:1 ratio
Indication[a]	For the treatment of: • Acute iron intoxication • Chronic iron overload due to transfusion-dependent anemias • Aluminum overload (deferoxamine infusion test) • Chronic aluminum overload in patients with ESRF under • maintenance dialysis	For the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate	For the management of: • Chronic iron overload in patients with transfusion-dependent anemias aged 6 years or older • Patients with transfusion-dependent anemias aged two to five who cannot be adequately treated with DFX • Chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older
Route of Administration	Parenteral (subcutaneous or intravenous)	Oral	Oral
Recommended Dose	20 mg/kg/day to 60 mg/kg/day	75 mg/kg/day (divided in three doses)	10 mg/kg/day to 30 mg/kg/day (once daily)
Serious Side Effects/Safety Issues	Disturbances in hearing or vision; fungal or bacterial infections; dizziness and light-headedness	Agranulocytosis and neutropenia, arthropathy, transient elevation in ALT, and gastrointestinal upset	Acute kidney failure, liver failure, and ulcer or bleeding in the stomach or intestine

ALT = Alanine Aminotransferase; ESRF= end-stage renal failure; DFX = deferasirox.
[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objective

To perform a systematic review of the beneficial and harmful effects of DFP (500 mg, 1,000 mg tablets, and 100 mg/mL oral solution) for the treatment of transfusional iron overload in patients with thalassemia.

2.2 Methods

All manufacturer-provided studies considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3. If trial phase is not explicitly reported, trial size will be used to determine eligibility; trials smaller than the smallest pivotal study will be excluded.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate • Transfusion-dependent (> 8 transfusions/year) vs. transfusion-independent patients • Age groups
Intervention	Deferiprone 25 mg/kg to 33 mg/kg body weight, orally (tablets or solution), three times a day, for a total daily dose of 75 mg/kg to 100 mg/kg body weight
Comparators	Deferasirox, deferoxamine Combination therapies
Outcomes	**Key efficacy outcomes:** Survival Treatment failure Clinical cardiac outcomes Cardiac iron concentration Clinical liver-related outcomes Liver iron concentration Serum ferritin Quality of life, treatment adherence, and satisfaction[a] Work/school absenteeism Hospitalization **Other efficacy outcomes:** Endocrine-related outcomes[a] **Harms outcomes*:*** AEs, SAEs, WDAEs, and mortality **Notable harms:** Agranulocytosis, neutropenia, chromaturia, nausea, abdominal pain, vomiting, arthropathies (arthralgia, arthritis, and arthropathy), and alanine aminotransferase increase
Study Design	Published and unpublished RCTs

AE = adverse event; DB = double-blind; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Outcomes reported in the patients' input submission.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid. A limited PubMed search was performed to capture records not found in MEDLINE.

The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Ferriprox/deferiprone and thalassemia. No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies. The initial search was completed on October 23, 2015. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on February 17, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the Literature

A total of 610 studies were identified from the literature for potential inclusion in the systematic review (Figure 1). The seven included studies are summarized in Table 4 (three pivotal studies) and

Table 5 (four non-pivotal randomized controlled trials [RCTs]) and described in Section 3.2 Included Studies. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

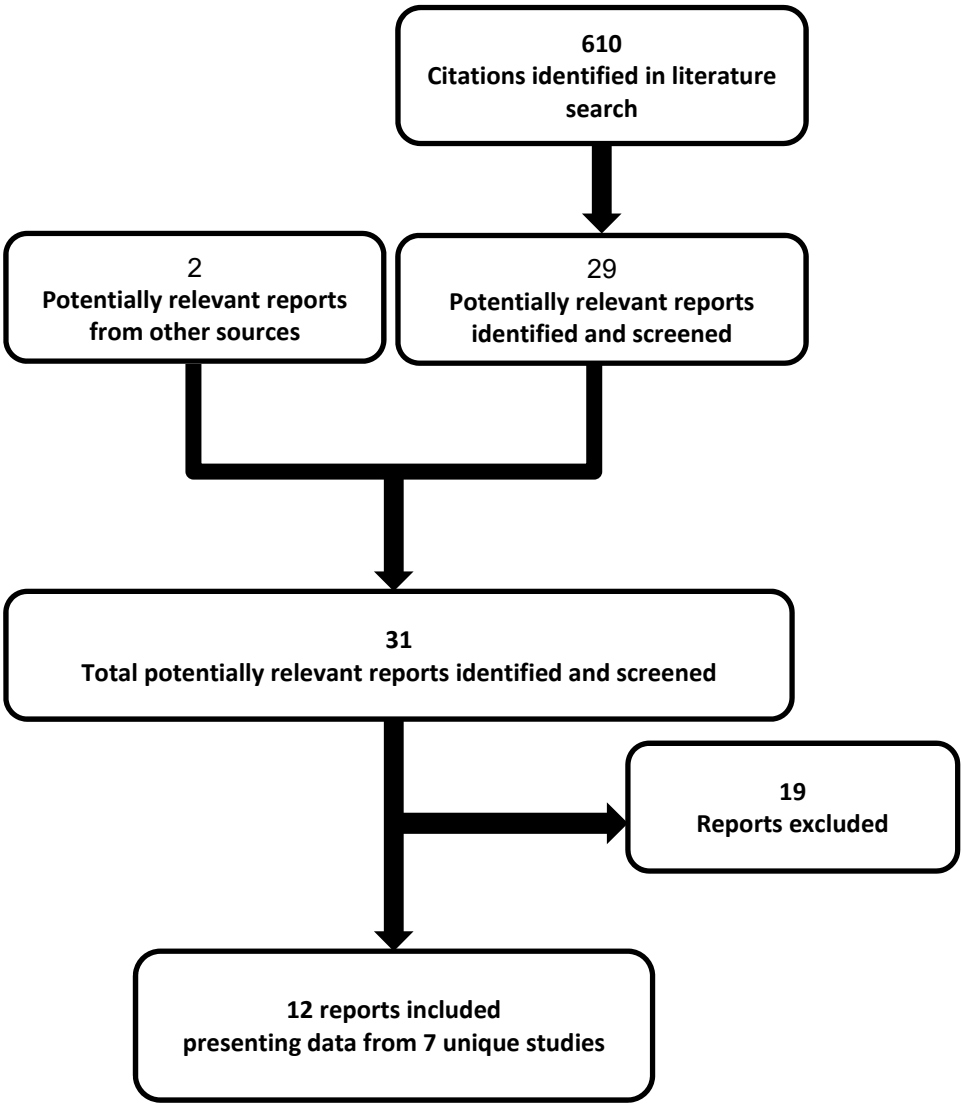

TABLE 4: DETAILS OF INCLUDED PIVOTAL STUDIES

		LA16[1,12,13]	LA12[3,14]	Borgna-Pignatti 2006[4]
DESIGNS & POPULATIONS	**Study Design**	OL RCT	OL **retrospective** study	OL **retrospective** study
	Locations	Italy and Greece	Italy (single centre)	Italy (seven centres)
	Randomized (N)	61	None (168 patient records were analyzed)	None (516[c] patient records were analyzed)
	Inclusion Criteria	Beta TM chelated with SC DFO; 18 years to 36 years; ≤ 8ms cardiac T2* < 20 ms Hb ≥ 9 g/dL/transfusion	Transfusion-dependent beta TM; ≥ 5 years; ≥ 4 years of chelation with DFO or DFP	All TM patients treated in the included centres, born between 1970 and 1993
	Exclusion Criteria	Symptomatic heart failure; severe/significant arrhythmia LVEF < 56%; pre-transfusional Hb < 90 g/L	< 3 SFC records during the last 2 years in file; history of malignancy; HIV infection	Bone marrow transplant; previous cardiac events
DRUGS	**Intervention**	DFP mean dose: 92 mg/kg/d (initial: 75 mg/kg/d; target: 100 mg/kg/d)	DFP: 35 mg/kg/d to 100 mg/kg/d	DFP: 75 mg/kg/d
	Comparator(s)	DFO mean dose: 43 mg/kg for 5.7 d/wk (target: 50 mg/kg/d for ≥ 5 d/wk)	DFO: subcutaneous 20 mg/kg/d to 60 mg/kg/d (4 to 7 d/wk)	DFO: 30 mg/kg/d to 50 mg/kg/d (5 to 6 times/wk)
DURATION	**Phase**	**Phase 3**		
	Run-in			
	Trial treatment	12 months	≥ 4 years (1995 to 2001)	Up to 8 years (1995 to 2003)
	Follow-up			
OUTCOMES	**Primary End Point**	Cardiac T2* MRI	Occurrence of cardiac disease and survival[a]	Incidence of cardiac events
	Other End Points	Cardiac volume and function LIC and SFC	Heart disease-free survival; change in cardiac disease[b]; SFC, LIC, and treatment compliance	All-cause death rate; rate of change in ferritin levels
NOTES	**Publications**	Pennell et al. 2006,[1] Smith et al. 2011[13]	Piga et al. 2003[14]	Borgna-Pignatti et al. 2006[4]

CT = controlled trial; d = day; DFO = deferoxamine; DFP = deferiprone; Hb = hemoglobin; LIC = liver iron concentration; LVEF = left ventricular ejection fraction; OL = open-label; RCT = randomized controlled trial; SC = subcutaneous; SFC = serum ferritin concentration; TM = thalassemia major; wk = week.

[a] Frequency (%) of patients with cardiac disease at the last cardiac assessment, development of cardiac disease during the study among patients who were cardiac disease-free at the first assessment, and heart disease-free survival using the Kaplan–Meier method.

[b] Changes in cardiac condition were classified as deterioration or improvement.

[c] 68/516 (13%) were included in Study LA12.[3,14]

Note: Two additional reports were included: FDA medical reviewers' report,[22] and Health Canada reviewers' report.[23]

TABLE 5: DETAILS OF INCLUDED NON-PIVOTAL RANDOMIZED CONTROLLED TRIALS

	Study	Design	Population	Drugs	Outcomes
1	**LA-01**[5-7,7]	OL RCT: 2-year randomized treatment and 1 year follow-up, Canada	**Randomized: 71** **Inclusion criteria:** patients with homozygous beta thalassemia; 10 ≥ years **Exclusion criteria:** Default on > 20% of visits in the first 3 months of the study; history of malignancy	**DFP:** 75 mg/kg/d for 7 days/week **DFO:** subcutaneous 50 mg/kg/d for 4 to 7 nights/week	**Primary outcome:** LIC **Secondary outcome:** SFC, disease progression,[a] treatment compliance
2	**Calvaruso et al. 2015**[8]	OL RCT: blinded analysis; 5 years (2001-2006) and 5-year follow-up; Italy (multi-centre)	**Randomized: 88** **Inclusion criteria:** TI patients; SFC 800 to 3000 µ/L; ≥ 13 years **Exclusion criteria:** Platelets < 100,000 mm^2 or leukocytes < 3,000/mm^3; severe liver damage; heart failure	**DFP:** 75 mg/kg/d for 7 days/week **DFO:** 50 mg/kg/d for 5 days/week	**Primary outcome:** 5 years' change in SFC **Secondary outcome:** 5-year survival Safety
3	**Maggio 2009**[9,15] **Pantalone 2011**[10]	OL RCT: planned 5 years (2005-2010); actual 2.7 years (2005-2008); Italy (multi-centre)	**Randomized: 213** **Inclusion criteria:** Consecutive TM patients; SFC 800 to 3,000 µ/L; ≥ 13 years **Exclusion criteria:** Platelets < 100,000 mm^2 or leucocytes < 3,000/mm^3; severe liver damage; heart failure	**DFP:** 75 mg/kg/d for 7 days/week **Sequential DFP** for 4 days/week and **DFO** 40 mg/kg/d to 50 mg/kg/d for 3 nights/week	**Primary outcome:** 5 years change in SFC **Secondary outcome:** Survival rate Safety
4	**Maggio 2002**[2,11]	OL RCT: 1 year, Italy	**Randomized: 144** **Inclusion criteria:** Consecutive TM patients treated between 1994 and 1997; SFC ≤ 3,000 mcg/L **Exclusion criteria:** Platelets < 100,000 mm^2 or leucocytes < 3,000/mm^3; severe hepatic insufficiency; symptomatic heart failure	**DFP:** 75 mg/kg/d for 7 days/week **DFO:** 50 mg/kg/d for 5 days/week	**Primary outcome:** SFC at one year **Secondary outcome:** LIC, heart functions (LVEF), treatment compliance, AEs

AE = adverse event; CT = controlled trial; DFO = deferoxamine; DFP = deferiprone; LIC = liver iron concentration; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; OL = open-label; RCT = randomized controlled trial; SC = subcutaneous; SFC = serum ferritin concentration; TI = thalassemia intermedia; TM = thalassemia major.
[a] Disease progression involving specific organ systems known to be affected by iron overload (heart, liver, pituitary) as determined by MRI, MUGA, and quality of life.

3.2 Included Studies

3.2.1 Description of studies

A total of seven studies were included in this review. Three studies were defined as pivotal in the manufacturer's submission: one RCT (LA16 [N = 61])[1] and two observational retrospective studies (LA12[2,3] [N = 168] and Borgna-Pignatti 2006[4] [N = 516]). LA16 was conducted in Italy and Greece, while both observational studies were conducted in Italy. Sixty-eight (13%) of the included patients in Borgna-Pignatti's study had already been included in the LA12 study. In addition to the pivotal studies, four RCTs met the inclusion criteria for this review: one two-year Canadian RCT (LA01)[5-7,7] [N = 71] and three Italian

RCTs (Calvaruso 2015[8] [N = 88], Maggio 2009[9,10] [N = 213], and Maggio 2002[2,11] [N = 144]). Calvaruso 2015 and Maggio 2009 were five-year RCTs, while Maggio 2002 was one-year study.

3.2.2 Populations

a) Inclusion and exclusion criteria

All studies except Calvaruso 2015 included thalassemia major patients, while Calvaruso 2015 included thalassemia intermedia patients.[8] Thalassemia major occurs when a child inherits two mutated genes, one from each parent, while thalassemia intermedia is a term that describes the clinical severity of the disease, usually somewhere between the mild symptoms of the beta thalassemia trait and the severe manifestations of beta thalassemia major. Patients were excluded if they had symptomatic heart failure[1,4,8,9,11] or leukocytopenia.[8,9,11] It appeared that no study had included only patients with currently inadequate therapy.

b) Baseline characteristics

Patient baseline characteristics are summarized in Table 6.

In all included studies except Calvaruso 2015,[8] the mean age of patients ranged from 17[4] years to 26[1] years; the mean age in Calvaruso 2015 was 41 years. In the pivotal observational study LA12, the patients in the DFP group were significantly younger at the start of their first chelation therapy (4.5 years versus 6.8 years) and at the start of the study (17.1 years versus 19.4 years).

The mean serum ferritin concentration (SFC) ranged from 1,122 mcg/L[8] to 2,795 mcg/L.[1] In the pivotal study (LA16), patients randomized to the DFP group had statistically significantly lower SFC (1,791 mcg/L) than those in the DFO group (2,795 mcg/L). In contrast, Borgna-Pignatti's study had relatively more patients with ferritin levels greater than 2,500 g/L among patients in the DFP group (31%) than in the DFO group (21%).[4]

The dry liver weight iron concentration ranged from 3.36 mg/g[11] to 9.15 mg/g.[5] In the observational study LA12, liver iron concentration (LIC) was reported in wet weight, and was statistically significantly higher among patients in the DFP group (1.6 mg/g) than among those in DFO group (0.9 mg/g).[3]

Other variations between treatment groups were also identified within studies. In study LA16, for example, there were more patients who had splenectomy in the DFO group (34%) than in the DFP group (14%).[1] Lower cardiac disease rates were reported at baseline in the DFP groups in LA12 and Maggio 2009 (13% and 1.7%, respectively) compared with the DFO (16%) and DFO-DFP (5%) groups in the two studies, respectively.[3,9]

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS

Study	Study Group	Mean Age, y (SD)	Male n (%)	Cardiac T2* ms (CV%)	EF, % (SD)	LIC, mg/g (SD)	SFC, mcg/L (SD)
LA16[1,12,13]	DFP, N = 29	25.1 (3.8)	15 (52)	13.0 (32)	69.7 (5.4)	6.16 (6.0)	1,791 (1,029)[a]
	DFO, N = 32	26.2 (4.7)	16 (50)	13.3 (30)	68.4 (4.9)	6.32 (5.8)	**2,795 (2,441)**[a]
LA12[3,14b]	DFP, N = 54	17.1 (4.1)[a]	30 (56)	Not reported	Not reported	1.6 (0.7)[a, c]	2,033 (919)
	DFO, N = 75	19.4 (6.9)[a]	38 (51)			0.9 (0.6)[a, c]	1,809 (1,464)
Borgna-Pignatti 2006[4b]	DFP, N = 157	17.5[d]	79 (50)				Reported in ranges[e]
	DFO, N = 359	17.4[d]	184 (51)				
LA-01[5-7]	DFP, N = 35	15.5 (5.5)	18 (51)			9.15 (5.6)	23% had SFC > 2,500 mcg/L
	DFO, N = 36	16.7 (6.6)	18 (50)			7.77 (5.0)	26% had SFC > 2,500 mcg/L
Calvaruso et al. 2015[8]	DFP, N = 47	41.3 (15)	23 (50)		61.6 (5.8)	3.8 (2.8)	1,221 (743)
	DFO, N = 41	41.2 (14)	18 (49)		62.3 (5.6)	3.8 (4.7)	1,122 (910)
Maggio 2009[9,15] **Pantalone 2011**[10]	DFP, N = 108	23 (7.8)	42 (39)	25 (13.3)	Not reported	4.0 (2.3)	1,868 (845)
	DFP-DFO seq, N = 105	23 (8.0)	50 (49)	20.1 (11.9)		4.6 (2.8)	1,727 (669)
Maggio 2002[2,11]	DFP, N = 71	20 (5.3)	37 (48)	Not reported	63 (6)	3.36 (5.49)	2,159 (668)
	DFO, N = 73	19 (3.1)	34 (47)		62 (7)	3.52 (2.97)	2,074 (608)

Cardiac T2* = cardiac magnetic resonance method; CV = coefficient of variation; DFO = deferoxamine; DFP = deferiprone; EF = ejection fraction; LIC = liver iron concentration; SC = subcutaneous; SD = standard deviation; seq = sequential; SFC = serum ferritin concentration; TM = thalassemia major.

[a] Statistically significant difference between the trial groups.

[b] Retrospective observational studies.

[c] Wet weight.

[d] Median.

[e] More than 1,000 mcg/L: DFP = 19 (14%), DFO = 87 (28%); 1,000 to 2,500 mcg/L: DFP = 74 (55%), DFO = 160 (51%); > 2,500 mcg/L: DFP = 42 (31%), DFO = 66 (21%).

c) Previous experience with chelation therapy

Table 7 provides a summary of patients' previous chelation experiences.

In all included RCTs, patients were treated with DFO before study entry. However, none of these studies explicitly restricted trial eligibility based on DFO chelation adequacy. Borgna-Pignatti et al.[4] reported that during the period between 1995 and 2000, eligibility to DFP was a conditioned serum ferritin level greater than 2,000 g/L or an LIC greater than 4 mg/g liver dry weight; patients had to be either non-compliant or intolerant to DFO. At levels beyond 2,000 g/L, DFP became available to all patients.[4]

TABLE 7: SUMMARY OF PATIENTS' PREVIOUS CHELATION EXPERIENCE

Study	Study Group	Mean Age at the Start of Chelation Therapy, y (SD)	Chelation Before Study	Chelation Inadequacy Was a Condition for Study Entry
LA16[1,12,13]	DFP, N = 29	Not reported	DFO ≥ 5 years[a]	No
	DFO, N = 32			
LA12[3,14b]	DFP, N = 54	4.5 (2.7)[a]	All patients received DFO	
	DFO, N =75	6.8 (4.7)[a]		
Borgna-Pignatti 2006[4b]	DFP, N = 157	Not reported	DFO was the first chelator for all patients	Before 2000, DFP was given to non-responders[b] only
	DFO, N = 359			
LA-01[5-7]	DFP, N = 35		Not reported	No
	DFO, N = 36			
Calvaruso et al. 2015[8]	DFP, N = 47		All patients received DFO	
	DFO, N = 41			
Maggio 2009[9,15] **Pantalone 2011**[10]	DFP, N = 108	4.3 (4.1)		
	DFP-DFO seq, N = 105	5.1 (5.2)		
Maggio 2002[2,11]	DFP, N = 71	Not reported		
	DFO, N = 73			

DFO = deferoxamine; DFP = deferiprone; SD = standard deviation.

[a] Patients who received DFP for ≤ 6 months before the trial were considered for eligibility.

[b] Patients had to have a serum ferritin level greater than 2,000 g/L or a liver iron concentration greater than 4 mg/g liver dry weight, and had to be either non-compliant with or intolerant to DFO. Beyond the 2,000 g/L level, DFP became available to all patients. Actual data on inadequate chelation, non-compliance, or intolerance to DFO were not reported.

3.2.3 Interventions

Five studies reported that patients received DFP 75 mg/kg/day;[4,5,8,9,11] the average DFP dose in LA16 was 92 mg/kg/day,[1] and it ranged from 25 mg/kg/day to 100 mg/kg/day in LA12.[3] The clinical expert consulted for this review explained that these variations represent doses used in clinical practice. DFO doses also varied in the included studies, ranging from 20 mg/kg/day to 50 mg/kg/day for four to seven days per week.

In LA12, the definition of analysis groups (DFP or DFO) was based on the total drug exposure for more than four years with each chelator.[3] However, in Borgna-Pignatti 2006, the definition of analysis groups varied from one year to another, and was based on the treatment received by the patient on January 1 of the given year. Therefore, it was possible for patients to be classified as receiving one treatment on January 1, switch treatments during the year, and have a cardiac event at a later date in that year. In this case, the event would be attributed to the January 1 treatment.[4]

Three studies reported the mean blood transfused[11] or transfusional iron input[1,3] (Table 8). The overall mean transfusional iron input was 151.6 mL/kg/year and 157 mg Fe/kg/day for the DFP groups, and 144.3 mL/kg/year and 149.7 mg Fe/kg/year for the DFO groups in LA16 and LA12, respectively.[1,3] The differences between groups were not statistically significant. Maggio et al. 2002 reported that a total of 10,142 mL and 8,380 mL of blood was transfused for DFP and DFO patients, respectively.[11]

TABLE 8: SUMMARY OF AVERAGE TRANSFUSIONAL IRON INPUT

Study	Study Group	Included Patients	Mean (SD)
LA16[1,12,13]	DFP, N = 29	29	151.6 (43.4) mL/kg/year
	DFO, N = 32	31	144.3 (44.4) mL/kg/year
LA12[3,14]	DFP, N = 54 at 6 years	53	157.0 (27.7) mg Fe/kg/year
	DFO, N = 75 at 6 years	71	149.7 (31.0) mg Fe/kg/year
Maggio 2002[2,11]	DFP, N = 71	71	10,142 mL (1,071) total blood transfused during trial
	DFO, N = 73	73	8,380 mL (1,043) total blood transfused during trial

DFO = deferoxamine; DFP = deferiprone; SD = standard deviation.

3.2.4 Outcomes

a) Survival

Two non-pivotal RCTs, Calvaruso 2015 and Maggio 2009,[8,9] used survival as secondary outcomes. The two studies used all-cause death for this analysis. Borgna-Pignatti 2006[4] reported all-cause death rate.

Treatment failure

Treatment failure was defined in three studies as a criterion for stopping the study treatment.[8,9,11] In general, treatment was stopped and alternative therapy was started if ferritin levels increased more than 1,000 mcg/L. Only two studies reported the number of patients who had treatment failure.[9,11]

b) Cardiac-related outcomes

Cardiac-related outcomes were the primary end points in four studies, including the three pivotal studies.[1,3,4,9] In LA16, the primary outcome was the change in cardiac iron concentration (CIC) as measured by T2* magnetic resonance imaging (MRI); the same measure was reported as a secondary outcome in Maggio 2009.[1,9] T2* MRI is commonly used to estimate CIC, with lower T2* values indicating higher concentrations of iron. However, T2* MRI does not directly correlate to left ventricular ejection fraction (LVEF), a measure of heart dysfunction.[24] Transfusion-dependent thalassemia patients with T2* values below 20 ms do not necessarily exhibit LVEF dysfunction; however, those with LVEF dysfunction usually have T2* values below 20 ms.[24] More information about the validity of T2* MRI is provided in APPENDIX 4. LA16 included cardiac functions (LVEF and left ventricular systolic function [LVSF]) as secondary outcomes, and they were measured by cardiac magnetic resonance and echocardiogram.

The primary outcome in the observational LA12 study was incidence of cardiac disease and heart disease-free survival.[3] This was a composite outcome of the following:

- frequency (%) of patients with cardiac disease at the last cardiac assessment
- development of cardiac disease during the study among patients who were cardiac disease-free at the first assessment
- heart disease-free survival using the Kaplan–Meier method.

Secondary cardiac outcomes in LA12 included change in cardiac health status, improvement, or deterioration.[3]

Improvement of cardiac status was defined as:
- shifting from congestive heart failure to asymptomatic cardiopathy (> 6 months)
- improvement of New York Heart Association (NYHA) class (not applicable to class IV)
- improvement of arrhythmia: regression of medication dependence
- improvement of echocardiogram: regression of medication dependence.

Worsening of cardiac status was defined as:
- shifting of congestive heart disease from acute to chronic
- worsening of NYHA class (I to IV)
- worsening of arrhythmia, requiring additional medication or a significant change of it, or indication to ablation or pacemaker
- worsening of the echocardiogram findings (shortening fraction [SF], ejection fraction [EF]) despite the use of medication.

The primary outcome in Borgna-Pignatti was the incidence of cardiac events, including death due to cardiac cause.[4] Cardiac events were defined as cardiac failure or arrhythmias requiring the use of inotropic or antiarrhythmic drugs.

c) Liver-related outcomes

Maggio 2002 was the only study to report liver fibrosis as a measure of liver disease progression. Liver fibrosis was rated according to the Ishak scoring system.

LIC was reported in four studies;[1,3,5,11] it was the primary outcome in LA01 study.[5] LIC is a measure of the level of iron in the liver; it can be evaluated by biopsy or MRI using a superconducting quantum interference device (SQUID). LIC was estimated using SQUID in two studies,[3,5] by liver tissue biopsy in the Maggio 2002 study,[11] and using a combination of SQUID and biopsy in the LA16 study.[1] Iron concentration was reported as mcg/g dry weight in three studies,[1,5,11] and as mcg/g wet weight in LA12.[3] The problems associated with repeated LIC measurements as a means of assessing liver iron burden and response to therapy include: (1) it is an invasive method associated with a certain level of complications; (2) it does not necessarily reflect the degree of iron overload in other tissues, particularly the heart; and (3) it may not provide consistent results due to the variability of iron dispersion in the liver (heavily dependent on size of the sample).[25] Despite these drawbacks, currently, the standard measurement of the degree of excess iron in the body is LIC by biopsy. An MCID for LIC in patients with transfusion-dependent thalassemia was not identified. More information about LIC is provided in APPENDIX 4.

d) Serum ferritin concentration

SFC was the primary outcome in Calvaruso 2015,[8] Maggio 2009,[9] and Maggio 2002,[11] and it was a secondary outcome in the remaining studies. All studies compared the mean change from baseline between the treatment groups except LA12; LA12 compared SFC at one year, two years, and five years, but did not evaluate the mean change from baseline line.[3]

A target SFC of approximately 1,000 mcg/L is generally recommended standard practice in thalassemia and other conditions associated with transfusion-dependent iron overload.[26] Brittenham et al. found an association between hepatic iron concentration and SFC, but point out that a single determination of SFC cannot help to provide a reliable estimate of hepatic iron levels.[27] There seems to be some

uncertainty around the extent to which SFC values are associated to total body iron stores. Furthermore, the correlation of SFC with clinical outcomes, such as cardiac morbidity and mortality, also appears to be unfounded.[28] An MCID for SFC in patients with transfusion-dependent thalassemia was not identified. More information about SFC is provided in APPENDIX 4.

e) Quality of life

One study, LA16, reported QoL data using the RAND 36-Item Health Survey, Version 1 (RAND 36). RAND 36 is a QoL questionnaire composed of eight domains: physical functioning (10 items), role physical (four items), pain index (two items), general health (five items), energy/fatigue (four items), social functioning (two items), role emotional (three items), and emotional well-being (five items), for a total of 35 items. In addition, the survey contains a 36th item, a health transition item used to rate patients' present health compared with their health the previous year.[12]

The APPENDIX 4 provides a summary of the scoring system for the RAND 36 questionnaire. The RAND 36 was validated as a general health survey in its initial development; however, no additional literature assessing the reliability and validity of its psychometric properties in a population with thalassemia or iron overload was identified. An MCID for SFC in patients with transfusion-dependent thalassemia was not identified.

f) Work and school absenteeism, hospitalization, and endocrine disorders

None of the included studies reported on these outcomes.

g) Treatment compliance

Treatment compliance was estimated in five studies.[1,3,5,8,9] Estimation was done mainly by counting the number of returned or used DFP pills and by assessing the total volume of infusions of DFO registered on the electronic pump. No data were reported regarding compliance with the assigned treatment in Borgna-Pignatti.[4]

h) Safety

Safety data were not consistently reported in the included studies. For example, Study LA12 did not report safety information at all.[3] Conversely, in Study LA01, safety reporting emphasized adverse drug reactions rather than general AEs. Adverse drug reactions were defined as AEs that were thought by the investigator to be at least possibly associated with the drug.[5]

3.2.5 Statistical analysis

In study LA16, efficacy outcome analyses were conducted using mixed model analysis.[1] Treatment effect was adjusted for baseline splenectomy status (yes or no) and baseline serum ferritin status (≤ 2,500 mcg/L or > 2,500 mcg/L). QoL data from RAND 36 were analyzed using the Wilcoxon rank-sum test. Responses to the supplemental thalassemia questions were to be summarized categorically, and a categorical regression model was to be used to analyze the data with visit as the repeated measure and treatment, visit-treatment interaction, and baseline response as the covariates.

In Study LA12, no adjustment for demographic or baseline measurement was made in the analysis of various cardiac measures; the author of the trial report claimed that no covariates were identified prior to the study that might influence the comparison of cardio-protective effects between the two therapies. Furthermore, multiplicity (multiple outcome testing) was not considered in this trial.[3]

Borgna-Pignatti used time-to-event analysis.[4] "*The incidence of cardiac events was calculated by treatment group for each calendar year. The definition of "group" for each year was based on the treatment that the patient was receiving on January 1 of the given year. It was possible to therefore be classified on one treatment on January 1, switch treatments during the year, and have a cardiac event at a later date in the year. In this case, the event would be attributed to the January 1 treatment.*" (page 3734)[4]

In Study LA01,[5,7] patients were stratified into two groups prior to randomization: high LIC (≥ 7 mg Fe/g dry weight liver tissue) or low LIC (< 7 mg Fe/g dry weight liver tissue) as determined by chemical assays of their liver tissue obtained by biopsy. Within each stratum, patients were randomized to either treatment.[5] The analysis was based on the mixed model analysis. However, the reviewed reports did not specifically define the covariates used in the mixed models.[5-7]

Calvaruso et al. 2015[8] reported that they accounted for repeated measurements of the primary outcome when they estimated the sample size. The authors used a generalized linear mixed effects model to analyze repeated measurements of serum ferritin levels over time. The model included patient and treatment effects as well as total volume of transfusions.[8]

Maggio et al. 2009[9] accounted for the repeated measurements in their sample size estimation; however, they did not specify if efficacy analyses were adjusted for any covariates.

Maggio et al. 2002[11] used a multiple linear regression model to analyze efficacy variables. The model adjusted for the effects of each patient's sex, age, splenectomy status, total number of transfusions in the year preceding the trial and during the study, cirrhosis, HBsAg, anti-HCV, diabetes, LVEF, and endocrine dysfunction.[11]

a) Analysis populations

Analysis populations were not consistently defined in the included studies. Study LA16 was the only trial to define analysis datasets explicitly, including intention-to-treat (ITT) and per-protocol (PP) populations. These were defined as follows:

ITT population: Patients who had received at least one dose of the drug, and who had at least two measurements, of which one was made after baseline, were included in the ITT analysis. When there were no data available at a particular visit, last observation carried forward was used to fill in the missing data.

PP population: All randomized patients who had completed the study were included in the PP analysis. Patients who were withdrawn from the study because they did not comply with the protocol were not included in the PP population.

For Study LA12,[3] the authors specified full group analysis that included all 129 included patients. In Study LA01,[5] the authors reported that ITT analysis would be used, but they did not provide an explicit definition for this dataset. Calvaruso et al. 2015[8] and Borgna-Pignatti et al. 2006[4] did not specify any analysis dataset. Maggio et al. 2009[9] did not define analyses datasets in the reviewed report. However, the number of patients decreased from 108 and 105 at the beginning of the trial to 26 and 32 in the DFP and DFP-DFO groups, respectively. It is uncertain how the missing observations were accounted for in the analysis. Maggio et al. 2002[11] reported that intention to treatment method was used, but the authors did not specify a definition for the ITT population.

3.3 Patient Disposition

Patient disposition is summarized in Table 9. In LA16,[1] 61 patients were enrolled; 29 were randomized to treatment with DFP and 32 were randomized to treatment with DFO. Two patients (0.7%) in the DFP treatment group and three patients (0.9%) in the DFO treatment group withdrew from the study prior to the end of study.

In Study LA12,[3] the clinical records of 168 patients with beta thalassemia were screened, and 129 patients met all the inclusion and exclusion criteria. Fifty-four patients were analyzed in the DFP group and 75 patients in DFO group.

Borgna-Pignatti et al. 2006[4] included all patients treated for thalassemia major at the participating centres. A total of 516 patients met the study criteria: 359 (70%) were treated with DFO only and 157 (30%) were treated with DFP at some point during the study. A total of 62 DFP patients discontinued treatment before the end of the trial; 46 (31%) patients discontinued as a consequence of clinical or laboratory AEs, and 16 (10%) patients discontinued for other reasons.[4]

In LA01,[5-7,7] four (three DFP, one DFO) of the 75 patients randomized to the study never received therapy. Furthermore, 14 (40%) and 15 (42%) of DFP and DFO patients, respectively, discontinued treatment early. The per-protocol analysis included 23 (65.7%) and 21 (58.3%) of the originally randomized patients in the DFP and DFO groups, respectively.

Calvaruso et al. 2015[8] screened 111 consecutive patients and randomized 88 patients to DFP (N = 47) and DFO (N = 41) groups. Eight patients (19.5%) from the DFO group had early discontinuations of the trial treatment.

Maggio et al. 2009[9] randomized 213 patients to receive DFP alone (N = 108) or DFP-DFO sequentially (N =105). Of these patients, only 26 (24.1%) and 32 (30.5%) were included in the analysis at year 5.

Maggio et al. 2002[11] included 71 and 73 patients in the DFP and DFO groups, respectively, and had five (0.7%) early discontinuations in the DFP group.

TABLE 9: PATIENT DISPOSITION

Study	Screened	Randomized	Study Group	Early Discontinuation	ITT	PP	Safety
LA16[1,12,13]	160	61	DFP, N = 29	2 (0.7%)	29	27	Not reported
			DFO, N = 32	3 (0.9%)	32	29	
LA12[3,14a]	168	0 randomized; 129 included in the analysis	DFP, N = 54	Not reported	54	Not reported	
			DFO, N = 75		75		
Borgna-Pignatti 2006[4a]	Not reported	0 randomized; 516 included in the analysis	DFP, N = 157	62 (39%)	Not reported		
			DFO, N = 359	Not reported			
LA-01[5-7]	Not reported	75	DFP, N = 35	14 (40%)	35	23	Not reported
			DFO, N = 36	15 (42%)	36	21	
Calvaruso et al. 2015[8]	111	88	DFP, N = 47	0	Not reported		
			DFO, N = 41	8 (19.5%)			
Maggio 2009[9,15]	275	213	DFP, N = 108	Not reported		26 at year 5	Not reported

Study	Screened	Randomized	Study Group	Early Discontinuation	ITT	PP	Safety
Pantalone 2011[10]			DFP-DFO seq N = 105			32 at year 5	
Maggio 2002[2,11]	246	144	DFP, N = 71	5 (0.7)	71	Not reported	
			DFO, N = 73	0	73		

DFO = deferoxamine; DFP = deferiprone; ITT = intention-to-treat; PP = per-protocol; seq = sequential.
[a] Retrospective observational studies.

3.4 Exposure to Study Treatments

Only four studies reported drug exposure time (Table 10). The exposure time ranged from one year (27 patient-years) in LA16[1] to almost six years in LA12.[3] In Borgna-Pignatti,[4] the exposure time to DFP was twice that to DFO (4.3 versus two years). Study LA12, in contrast, had statistically significantly lower exposure time to DFP (5.3 years) than to DFO (5.9 years).

TABLE 10: SUMMARY OF AVERAGE DRUG EXPOSURE TIME

Study	Study Group	Mean (SD)
LA16[1,12,13]	DFP, N = 29	27 patient-years
	DFO, N = 32	30 patient-years
LA12[3,14]	DFP, N = 54	5.26 years (0.84)
	DFO, N = 75	5.91 years (0.60)
Borgna-Pignatti 2006[4]	DFP, N = 157	Median 4.3 years
	DFO, N = 359	Median 2 years
LA-01[5-7]	DFP, N = 35	19.7 months
	DFO, N = 36	22 months

DFO = deferoxamine; DFP = deferiprone; SD = standard deviation.

3.5 Critical Appraisal

3.5.1 Internal validity

All included studies were open-label, but they all reported that outcome assessment and data analyses were conducted without knowledge of the allocated therapy. In Studies LA16 and LA12,[1,3] single investigators conducted all assessments of the primary outcomes. This would reduce interpretation variability.

Two pivotal studies had retrospective observational design, and treatment allocation was not randomized.[3,4] Therefore, some patient characteristics or baseline health statuses could potentially affect the choice of treatment and response to treatment in the same time. The authors of LA12 did not adjust for demographic or baseline measurements, and claimed that no covariates were identified prior to the study that might influence the comparison of cardio-protective effect between the two therapies. However, baseline information showed that the DFP group had younger patients at the initiation of trial and chelation therapy, and that the DFP group had higher baseline LICs. However, the effects of these variables on treatment efficacy are unknown. Borgna-Pignatti et al.[4] reported that they adjusted for some of the baseline variables, but none of these adjustments could completely eliminate the effects of unknown confounders. Furthermore, Borgna-Pignatti et al.[4] defined treatment groups for each year based on the treatment the patient was receiving on January 1 of the given year. Therefore, it was possible to be classified on one treatment on January 1, switch treatments during the year, and have a

cardiac event at a later date in the year. In this case, the event would be attributed to the January 1 treatment.[4]

Randomization in the remaining five studies was computer-generated, and was concealed by assigning treatments by telephone contact in three studies.[8,9,11] In Study LA16, allocation concealment was done by enclosing the randomization sequence in paper envelopes.[1] The authors of LA16 did not provide details regarding whether or not attempts were made to hide the sequence with dull or no transparent papers.[1] The authors of Study LA01 did not provide information about the allocation concealment method.

Early discontinuations varied from one study to another, and were relatively high in Borgna-Pignatti (39% in the DFP group) and LA01 (40% and 42% in the DFP and DFO groups).[4,5,7] It was not clear from the reviewed how these discontinuations were handled in the analyses. Furthermore, Borgna-Pignatti et al. did not report the rate of early discontinuation in the DFO group; this could not be interpreted as null early discontinuation in this groups.

3.5.2 External validity

The PICOs of the included studies were discussed with the clinical expert consulted for this review, who confirmed that these characteristics represent the Canadian patient population and clinical practices for the management of iron overload in thalassemia patients. Of the discussed issues, none of the studies really assessed patients with inadequate chelation therapy, while the approved indication is limited to patients who are inadequately chelated with their current therapy. Evidence about DFP efficacy and safety for this subgroup of patients was not identified. Another limitation was the dose of DFO used in the included studies; it ranged from 20 mg/kg/day to 50 mg/kg/day for four to seven days/week. These variations reflected the flexibility of DFO dosing depending on disease progression and patient tolerance of treatment. Another discussed aspect was patient age, which ranged from 15 to 41 years. Although the inclusion criteria in some of the included studies allowed pediatric patients as young as five years old,[3] it seemed that patients younger than 10 years old were under-represented in the included studies. Furthermore, none of these studies conducted subgroup analysis based on patient age to tease out any differences in treatment response based on age.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Section 2.2, Table 3.

3.6.1 Patient survival

Calvaruso et al.[8] compared survival rates between DFP groups and DFO alone, while Maggio et al.[9] compared survival rates between DFP and sequential DFP-DFO at five years (Table 11). Both studies reported that the survival rate between treatment groups did not differ with statistical significance.

TABLE 11: OVERALL SURVIVAL IN THE INCLUDED STUDIES

Study	Study Group	Mortality at 5 Years	Difference in Survival, *P* Value
Calvaruso 2015[8]	DFP, N = 47	2 (4%)	Difference/ratio not reported; *P* = 0.360
	DFO, N = 41	4 (9.8%)	
Maggio 2009[9,15] **Pantalone 2011**[10]	DFP, N = 108	4 (3.7%)	Difference/ratio not reported; *P* = 0.32
	DFP-DFO seq, N = 105	2 (1.9%)	

DFO = deferoxamine; DFP = deferiprone.

3.6.2 Treatment failure

Maggio et al. 2009[9] reported that there was no difference in treatment failure between the two groups (eight [7.4%] on DFP versus two [1.9%] on DFP-DFO sequential; *P* = 0.088). Maggio et al. 2002[11] reported that one patient in each group was withdrawn from the trial because of treatment failure (SFC > 1,000 mcg/L). Of note, none of the included studies was powered to detect differences in survival or treatment failure.

3.6.3 Cardiac-related outcomes

a) Cardiac disease-free survival

Among patients who were initially cardiac disease-free, a total of 10 patients in LA12 had cardiac disease: two (5%) in the DFP group and eight (19.1%) in the DFO group. Heart disease-free survival analysis showed a statistically significant difference between therapy groups in favour of DFP (*P* = 0.0033).[3]

Borgna-Pignatti et al.[4] reported a total of 52 cardiac events during the eight-year studied period, 10 of which were cardiac deaths; all events occurred while on DFO. Of the surviving 42 patients, five died of cardiac disease within four to 47 months after the first cardiac event. Six events occurred in patients who had previously received DFP but were on DFO at the time of the event. The time interval between stopping DFP treatment and the occurrence of the cardiac event ranged from one year and eight months to five years and four months. Eight patients were switched to DFP after developing a cardiac event.[4] The hazard ratio between the two groups was zero.

b) Change from baseline in left ventricular ejection fraction

Table 12 summarizes the mean changes from baseline in LVEF.

In LA16,[1] the mean change from baseline in LVEF showed that patients treated with DFP had significantly greater improvement in LVEF compared with patients treated with DFO (3.07% versus 0.32%; *P* = 0.0034). These results were consistent in both the ITT and PP analyses. Results for LA01 at one year and two years,[7] as well as from Maggio 2002,[11] showed that the differences in mean change from baseline in LVEF were not statistically significant.

TABLE 12: LEFT VENTRICULAR EJECTION FRACTION: MEAN CHANGE FROM BASELINE (%)

Study	Study Group	Included Patients	Cardiovascular Magnetic Resonance	
			Mean (SD)	Mean Difference (95% CI),*P* value
LA16[1,12,13]	DFP, N = 29	28, at 1 year	3.07 (3.58)	2.8 (1.0 to 4.6), *P* = 0.0034
	DFO, N = 32	31 at 1 year	0.32 (3.38)	
LA-01[5-7]	DFP, N = 35	21 at 1 year	6.1 (10.6)	4.9 (–0.53 to 10.3); *P* = 0.54
	DFO, N = 36	20 at 1 year	1.2 (6.8)	
	DFP, N = 35	11 at 2 years	7.3 (16.5)	MD not reported; *P* = 0.4027
	DFO, N = 36	10 at 2 years	1.9 (11.5)	
Maggio 2002[2,11]	DFP, N = 71	71 at 1 year	0 (8)	–1.0 (–3.3 to 1.3), *P* value not reported
	DFO, N = 73	73 at 1 year	1 (6)	

CI = confidence interval; DFO = deferoxamine; DFP = deferiprone; MD = mean difference; SD = standard deviation.

c) Change from baseline in cardiac health status

Results from LA12[3] showed that there were no significant differences in the rates of cardiac health improvement between the DFP and DFO groups (42.9% versus 25.05; *P* = 0.617). However, the same trial showed that DFP was associated with statistically significantly lower rates than DFO of patients with onset of cardiac disease (4% versus 21%; *P* = 0.013) or worsening of cardiac disease (4% versus 20%; *P* = 0.007) during the study.

d) Change from baseline in echocardiogram status

Study LA12[3] showed that the change in cardiac status as measured by SF and EF showed that there were no significant differences in mean SF (Table 13) or mean EF (Table 14) between the two therapy groups from year 0 to the end of the study.

TABLE 13: SHORTENING FRACTION (%) IN PATIENT ECHOCARDIOGRAPHY DURING LA12 STUDY PERIOD

Study	Time Interval During the Study (Years)	DFP Mean ± SD (N)	DFO Mean ± SD (N)	*P* value
LA012[3,14]	0 to 1	37.0 ± 6.1 (28)	36.3 ± 6.6 (24)	0.6725
	1 to 2	32.1 ± 7.4 (5)	33.3 ± 6.6 (9)	0.7686
	2 to 3	35.9 ± 4.0 (39)	35.7 ± 6.1 (57)	0.8297
	3 to 4	36.9 ± 5.8 (20)	36.8 ± 6.4 (32)	0.9212
	4 to 5	35.1 ± 3.8 (31)	34.4 ± 6.4 (54)	0.5104
	≥ 5	36.8 ± 4.2 (49)	35.4 ± 5.1 (59)	0.1290

DFO = deferoxamine; DFP = deferiprone; SD = standard deviation.

TABLE 14: EJECTION FRACTION (%) IN PATIENT ECHOCARDIOGRAPHY DURING LA12 STUDY PERIOD

Study	Time Interval During the Study (years)	DFP Mean ± SD (N)	DFO Mean ± SD (N)	*P* value
LA012[3,14]	0 to 1	70.9 ± 7.2 (28)	69.0 ± 7.0 (24)	0.3235
	1 to 2	64.0 ± 12.6 (5)	63.0 ± 9.8 (9)	0.8748
	2 to 3	72.6 ± 5.4 (39)	71.8 ± 8.1 (57)	0.5711
	3 to 4	73.4 ± 9.7 (20)	73.7 ± 7.5 (32)	0.9051
	4 to 5	72.5 ± 6.0 (31)	69.9 ± 9.0 (54)	0.119, 89578
	≥ 5	69.4 ± 6.6 (49)	69.2 ± 8.4 (59)	0.8848

DFO = deferoxamine; DFP = deferiprone; SD = standard deviation.

e) Arrhythmia

In study LA012,[3] seven patients in the DFP group versus 27 patients in the DFO group had at least two 24-hour Holter assessments performed during the study period. Results showed that there were no significant differences in arrhythmia status (worsening, no change, or improvement) between the two therapy groups from baseline to the end of the study (Table 15).

TABLE 15: FREQUENCY OF PATIENTS (%) WITH CHANGE IN STATUS OF ARRHYTHMIA ASSESSED BY 24-HOUR HOLTER FROM THE FIRST TO LAST ASSESSMENT IN STUDY LA012

Study	Therapy	Worsening		No Change		Improvement		Total
		Cases (%)	*P* value	Cases (%)	*P* value	Cases (%)	*P* value	
LA012[3,14]	DFP	0	0.92	7 (100)	0.81	0	0.92	7
	DFO	1 (3.7)		25 (92.6)		1 (3.7)		27

DFO = deferoxamine; DFP = deferiprone.

3.6.4 Cardiac iron concentration

A summary of change in CICs is provided in Table 16.

In study LA016,[1] the geometric mean of T2* MRI increased to 16.5 ms after 12 months of treatment in patients with DFP, with a significantly greater percentage increase from baseline compared with patients treated with DFO (27% versus 13%; *P* = 0.0228). These results indicate that DFP showed a significantly greater decrease in myocardial iron concentration as determined by the greater increase in T2* MRI values when compared with DFO. Maggio et al. 2009,[9] in contrast, reported that the difference between the two treatments in change from baseline was not statistically significant after five years of treatment.

TABLE 16: MEAN CHANGE FROM BASELINE IN MYOCARDIAL T2*

Study	Study Group	Included Patients	Geometric Mean (SD)	Difference (%), *P* value
LA16[1,12,13]	DFP, N = 29	29 at 1 year	16.51 (NR)	Ratio of means = 112, *P* = 0.0228
	DFO, N = 32	31 at 1 year	15.01 (NR)	
Maggio 2009[9,15] **Pantalone 2011**[10]	DFP, N = 108	34 at 5 years	Not reported	*P* > 0.05
	DFP-DFO seq, N = 105	20 at 5 years		

DFO = deferoxamine; DFP = deferiprone; NR = not reported; SD = standard deviation.

3.6.5 Clinical liver-related outcomes

Maggio et al. 2002 reported that 1.5% versus 1.2% of patients in DFP and DFO groups, respectively, had liver fibrosis during the one-year trial period. The difference between the two treatments was not statistically significant.

3.6.6 Liver iron concentration

Table 17 provides a summary of changes from baseline in LICs.

Studies LA16,[1] LA01,[7] and Maggio 2002[11] showed that there were no significant differences in changes to LIC between the DFP and DFO groups at one and two years. Study LA12 reported the results at one, two, and five years; results showed that the differences in mean changes were not consistent with time. By the end of the first year, the difference between DFP and DFO was not statistically significant, but it became statistically significant at the end of the second year (1.9 mcg/g versus 1.3 mcg/g for DFP and DFO, respectively; *P* = 0.015). This difference became marginally not significant by the end of the fifth year (*P* = 0.055).

TABLE 17: MEAN CHANGE FROM BASELINE IN LIVER IRON CONCENTRATION

Study	Study Group	Included Patients	Dry Weight (mcg/g)		Wet Weight (mcg/g)	
			Mean Change (SD)	MD vs. DFP (95% CI)	Mean Change (SD)	MD, *P* Value
LA16[1,12,13]	DFP, N = 29	27 at 1 year	–0.93 (2.9)	0.61; *P* = 0.3961	Not reported	
	DFO, N = 32	30 at 1 year	–1.54 (2.5)			
LA12[3,14]	DFP, N = 54	8 at 1 year	Not reported		2.1 (1.1)	–0.1; *P* = 0.906
	DFO, N = 75	21 at 1 year			2.2 (2.3)	
	DFP, N = 54	44 at 2 years			1.9 (0.9)	0.6; *P* = 0.0151
	DFO, N = 75	15 at 2 years			1.3 (0.6)	
	DFP, N = 54	21 at 5 years			2.8 (1.1)	0.6; *P* = 0.055
	DFO, N = 75	24 at 5 years			2.2 (1.0)	
LA-01[5-7]	DFP, N = 35	13 at 2 years	0.36 (4.9)	–0.3 (–3.6 to 2.9); *P* = 0.8426	Not reported	
	DFO, N = 36	13 at 2 years	0.69 (3.4)			
Maggio 2002[2,11]	DFP, N = 71	20 at 1 year	1.02 (3.5)	*P* > 0.05		
	DFO, N = 73	15 at 1 year	0.35 (0.5)			

CI = confidence interval; DFO = deferoxamine; DFP = deferiprone; MD = mean difference; SD = standard deviation; vs. = versus.

3.6.7 Serum ferritin

Table 18 summarizes the mean changes in SFC.

Maggio et al. 2009[9] reported that the sequential use of DFP-DFO was associated with a higher decrease in SFC than DFP at the end of first year of study (–417 mcg/L versus –132 mcg/L for DFP-DFO and DFP, respectively). However, this difference became not significant by the end of the fifth year. Borgna-Pignatti et al.[4] reported that the difference between DFP and DFO was statistically significant favouring DFO; the median slope of annual rate of change was reported for DFP (16 mcg/L per year) and DFO (1.3 mcg/L per year). These results showed that ferritin levels were higher in the DFP group.[4] Results from the remaining studies showed that the differences in change in SFC were not statistically significant.[1,3,5,8,11]

TABLE 18: CHANGE IN SERUM FERRITIN CONCENTRATION

Study	Study Group	Included Patients	Mean Change, mcg/L (SD)	MD; *P* Value
LA16[1,12,13]	DFP, N = 29	29 at 1 year	–181 (840)	285; *P* = 0.1598
	DFO, N = 32	32 at 1 year	–466 (739)	
LA12:[3,14] **mean at end point**	DFP, N= 54	46 at 1 year	2,488 (1,216)[a]	*P* = 0.0631
	DFO, N =75	59 at 1 year	1,967 (1624)[a]	
	DFP, N= 54	49 at 5 years	2,142 (957)[a]	*P* = 0.994
	DFO, N =75	64 at 5 years	2,143 (1,481)[a]	
Borgna-Pignatti 2006[4]	DFP, N = 157	Not reported		*P* < 0.001
	DFO, N = 359			
LA-01[5-7]	DFP, N = 35	35 at 2 years	187 (840)	185 (–270.5 to 640.5)
	DFO, N = 36	36 at 2 years	2 (1,104)	

Study	Study Group	Included Patients	Mean Change, mcg/L (SD)	MD; *P* Value
Calvaruso et al. 2015[8]	DFP, N = 47	47 at 5 years	Not reported	*P* = 0.278
	DFO, N = 41	41 at 5 years		
Maggio 2009[9,15] **Pantalone 2011**[10]	DFP, N = 108	74 at 1 year	–132 (724)	285 (74.5 to 495.5)
	DFP-DFO seq, N = 105	78 at 1 year	–417 (589)	
	DFP, N = 108	26 at 5 years	–115 (1,009)	281 (–215.4 to 777.4)
	DFP-DFO seq, N = 105	32 at 5 years	–396 (894)	
Maggio 2002[2,11]	DFP, N = 71	71 at 1 year	–222 (783)	10.0 (–220.9 to 240.9)
	DFO, N = 73	73 at 1 year	–232 (619)	

DFO = deferoxamine; DFP = deferiprone; MD = mean difference; SD = standard deviation; seq = sequential.
[a] Mean at the end of period (not the mean change from baseline).

3.6.8 Quality of life

Table 19 summarizes RAND 36 scores in study LA16.

Study LA16 showed that there were no differences between DFP and DFO in all domains of RAND 36 except the emotional role. Emotional role scores showed that DFP was associated with a statistically significant positive score change (1.2), indicating improvement from baseline, while the DFO score showed a negative change from baseline (–11.1), indicating worsening; *P* = 0.049.

TABLE 19: CHANGE IN RAND 36 SCORE IN STUDY LA16

Study	Domain	Study Group	Baseline	At 1 Year	Mean Change (SD)	Mean Difference
LA16[1,12,13]	**Physical Functioning**	DFP	90 (13.5)	88.5 (13.1)	–1.5 (7.8)	*P* = 0.19
		DFO	88.7 (9.0)	88.2 (13.0)	0.8 (14.0)	
	Physical Role	DFP	95.7 (9.6)	89.8 (24.3)	–4.6 (23.0)	*P* = 0.56
		DFO	91.4 (21.6)	86.7 (21.5)	–8.3 (25.7)	
	Pain Index	DFP	91.4 (10.7)	88.6 (17.3)	0 (19.3)	*P* = 0.29
		DFO	89.2 (12.1)	81.1 (18.4)	–2.5 (20.0)	
	General Health	DFP	57.1 (20.5)	55.6 (21.6)	–0.6 (12.0)	*P* = 0.65
		DFO	58.3 (17.8)	56.2 (21.4)	1.5 (12,6)	
	Energy/Fatigue	DFP	67.8 (15.8)	68.9 (13.7)	0.6 (8.1)	*P* = 0.11
		DFO	71.7 (12.7)	70.8 (16.2)	4.5 (12.0)	
	Social Functioning	DFP	88.4 (16.0)	88.4 (22.7)	–1.4 (20.6)	*P* = 0.81
		DFO	88.7 (15.0)	86.3 (20.1)	–0.4 (21.1)	
	Emotional Role	DFP	90.8 (23.4)	90.1 (27.4)	1.2 (17.3)	*P* = 0.049
		DFO	90.6 (24.3)	75.6 (36.0)	–11.1 (23.7)	
	Emotional Well-being	DFP	74.3 (13.4)	73.5 (16.2)	–1.0 (10.6)	*P* = 0.52
		DFO	71.6 (17.9)	69.7 (19.1)	–0.4 (14.8)	
	Health Transition	DFP	51.7 (11.4)	64.8 (19.9)	1.9 (25.9)	*P* = 0.32
		DFO	57.0 (18.2)	59.2 (20.2)	–3.3 (19.4)	

DFO = deferoxamine; DFP = deferiprone; SD = standard deviation.

3.6.9 Work and school absenteeism

No relevant data were reported in the included studies.

3.6.10 Hospitalization

No relevant data were reported in the included studies.

3.6.11 Endocrine disorders

No relevant data were reported in the included studies.

3.6.12 Treatment compliance

Table 20 provides a summary of treatment compliance in the included studies.

In general, treatment compliance was higher among patients in the DFP groups than those on DFO. The difference between DFP and DFO was not statistically significant in LA16. However, in Studies LA12 and LA01, DFP was associated with statistically significantly higher percentages of compliance (89% and 94.9%) than DFO (85% and 71.6%), respectively. Calvaruso 2015 and Maggio 2002 reported higher compliance percentages in the DFP groups (85% and 93.6%) than in the DFO groups (76% and 70.6%) in the two studies, respectively, but the statistical significance of these differences was not reported.

TABLE 20: SUMMARY OF PATIENT COMPLIANCE

Study	Study Group	Included Patients	Mean % (SD)	Mean Difference (95% CI)
LA16[1,12,13]	DFP, N = 29	29 at 1 year	93.7 (5.3)	1.0 (–18.7 to 20.7)
	DFO, N = 32	32 at 1 year	93.2 (9.7)	
LA12[3,14]	DFP, N = 54	53 at 5 years	89 (7)	4.0 (0.9, 7.2)
	DFO, N = 75	73 at 5 years	85 (11)	
LA-01[5-7]	DFP, N =	19 at 3 years	94.9 (1.1)	23.3 (21.5 to 25.1)
	DFO, N =	18 at 3 years	71.6 (3.7)	
Calvaruso et al. 2015[8]	DFP, N = 47	47 at 5 years	85%	Not reported
	DFO, N = 41	41 at 5 years	76%	
Maggio 2009[9,15] **Pantalone 2011**[10]	DFP, N = 108	Not reported	93.6 (9.7)	
	DFP-DFO seq, N = 105		70.6 (24.1) for DFO and 92.7 (15.2) for DFP	

CI = confidence interval; DFO = deferoxamine; DFP = deferiprone; SAE = serious adverse events; SD = standard deviation; seq = sequential; WDAE = withdrawal due to adverse event.

TABLE 21: KEY EFFICACY OUTCOMES

	LA16[1,12,13]		LA12[3,14]		Borgna-Pignatti[4]		LA01[5-7,7]		Calvaruso 2015[8]		Maggio 2009[9,10,15]		Maggio 2002[2,11]	
Treatment group	DFP	DFO	DFP	DFO	DFP	DFO	DFP	DFO	DFP	DFO	DFP	DFP-DFO	DFP	DFO
Study duration	**1 year**		**5 years**		**5 years**		**2 years**		**5 years**		**5 years**		**1 year**	
Survival	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**N = 47**	**N = 41**	**N = 108**	**N = 105**	**NA**	**NA**
Deaths (%)	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	2 (4%)	4 (9.8%)	4 (3.7%)	2 (1.9%)	**NA**	**NA**
Hazard ratio	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	Not reported		Not reported		**NA**	**NA**
P value	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	0.360		0.32		**NA**	**NA**
Treatment failure	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**N = 108**	**N = 105**	**N = 71**	**N = 73**
Events (%)	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	8 (7.4%)	2 (1.9%)	1 (1.4%)	1 (1.4%)
Hazard ratio	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	Not reported		Not reported	
P value	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	0.088		Not significant	
Cardiac disease-free survival	**NA**	**NA**	**N = 50**	**N = 57**	**N = 157**	**N = 359**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Events (%)	**NA**	**NA**	2 (5%)	8 (19.1%)	0	52	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Hazard ratio	**NA**	**NA**	Not reported		0		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
P value	**NA**	**NA**	0.0033		Not calculated		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Change in LVEF	**N = 28**	**N = 31**	**N = 11**	**N = 10**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**N = 71**	**N = 73**
Mean %	3.07%	0.32%	7.3%	1.9%	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	0%	1%
MD (95% CI)	2.8% (1.0 to 4.6)		5.4%		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	–1% (–3.3 to 1.3)	
P value	0.0034		0.4027		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	Not reported	
Cardiac iron[a]	**N = 29**	**N = 32**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**N = 34**	**N = 20**	**NA**	**NA**
Mean, mLsec	16.51	15.01	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	Not reported		**NA**	**NA**
MD	Not reported		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**			**NA**	**NA**
P value	0.0228		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	> 0.05		**NA**	**NA**
Liver iron	**N = 27**	**N = 30**	**N = 21**	**N = 24**	**NA**	**NA**	**N = 13**	**N = 13**	**NA**	**NA**	**NA**	**NA**	**N = 20**	**N = 15**
Mean, mcg/g	–0.93	–1.54	2.8	2.2	**NA**	**NA**	0.36	0.69	**NA**	**NA**	**NA**	**NA**	1.02	0.35
MD	0.61		0.6		**NA**	**NA**	–0.3		**NA**	**NA**	**NA**	**NA**	0.67	

	LA16[1,12,13]		LA12[3,14]		Borgna-Pignatti[4]		LA01[5-7,7]		Calvaruso 2015[8]		Maggio 2009[9,10,15]		Maggio 2002[2,11]	
Treatment group	DFP	DFO	DFP	DFO	DFP	DFO	DFP	DFO	DFP	DFO	DFP	DFP-DFO	DFP	DFO
Study duration	**1 year**		**5 years**		**5 years**		**2 years**		**5 years**		**5 years**		**1 year**	
P value	0.3961		0.055		**NA**	**NA**	0.8426		**NA**	**NA**	**NA**	**NA**	> 0.05	
Serum ferritin	**N = 29**	**N = 32**	**N = 49**	**N = 64**	**N = 157**	**N = 359**	**N = 35**	**N = 36**	**N = 47**	**N = 41**	**N = 26**	**N = 32**	**N = 71**	**N = 73**
Mean, mg/L	–181	–466	2142[b]	2143[b]	Not reported		187	2	Not reported		–115	–396	–222	–232
MD	285		Not reported				185 (–270.5 to 640.5)				281 (–215.4 to 77.4)		10 (–22.9 to 240.9)	
P value	0.1598		0.994		< 0.001[c]		Not reported		0.278		Not reported		Not reported	

CI = confidence interval; DFO = deferoxamine; DFP = deferiprone; LVEF = left ventricular ejection fraction; MD = mean difference; NA = not available; SD = standard deviation.
[a] As measured with T2* MRI.
[b] Mean at the end of period (not the mean change from baseline).
[c] Favouring DFO.

3.7 Harms

Only those harms identified in the review protocol are reported (see 2.2.1, Protocol). Table 22 summarizes safety findings from the included studies.

3.7.1 Adverse events

In Study LA016,[1] all included patients reported AEs in both the DFP and DFO treatment groups. Statistical analysis of AEs showed that there was a significantly higher incidence of gastrointestinal disorders among patients in the DFP treatment group compared with the DFO treatment group, specifically for nausea (38% versus 0%) and eructation (14% versus 0%). Statistical analysis also showed a significantly higher incidence of increased aspartate aminotransferase (21% versus 3%), electrocardiogram T-wave inversion (17% versus 0%), and increased appetite (31% versus 0%) in the DFP treatment group compared with the DFO treatment group, as well as a significantly higher incidence of weight decrease (0% versus 9%) and cough (0% versus 19%) in the DFO treatment group versus the DFP treatment group.

In Study LA01,[5-7,7] 35 (97.2%) of the 36 DFO patients reported AEs, while 34 (97.1%) of the 35 DFP patients had AEs. Adverse drug reactions, rather than AEs, were detailed in the included reports of this trial. Seventeen (48.6%) DFP patients and 22 (58.3%) DFO patients experienced adverse drug reactions during the study. The most common adverse reaction to DFP was abdominal pain (17%). Other gastrointestinal disturbances included nausea (8.6%), vomiting (8.6%), and dyspepsia (5.7%). Musculoskeletal reactions, such as arthralgia (11%) and arthrosis (5.7%), were also reported with DFP.

Maggio et al. 2009[9] reported that 59 (56%) patients in the DFP group and 49 (46.7%) patients in the DFO-DFP group reported AEs. Three DFP patients (3.4%) were reported to have agranulocytosis, while neutropenia was reported in 12.5% and 23.1% of the DFP and DFP-DFO groups, respectively. Arthralgia was reported in 6.85% and 7.7%, and gastrointestinal (GI) problems were reported in 18.2% and 10.8%, of DFP and DFP-DFO groups, respectively.

Maggio et al. 2002[11] reported that 33.8% and 21.9% of patients in the DFP and DFO groups reported AEs, but they did not specify these AEs. Studies LA12,[3] Borgna-Pignatti,[4] and Calvaruso[8] did not report on AEs.

3.7.2 Serious adverse events

SAEs were reported in three studies. In Study LA016,[1] two DFP patients experienced a total of two SAEs; no patient in the DFO treatment group experienced an SAE. One patient had an episode of cytomegalovirus hepatitis; this was considered possibly related to Ferriprox use, and the patient withdrew from the study prematurely. The other SAE was a corneal abscess (3.5%), and was considered unrelated to the study therapy. In LA01,[5-7,7] five serious adverse drug reactions were reported in the DFP group. Two patients experienced agranulocytosis that resolved upon discontinuation of DFP and treatment with G-CSF. Three other patients experienced transient drops in their neutrophil counts, but these were not confirmed as neutropenia. One patient with congestive cardiac failure was reported in DFO group. Calvaruso et al.[8] reported that four patients in the DFP group and none in the DFO group had agranulocytosis. The development of neutropenia was significantly different between the two groups, affecting six (12.5%) of the DFP patients versus none of the DFO patients ($P = 0.027$).

3.7.3 Withdrawals due to adverse events

In Study LA16,[1] withdrawals due to adverse events (WDAEs) were equally reported in both treatment groups (6.9% of patients on DFP versus 6.3% of patients on DFO). However, in the remaining three studies that reported WDAEs, the withdrawal rate was higher in DFP groups than in DFO groups: 29.3% versus 0,[4] 8.6% versus 2.8%,[5] and 7% versus 0.[11] Borgna-Pignatti et al.[4] reported that 46 (29%) patients discontinued DFP due to AEs that included: an increase in ferritin levels or LIC (13%), arthropathy or arthralgia (6%), neutropenia (5%), agranulocytosis (> 1%), increased levels of alanine aminotransferase (1%), gastric discomfort (1%), worsening of renal failure (1%), and worsening of hepatic insufficiency in a cirrhotic, hepatitis C virus-positive patient (> 1%). In Study LA01,[5-7,7] three DFP patients were withdrawn due to AEs, two because of agranulocytosis, and one due to congestive heart failure related to iron toxicity of the heart tissue. One DFO patient was withdrawn due to congestive heart failure related to iron toxicity of the heart tissue. Maggio et al.[11] reported that five DFP patients were withdrawn from treatment because of recurrences of hypertransaminasemia or leukocytopenia.

3.7.4 Mortality

A total of eight patients treated with DFP and 34 patients treated with DFO died while in the included studies; of these, 24 patients were reported in DFO group in the Borgna-Pignatti study. Calvaruso et al.[8] reported that two DFO patients died due to heart damage and one died due to a surgical complication. Two patients died of cancer (one in each treatment group), and one DFP patient died from an infection (no further details were reported).

TABLE 22: SUMMARY OF SAFETY FINDINGS FROM THE INCLUDED STUDIES

Study	Study Group	Mortality	AE	SAE	WDAE	Leukopenia, Neutropenia, or Agranulocytosis
LA16[1,12,13]	DFP, N = 29	0	29 (100%)	2 (6.9%) (cytomegalo-virus hepatitis; corneal abscess)	2 (6.9%)	1 (3.4)
	DFO, N = 32	0	32 (100%)	0	2 (6.3%)	0
LA12[3,14]	DFP, N= 54	0	Not reported		Not reported	Not reported
	DFO, N = 75	4 (5.3)				
Borgna-Pignatti 2006[4]	DFP, N = 157	2 (1.3%)			46 (29.3%)	
	DFO, N = 359	24 (6.7)			0	
LA-01[5-7]	DFP, N = 35	0	34 (97%)	5 (14.3%)	3 (8.6%)	2 (5.7%)
	DFO, N = 36	0	35 (97%)	0	1 (2.8%)	1 (2.8%)
Calvaruso et al. 2015[8]	DFP, N = 47	2 (4.3%)	Not reported	4 (8.6%)	Not reported	
	DFO, N = 41	4 (9.8%)		0		
Maggio 2009[9,15] **Pantalone 2011**[10]	DFP, N = 108	4 (3.7%)	59 (56%)	Not reported		14/88 (15.9%)
	DFP-DFO seq; N = 105	2 (1.9%)	49 (46.7%)			15/65 (23.1%)
Maggio 2002[2,11]	DFP, N = 71	0	24 (33.8%)	Not reported	5 (7%)	2 (2.8%)
	DFO, N = 73	0	16 (21.9%)		0	0

AE = adverse event; DFO = deferoxamine; DFP = deferiprone; SAE = serious adverse event; seq = sequential; WDAE = withdrawal due to adverse event.

4. DISCUSSION

4.1 Summary of Available Evidence

Seven open-label studies were included in this systematic review; of these, three were defined as pivotal in the manufacturer's submission: a one-year RCT (LA16)[1] and two five-year observational retrospective studies (LA12[2,3] and Borgna-Pignatti 2006[4]). Four published RCTs met the inclusion criteria of this review: one two-year Canadian RCT (LA01)[5-7] and three Italian RCTs (Calvaruso 2015,[8] Maggio 2009,[9,10] and Maggio 2002[2,11]). Calvaruso 2015 and Maggio 2009 were five-year RCTs, while Maggio 2002 was a one-year study. Maggio 2009 was the only study that compared DFP with the sequential use of DFP-DFO; all other studies compared DFP with DFO alone. None of the included studies compared DFP with DFX. DFX is an oral chelator that is recommended after failure of, intolerance to, or non-compliance with DFO;[16] therefore, it might be more appropriate to compare DFP with DFX rather than DFO. Direct and indirect evidence comparing DFX with DFP was not identified in this review.

4.2 Interpretation of Results

4.2.1 Efficacy

According to the clinical expert involved in this review, all included studies' populations were generally reflective of thalassemia patients with transfusional iron overload treated in Canadian practices. However, concerns were raised by the poor representation of pediatric patients. Overall, the patients recruited had been treated with DFO as a chelation drug before switching to DFP, but chelation inadequacy was not an eligibility criterion for trial entry or use of DFP. The use of DFP in these studies is reflective of the Health Canada indication for DFP use as a second-line chelation therapy; however, evidence about the efficacy and safety of DFP in patients who are inadequately chelated with their current therapies was not identified.

Two outcomes of importance identified from patient input were treatment adherence and QoL. Five included studies reported the rates of treatment compliance; in four studies, compliance with DFP was significantly higher (4% to 23%) than compliance with DFO, while the pivotal RCT LA16 showed similar rates of compliance for DFP and DFO (93.7% and 93.2%, respectively). This variation reflects the strict follow-up and patient motivation in the pivotal trial as compared with more naturalistic observational and investigator-initiated studies. Only LA16 reported data relevant to QoL using the RAND 36 questionnaire. The results of this questionnaire showed that DFP failed to show significant differences relative to DFO in QoL except in the emotional role domain. However, the clinical interpretation of this result is limited by the absence of a valid MCID to help with interpretation of the score differences.

Other outcomes of interest for this review were survival and clinical cardiac outcomes. Two RCTs reported survival analyses at five years;[8,9] both trials showed no statistically significant difference in survival between DFP and DFO,[8] or between DFP and sequential DFP-DFO.[9] These findings are in line with a meta-analysis published by Kuo et al.[29] (summarized in APPENDIX 5). Kuo et al. included 157 patients from two studies to compare patient survival between DFP and DFO; they reported a risk ratio of 3.43 (95% confidence interval [CI], 0.16 to 71.36), favouring DFP.[29] Cardiac disease-free survival was reported in both observational studies, LA12 and Borgna-Pignatti.[3,4] The two studies reported that DFP was associated with statistically significant reduction of cardiac events during the observation periods as compared with DFO. However, these findings should be interpreted with caution because the nature of these studies potentially introduces bias relative to treatment allocation and outcome assessment. Borgna-Pignatti, for example,[4] defined treatment groups for each year based on the treatment the patient was receiving on January 1 of the given year. Therefore, it was possible to be classified as

receiving one treatment on January 1, switch treatments during the year, and have a cardiac event at a later date in the year. In this case, the event would be attributed to the January 1 treatment.[4] Furthermore, findings from the observational studies were not confirmed by the included RCTs in terms of LVEF. Three RCTs reported and compared the mean change from baseline in LVEF between DFP and DFO.[1,5,11] At one year, results were not consistent between LA16[1] and Maggio 2006;[11] LA16 showed that DFP was associated with statistically significant amelioration of LVEF compared with DFO (mean difference of 2.8%; *P* = 0.0034); but Maggio et al. 2002[11] reported that the difference between the two treatments was not significant. At five years however, LA01 showed no significant difference between DFP and DFO in terms of LVEF. These results are consistent with the findings of two meta-analyses that included results at one year;[29,30] both showed statistically significant differences between DFP and DFO in terms of LVEF at one year.[29,30] APPENDIX 5 provides a summary of these meta-analyses. A third meta-analysis showed that the difference between the two treatments was not statistically significant in terms of LVEF.[31]

In clinical practice, chelation therapy is commonly monitored through SFC and, to a lesser extent, through liver and CIC as estimated by MRI. In general, the included studies showed that there were no significant differences between DFP and DFO in reducing serum ferritin LICs.[1,3,5,8,9,11] These findings were confirmed by two meta-analyses (Xia et al.[30] and Kuo et al.).[29] Both meta-analyses reported that the differences between DFP and DFO were not statistically significant in terms of SFC. A similar finding of no significant differences was also reported for LIC in the included studies (APPENDIX 5).

The findings for CIC were not consistent. For instance, study LA16 reported that DFP was associated with statistically significant lower CIC compared with DFO after one year of treatment (*P* = 0.0228),[1] while Maggio et al. 2009 reported that there was no significant difference at five years.[9] A meta-analysis by Xia et al.[30] showed that the combined results of three RCTs failed to show a statistically significant difference at one year between DFP and DFO in terms of CIC.

4.2.2 Harms

The patient input reported that DFO is associated with side effects that may hinder adherence to it. As mentioned above, treatment compliance was generally higher in patients treated with DFP compared with those treated with DFO. However, treatment WDAEs were higher in DFP groups than in DFO groups. DFP is expected to improve treatment compliance because of it is more convenient to administer, but it seems the gain is compromised by higher rates of treatment discontinuation due to AEs. AEs that were reported significantly in higher rates with DFP than DFO were nausea, eructation, increased aspartate aminotransferase, electrocardiogram T-wave inversion, and increased appetite. Leukopenia, neutropenia, and agranulocytosis were reported in higher rates with DFP (ranging from 2.8% to 15.9%) compared with DFO (ranging from 0% to 2.8%); 23% of patients treated with sequential DFP-DFO reported leukopenia, neutropenia, or agranulocytosis.[9] One Cochrane review and meta-analysis reported that DFP was associated with a statistically significantly higher rate of AEs than DFO;[31] the risk ratio (95% CI) was 2.24 (1.19 to 4.23). However, the two treatments did not differ statistically in terms of incidence of the composite of leukopenia, neutropenia, and agranulocytosis (risk ratio 2.51, CI 0.66 to 9.55).[31]

4.3 Potential Place in Therapy

This section is based on information provided in draft form by the clinical expert consulted by CDR for the purpose of this review. Chelating drugs have common and significant side effects as well as tolerability issues that limit their acceptability by patients for lifelong use. Along with improved survival of patients with thalassemia syndromes, there is renewed emphasis on the part of clinicians to reduce morbidity among these patients in terms of diabetes and gonadal and other endocrine dysfunctions. The availability of DFP in Canada represents a third chelation option, in addition to DFO and DFX, that will increase the number of options for chelation, permitting a more personalized approach to medicine that tailors treatment according to factors such as individual patient iron burdens, lifestyle choices, and AEs. This could provide optimal long-term adherence to treatment. The use of combination chelation in clinical practice, whereby two chelators are administered together to improve efficacy or reduce dose-limiting toxicities, has also been shown to be beneficial.[32]

5. CONCLUSIONS

Five open-label RCTs and two retrospective observational studies were included in this systematic review. Six studies compared DFP with DFO alone, and one RCT compared DFP with sequential DFP and DFO. Study durations ranged from one to five years. The results of these studies suggest that there is no differential effect on survival for DFP treatment compared with either DFO or sequential DFO and DFP, nor does the evidence suggest there is a difference in the likelihood of treatment failure with DFO and DFP. Similarly, the results of the included studies suggest there is no difference between DFP and DFO in terms of reducing serum ferritin and LICs.

The findings of the included studies were inconsistent with respect to the effects of these treatments on cardiac iron concentrations, and the lower rates of cardiac events reported for some studies suggest that DFP treatment might be associated with a potentially lower cardiac burden compared with DFO treatment. However, this is uncertain due to the absence of any difference between these treatments with respect to LVEF. Moreover, any differences between treatments with respect to cardiac burden were not translated into a survival benefit in the included studies. There is evidence that patients are more likely to adhere to DFP treatment compared with DFO, although there was no evidence of any major differences between the effects of these treatments on QoL. The results of the included studies indicated that compared with DFO, DFP treatment is associated with higher rates of discontinuation due to AEs, and that AEs such as leukopenia, neutropenia, or agranulocytosis occurred more frequently in DFP-treated patients compared with DFO-treated patients. The comparative efficacy and harms of DFP compared with the other oral chelator, DFX, are unclear, because none of the included studies compared DFP with DFX, either alone or in combination with DFO as sequential or add-on therapy.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Thalassemia Foundation of Canada (TFC) is a national not-for-profit organization that provides education and support to Canadians living with thalassemia syndromes. It was originally founded as a support group for patients, and has since grown to include fundraising for medical research, patient outreach programs, and participation in the Thalassemia International Federation (TIF), as well as national and international committees and conferences.

TFC receives funding for educational material and other important initiatives primarily from two pharmaceutical companies, ApoPharma Inc. and Novartis. In addition, the TFC generates funding from its own donor base and fundraising activities throughout the year. No conflicts of interest were declared in the preparation of this submission.

2. Condition-Related Information

TFC gathered information from various sources, including a search of the medical literature (PubMed), a collection of focus group reports, clinical practice guidelines, and other relevant materials from the Cooley's Anemia Foundation (US), TIF, the Canadian Organization for Rare Disorders, and other organizations representing the interests of patients with thalassemia.

TFC stated, based on published literature, that it believes the symptoms of excess iron to be numerous, including endocrine disorders (growth retardation, failure of sexual maturation, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, and, less commonly, adrenal glands), dilated cardiomyopathy, arrhythmias, liver fibrosis, and cirrhosis. TFC also stated that if left untreated, iron overload is usually fatal due to the iron build-up in the myocardium and consequent heart dysfunction. TFC cites the results of a comprehensive evaluation of the burden of transfusion-dependent thalassemia and associated iron overload conducted across 10 countries[33] in which patients and caregivers believed that this condition disrupted their ability to work or attend school, as well as their physical and social interactions. The same study reported that one in five patients felt it was not appropriate for them to have children, given their personal demands and the risk of passing on the syndrome. This study also reported that most patients believed they would have better personal and social lives if they did not have thalassemia and did not have to undergo treatment.[33]

3. Current Therapy-Related Information

There are two iron chelators, other than deferiprone (Ferriprox), that are currently used to treat iron overload in transfusion-dependent thalassemia patients: deferoxamine and deferasirox.

According to TFC, deferoxamine has a "demanding" administration schedule (subcutaneous or intravenous infusion for eight to 12 hours, five to seven times per week). Additionally, the patient group cites published associations of this drug with side effects such as local irritation, high-frequency hearing loss, deafness, retinal damage with impaired vision, growth retardation, and bone abnormalities.[34] TFC believes these side effects and the administration schedule hinder patients' adherence to this chelation regimen. In addition to the demanding administration schedule and side effects, the patient group believes there is a burden on patients' parents (since thalassemia manifests in early infancy), who may

themselves suffer from a thalassemia syndrome. They revealed that parents likely spend substantial amounts of time and effort treating their children.

Deferasirox is a once-daily tablet, and TFC cited published evidence to suggest that its efficacy is equivalent to that of deferoxamine with respect to reducing serum ferritin and liver iron.[20] TFC also cited evidence that patients switching from deferoxamine to deferasirox have improvements in quality of life (QoL), treatment adherence, and satisfaction with their therapy[35] that may be related to the less demanding oral route of administration and lack of injection site adverse events (AEs). Despite these benefits, the patient group cited focus groups conducted by the Cooley's Anemia Foundation identifying a dislike of the taste and texture of deferasirox as an important barrier to treatment adherence.[36] TFC also refers to gastrointestinal issues and skin irritations as being greater barriers for this treatment's adherence and tolerability.

4. Expectations About the Drug Being Reviewed

TFC cited focus groups conducted by the Cooley's Anemia Foundation suggesting that additional oral chelation options could improve adherence and QoL beyond current options.[36] TFC provided citations to numerous published studies to support its contention that deferiprone is as effective an iron chelator as deferoxamine and deferasirox, but is potentially superior to both in removing cardiac iron, which may translate into reduced cardiac mortality and morbidity, and may lead to increased survival.[1,4,21] TFC also cited a study in which patients suggested their lives improved due to improved endocrine function when they used a combined iron chelation therapy that included deferiprone.[32] Although TFC acknowledges the impact of the aforementioned reports on the cardiac benefit of deferiprone, it states that the years of life gained, and improvements in QoL, remain unknown. TFC believes that improved heart and endocrine function, reduced risk of premature death, and ease of oral administration (obtained by treating patients with deferiprone) are goals that will be meaningful to patients and their families.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 23 2015
Alerts:	Monthly search updates until February 17 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Embase, Ovid MEDLINE(R) in process…	
#	**Searches**
1	(deferiprone* or ferriprox or dmohpo or CP20 or apo-066 or apo066 or apo66 or apo-66 or brn1447108 or brn 1447108 or ccris8318 or ccris 8318).ti,ab,ot,rn,kw,hw,nm.
2	30652-11-0.rn,nm.
3	1 or 2
4	(thalassem* or thalassaem*).ti,ab,hw.
5	3 and 4
6	(deferiprone* or ferriprox or dmohpo or CP20 or apo-066 or apo066 or apo66 or apo-66 or brn1447108 or brn 1447108 or ccris8318 or ccris 8318).ti,ab.
7	*deferiprone/
8	6 or 7
9	*thalassemia/
10	thalassem*.ti,ab.
11	9 or 10
12	8 and 11
13	5 use pmez
14	12 use oemezd
15	13 or 14
16	remove duplicates from 15
17	conference abstract.pt.
18	16 not 17

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	October 23 2015
Keywords:	Ferriprox/deferiprone AND thalassemia
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Internet Search
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
El-Beshawy 2008[37]	Did not report outcomes of interest
Aydinok 2007[38]	Smaller studies than the pivotal RCT (N < 61 patients)
Ha 2006[39]	
Aydinok 2005[40]	
Di Stefano 2004[41]	
Gomber 2004[42]	
Elalfy MS, et al. Eur J Haematol. 2015.[43]	Design – not RCT – non-randomized trial
Hagag AA, et al. Infect Disord Drug Targets. 2015;15(2):98-105.[44]	
Ozturk Z, et al. Free Radic Res. 2015;49(3):309-16.[45]	
Pepe A, et al. J Cardiovasc Magn Reson. 2013;15:1.[46]	
Yadav M, et al. JK Practitioner. 2012;17(4):29-34.	
Xia S, et al. PLoS ONE. 2013;8(12):e82662.[30]	Design – not RCT – meta-analysis
Diav-Citrin O, et al. Ther Drug Monit. 2004;26(2):i.[47]	Errata
Galanello R, et al. Haematologica. 2006;91(9):1241-3.[48]	Not intervention of interest
Porter JB, et al. J Cardiovasc Magn Reson. 2013;15:38.[49]	
Tanner MA, et al. Circulation. 2007;115(14):1876-84.[50]	
Zareifar S, et al. Arch Iran Med. 2009;12(5):488-91.[51]	
Song TS, et al. In Vivo. 2014;28(4):645-9.[52]	Pharmacokinetic study – not clinical outcome of interest

RCT = randomized controlled trial.

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Serum ferritin concentration (SFC)
- Liver iron concentration (LIC)
- Cardiac iron concentration (CIC)
- 36-item Short Form Survey from the RAND Medical Outcomes Study (RAND 36)

Findings

TABLE 23: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Validated	MCID	References
SFC	SFC is a measure of the level of ferritin in the blood	No	Unknown	Brittenham et al.[27]
LIC	LIC is a measure of the level of iron in the liver and can be evaluated by biopsy or MRI	Yes		Villeneuve et al.[25]
CIC	CIC is a measure of the level of iron in the heart and can be evaluated by MRI			Carpenter et al.[24]
RAND 36	RAND 36 is a QoL questionnaire that is available to the public for use, and contains a set of generic, coherent, and easily administered QoL measures that rely upon patient self-reporting	No		None

CIC = cardiac iron concentration; LIC = liver iron concentration; MRI = magnetic resonance imaging; QoL = quality of life; RAND 36 = 36-item Short Form Survey from the RAND Medical Outcomes Study; SFC = serum ferritin concentration.

Cardiac Iron Concentration

Cardiac-related mortality due to iron overload is the leading cause of death in patients with transfusion-dependent thalassemia; therefore, early diagnosis and consistent monitoring of CIC is considered to be of the utmost importance.[53] T2* magnetic resonance imaging (MRI) is a technique currently used to assess the severity of cardiac siderosis.[54] MRI is not capable of directly quantifying the iron; however, it is capable of generating images of organs and tissues by subjecting them to a strong homogenous magnetic field and exciting protons with radio waves. The rate at which the protons return to their normal state can be interpreted to generate images. Different organs and tissues are represented by different contrasts in the image, and will darken at different rates depending on their composition.[55] The time in ms required for the image to become twice as dark represents the T2* value.[55] The presence of iron in the organs and tissues creates inhomogeneity in the otherwise homogenous magnetic field created by the MRI, which accelerates the darkening of the images, reducing the T2* value.[55] Therefore, the concentration of iron is inversely proportional to value of T2*, suggesting that shorter T2* values result in higher concentrations of iron.

Assessment of CIC by T2* MRI is recommended once a year for at-risk, transfusion-dependent thalassemia patients, such as those with poorly controlled total body iron.[56] Carpenter et al. report a median value for T2* (derived from a group of normal individuals with no history of transfusion or cardiac disease) of 40 ms.[24] Cardiac iron levels vary widely in thalassemic patients, and are only of concern once T2* values are below 20 ms.[24] Prior to the T2* MRI era, there was no accurate measure to

predict iron-induced cardiac disease; the use of T2* values is currently widely accepted to determine the risk of developing cardiac outcomes, such as morbidity and mortality caused by elevated levels of cardiac iron.[28] T2* values of less than 10 ms indicate a high concentration of cardiac iron, suggesting high risk for developing cardiac outcomes.[28,55] T2* values between 10 ms and 20 ms represent moderate CIC and moderate risk for developing cardiac outcomes.[28,55] T2* values above 20 ms indicate low concentration of cardiac iron and suggest low risk for developing cardiac outcomes.[28,55] Note: these T2* values are only valid when evaluated with a 1.5 T MRI scanner.

Although T2* is commonly used to evaluate the risk of cardiac outcomes, it is not directly correlated to left ventricular ejection fraction (LVEF), a measure of heart dysfunction.[24] Transfusion-dependent thalassemia patients with T2* values below 20 ms do not necessarily exhibit LVEF dysfunction; however, those with LVEF dysfunction usually have T2* values below 20 ms.[24] The discrepancy in correlation between T2* values and LVEF dysfunction is attributed to the latent effect caused by prolonged concentrated cardiac iron levels.[24] Despite this limitation, the use of T2* values in the assessment of risk for cardiac outcomes in thalassemic patients is becoming more prevalent because the technique is fast, robust, and accurate.[28] T2* MRI has also demonstrated good inter-study, inter-observer and inter-scanner reproducibility in multiple studies reported by coefficients of variation (COV) — standard deviation of the difference between two measures divided by the mean of the measures.[24,54,55,57-59] Inter-study reproducibility is demonstrated in multiple studies in which patients were assessed using T2* MRI twice at different time intervals (same day, same week, or same month); COV values ranged between 2.4% and 8.4%.[24,54,55,57,59] Inter-observer reproducibility is demonstrated in multiple studies in which the results were assessed by two different observers; COV values ranged between insignificant and 6.4%.[24,54] Inter-scanner reproducibility is demonstrated in multiple studies in which T2* MRI was evaluated on two different scanners (one of which is considered a reference scanner) for each patient; COV values ranged between small and 5.3%.[24,55] However, there are some limitations to the use of T2* MRI, such as availability and cost.[60] Furthermore, motion during the scan can create artifacts in the MRI image that reduce accuracy.[54] Further, there is no conclusive evidence indicating which software, hardware, or MRI technique is the most accurate for predicting cardiac outcomes.[56]

Liver Iron Concentration

Biopsy is a technique used to measure the level of iron in the liver by medically removing tissue (sampling) for examination. Biopsy is one of the most commonly reported measures used to estimate total body iron stores, and provides the most quantitative, sensitive, and specific means of assessing the body's iron burden. It is considered the reference method for comparison with other techniques, and provides direct assessment of liver iron burden, severity of inflammation, fibrosis, and cirrhosis.[61]

A conservative goal for iron chelation therapy in patients with thalassemia is to maintain optimal body iron corresponding to LICs ≤ 7 mg/g dry weight (dw).[61] Patients with LICs up to 15 mg/g dw are considered to be at increased risk of hepatic fibrosis, diabetes mellitus, and other complications. A normal LIC is less than 1.5 mg/g dw. In patients with hemosiderosis, LIC exceeds 2 mg/g dw, and may reach levels of 55 mg/g dw or higher.[61] The problems associated with repeated LIC measurements as a means of assessing liver iron burden and response to therapy include: it is an invasive method, with a certain level of complications; it is not necessarily reflective of the degree of iron overload in other tissues, particularly the heart; and it may not provide consistent results due to the variability of iron dispersion in the liver (heavily dependent on sample size).[25] Despite these drawbacks, the current standard measurement of the degree of excess iron in the body is LIC by biopsy.

Although LIC is considered the standard measurement, the factors mentioned previously question its relevance with respect to the degree of iron overload in the heart and, by consequence, its relevance to clinical outcomes of interest, such as cardiac morbidity and mortality. It has been suggested that LIC can be determined by MRI techniques with sufficient accuracy when compared with liver biopsy.[62] In a study by Merchant et al., MRI was used to evaluate levels of cardiac iron and liver iron.[28] The results suggested that the correlation between LIC and myocardial iron was poor, and that LIC is an unreliable and non-sensitive predictor of cardiac outcomes.[28]

A minimal clinically important difference (MCID) for LIC in patients with transfusion-dependent thalassemia was not identified.

Serum Ferritin Concentration

The serum ferritin test measures the level of ferritin in the blood, and is one of the most commonly reported measures used to indirectly estimate total body iron stores. SFC is widely used in clinical settings due to its availability, cost, and ease of execution, and because it is relatively non-invasive compared with other tests for iron overload.[63]

Clinically, serum ferritin is used as a marker to assess the progress of iron chelation treatment.[27] In addition, monitoring the ratio of the iron chelation dose to SFC can help reduce the risk of overdosing (which leads to adverse events [AEs]). A target SFC of approximately 1,000 mcg/L is generally recommended standard practice in thalassemia and other conditions associated with transfusion-dependent iron overload.[26] Brittenham et al. found an association between hepatic iron concentration and SFC, but point out that a single determination of SFC cannot contribute to a reliable estimate of hepatic iron levels.[27] There seems to be some uncertainty around the extent to which SFC values are associated with total body iron stores. Ferritin is an acute phase reactant; the correlation between serum ferritin and body iron is not sufficiently precise to be of strong prognostic value, and is also different for different hematological conditions. It is also known to be disproportionately raised in some conditions commonly associated with thalassemia (such as inflammation, tissue damage, ascorbate status, intensity of treatment, and liver disease) or falsely depressed in others (e.g., scorbutic patients; a rather frequent complication of iron overload).[64] Relying on SFC alone can lead to inaccurate assessment of total body iron burden due to the previously mentioned factors, making its validity as a marker for total body iron storage inadequate at best.[53] In addition to its uncertainty with respect to its relation to total body iron burden, the correlation of SFC with clinical outcomes, such as cardiac morbidity and mortality, also appears to be unfounded.[28]

In a study by Merchant et al., SFC was compared between a group of thalassemia patients with cardiac siderosis versus another group of thalassemia patients without cardiac siderosis. The study suggests that there was no statistically significant difference between the two groups.[28] It is important to note that SFC is not considered an adequate marker for the clinical outcomes of interest (cardiac morbidity and mortality) in patients with transfusion-dependent thalassemia, nor has it been systematically compared and validated against a quantitative measure of liver iron, such as biopsy.[63]

An MCID for SFC in patients with transfusion-dependent thalassemia was not identified.

36-item Short Form Survey from the RAND Medical Outcomes Study

The 36-item Short Form Survey from the RAND Medical Outcomes Study (RAND 36) is a quality of life (QoL) questionnaire that is available to the public for use. It contains a set of generic QoL measures that rely upon patient self-reporting.[12] It is a variant of the original 36-item Short Form Survey (SF-36)

questionnaire and differs only in terms of the scoring algorithm.[65] RAND 36 is composed of eight domains: physical functioning (10 items), role physical (four items), pain index (two items), general health (five items), energy/fatigue (four items), social functioning (two items), role emotional (three items), and emotional well-being (five items) for a total of 35 items. In addition, the survey contains a 36th item, a health transition item that is used to rate patients' current health compared with their health the previous year.[12] For each of the eight categories, a subscale score can be calculated. Scores range from 0 to 100, with higher scores indicating better health status. Scoring the RAND 36 is a two-step process. First, pre-coded numeric values are recoded per the scoring key using a predefined table. In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are 0 and 100, respectively.[65] In step two, items in the same domains are averaged together to create the eight domain scores.[65] Items that are left blank (i.e., missing data) are not taken into account when calculating the scale scores. Therefore, scale scores represent the average for all items in the scale to which the patient responded.[65]

RAND 36 was validated as a general health survey in its initial development; however, no additional literature assessing the reliability and validity of its psychometric properties in a population with thalassemia or iron overload was identified.

An MCID for SFC in patients with transfusion-dependent thalassemia was not identified.

Conclusion

The use of T2* MRI in the assessment of risk for cardiac outcomes for thalassemia patients is becoming more prevalent because the technique is fast, robust, and accurate. T2* MRI has demonstrated good inter-study, inter-observer, and inter-scanner reproducibility. Despite its drawbacks, at the present time, the standard measurement of the degree of excess iron in the body is LIC by biopsy. Results suggest that the correlation between LIC and myocardial iron load is poor, and that LIC is an unreliable and non-sensitive predictor of cardiac outcomes. To ensure accurate evaluation of total body iron burden, it is suggested that both the liver and heart be monitored due to their lack of correlation. Brittenham et al. found an association between hepatic iron concentration and SFC, but point out that a single determination of SFC cannot contribute to a reliable estimate of hepatic iron levels. It is important to note that SFC is not considered an adequate marker for the clinical outcomes of interest (cardiac morbidity and mortality) in patients with transfusion-dependent thalassemia, nor has it been systematically compared with and validated against a quantitative measure of liver iron, such as biopsy. RAND 36 was validated as a general health survey in its initial development; however, no additional literature assessing the reliability and validity of its psychometric properties in a population with thalassemia or iron overload was identified. The MCID for CIC, LIC, SFC, and RAND 36 in patients with transfusion-dependent thalassemia was not identified.

APPENDIX 5: SUMMARY OF META-ANALYSES

1. Introduction

The objective of this section is to summarize and critically appraise published and unpublished meta-analyses available for the assessment of comparative efficacy and harms of deferiprone (DFP) versus deferoxamine (DFO) or deferasirox (DFX). This summary will inform the pharmacoeconomic evaluation.

2. Methods

A meta-analysis submitted by the manufacturer was reviewed.[66] In addition, a literature search was undertaken to identify any additional relevant published meta-analyses. A total of nine meta-analyses published between 2005 and 2014 were identified in the literature. The most recent three meta-analyses were included in this section; two were published in 2013[30,31] and one in 2014.[30]

3. Description of Meta-Analyses Identified

A summary of the included meta-analyses is provided in Table 24.

LA36 was a meta-analysis submitted by the manufacturer.[66] The objective of the meta-analysis was to evaluate the efficacy of oral administration of DFP for the treatment of iron overload in patients in whom previous chelation had failed. Chelation failure was defined as iron accumulation above a boundary level, defined by high serum ferritin or liver iron content (LIC), or low cardiac T2* MRI (magnetic resonance imaging) levels. The authors of this meta-analysis included all patients who received DFP in the randomized and non-randomized trials (including single-group studies) submitted to the FDA as part of NDA 21-825; they did not include any comparative analysis against active or placebo treatments. A total of 11 studies were included in the analysis: two randomized controlled trials (RCTs) (LA01[7] and LA16[1]), seven uncontrolled studies, and two observational studies (Borgna-Pignatti[4] and LA12-9907[3]). The primary efficacy end point was change from baseline in serum ferritin; secondary outcomes included change from baseline in cardiac T2* MRI and change from baseline in LIC.

The objective of the Cochrane review by Fisher et al.[31] was to summarize the efficacy and safety data of DFP. The authors included 17 RCTs: eight compared DFP with DFO; five compared DFP with DFO-DFP; nine compared DFP-DFO with DFO; and one compared different doses of DFP. The primary outcome was mortality; secondary outcomes included evidence-reduced end organ damage due to iron deposition, such as cardiac failure, endocrine disease, and surrogate markers of end organ damage (e.g., liver damage, fasting glucose, and cardiac dysfunction). Other outcomes included liver fibrosis, patients' compliance, and measures of iron overload: serum ferritin and LIC.

Xia et al.[30] conducted a meta-analysis to evaluate the efficacy and safety of DFP, DFO, and DFX. The authors included a total of 16 RCTs, nine of which compared DFP with DFO. Efficacy evaluation was based on serum ferritin, LIC, myocardial iron concentration, and left ventricular ejection fraction (LVEF).

Kue et al.[29] included at total of 15 RCTs in their meta-analysis to evaluate the efficacy of DFP monotherapy compared with DFO (seven RCTs), and DFP-DFO combination therapy compared with DFP (four RCTs) or DFO monotherapy (seven RCTs). The authors evaluated mortality, heart failure, endocrine dysfunction, histological evidence of hepatic fibrosis, serum ferritin, myocardial iron content, and LIC as assessed.

TABLE 24: DESCRIPTION OF INCLUDED META-ANALYSES

	LA36[66]	Fisher et al.[31]	Xia et al.[30]	Kuo et al.[29]
Objectives	To evaluate the efficacy of deferiprone in the treatment of iron overload in patients in whom previous chelation[a] had failed.[b] This study was recommended by the FDA to evaluate deferiprone as a second-line treatment for transfusional iron overload.	To compare the clinical efficacy and safety of deferiprone with desferrioxamine for thalassaemia	To assess the efficacy and safety of iron chelators in thalassaemia major	To summarize evidence of the efficacy of DFP monotherapy compared with DFO, and of DFP-DFO combination therapy compared with deferiprone or DFO monotherapy in chronically transfused thalassemia major patients
Population	All patients who received deferiprone in the randomized and non-randomized trials submitted to the FDA as part of NDA 21-825	Patients with thalassaemia who are transfusion-dependent	Patients with thalassemia major	Chronically transfused thalassemia major patients
Intervention	Deferiprone 35 mg/kg/day to 100 mg/kg/day	Deferiprone	Not defined[c]	Deferiprone
Comparator	None	Placebo; deferoxamine; different doses of deferiprone	Deferiprone, deferoxamine, deferasirox, or the combination of deferiprone and deferoxamine	Deferoxamine or the combination of deferiprone and deferoxamine
Outcomes	Assessment of treatment success was based on efficacy data within one year of initiation of Ferriprox therapy: • Change in SFC • cardiac T2* MRI • LIC	Mortality; evidence of reduced end organ damage, including heart and endocrine system; iron concentration in serum or liver; adverse events; patient compliance; cost of interventions	Iron storage; adverse events	Cardiac ejection fraction; endocrine dysfunction; mortality; hepatic fibrosis score; cardiac T2* MRI; LIC
Included studies	**2 RCTs :** LA-01[5-7] and LA16-0102[1,12] **7 uncontrolled trials:** LA-02/06; LA-03; LA-04/06B; LA08-9701; LA-11; LA-15-002; and LA30-0307 **2 observational studies:** Borgna-Pignatti[4] and LA12-9907[3]	**17 unique RCTs:** **8 RCTs compared DFP vs. DFO:** Olivieri 1990; Olivieri 1997; Maggio 2002; Gomber 2004; Aydinok 2005; Ha 2006; Pennell 2006; El-Beshlawy 2008 **5 RCTs compared DFP vs. DFO-DFP:** Gomber 2004; Aydinok 2005; Aydinok 2007; El-Beshlawy 2008;	**16 RCTs:** **9 RCTs compared DFP vs. DFO:** Maggio et al. 2002; Galia 2003; Peng et al. 2003[d]; Gomber 2004; Ha et al. 2006; Pennell et al. 2006; Aydinok et al. 2007[e]; El-beshlawy 2008; Smith et al. 2011[f]	**15 RCTs:** **7 RCTs compared DFP vs. DFO:** Olivieri et al. 1997; Maggio et al. 2002; Di Stefano et al. 2004; Gomber 2004; Ha 2006; Pennell et al. 2006; El-beshlawy 2008 **4 RCTs compared DFP vs. DFP-DFO:** Aydinok et al. 2007; El-

	LA36[66]	Fisher et al.[31]	Xia et al.[30]	Kuo et al.[29]
		Maggio 2009 **9 RCTs compared DFP-DFO vs. DFO:** Mourad 2003; Gomber 2004; Aydinok 2005; Galanello 2006; Ha 2006; Abdelrazik 2007; Tanner 2007El-Beshlawy 2008; Tamaddoni 2010 **1 RCT compared different doses of DFP:** Choudhry 2004		beshlawy 2008; Gomber 2004; Maggio 2009 **7 RCTs compared DFP-DFO vs. DFO:** Mourad et al. 2003; Abdelrazik et al. 2007; Galanello et al. 2006; Ha 2006; Tanner et al. 2007; Kompany et al. 2009; Tamaddoni et al. 2010

DFO = deferoxamine; DFP = deferiprone; LIC = liver iron concentration; MRI = magnetic resonance imaging; RCT = randomized controlled trial; vs. = versus.

[a] Patients had to have standard chelation (deferoxamine and/or deferasirox) therapy.

[b] Chelation failure was defined as a baseline serum ferritin of > 2,500 mcg/L prior to the initiation of deferiprone therapy. Secondary analyses were conducted on patients who showed evidence of a failed response to previous chelation therapy, as defined by: excess cardiac iron stores as demonstrated by a cardiac T2* MRI < 20 ms; or LIC of > 7 mg/g dry weight. The analysis excluded patients who had a ≥ 20% improvement in serum ferritin, LIC, or cardiac T2* MRI values from first to last assessment within the year prior to initiation of deferiprone therapy.

[c] The authors included trials that compared any two treatments from the list.

[d] The study by Peng et al. 2003 was a prospective **non-randomized** study.

[e] The study by Aydinok et al. 2007 was a two-group RCT that compared DFP versus DFP-DFO. The study also included 12 patients who already been taking DFO as a natural control group, but this group was not part of the randomized interventions.

[f] Smith et al. 2011 is a publication related to the LA16 trial, and the main publication for this trial was Pennell et al. 2006.[1] Therefore, patients in this study (LA16) were double-counted.

4. Results

The included published RCTs in the reviewed meta-analyses are listed in Table 24. Of note, Xia et al.[30] included two publications as primary studies that were actually secondary publications for other included studies; Galia et al. 2003[2] is a publication related to Maggio et al. 2002,[11] and Smith et al.[13] 2011 is a publication related to the LA16 trial; the main publication for this trial was Pennell et al. 2006.[1] Therefore, these studies were double-counted in the Xia et al. meta-analysis. Furthermore, the same meta-analysis included one study as an RCT, Peng et al. 2003,[67] while in fact it was a prospective non-randomized study. Finally, Xia et al. included the primary RCT by Aydinok et al. 2007;[68] this study included two randomized groups (DFP versus DFP-DFO), as well as 12 patients who already been taking DFO as a natural control group that was not part of the randomized interventions. Xia et al. included this natural control group in the analysis as part of the randomized patients.

Due to the aforementioned limitations in the Xia et al. meta-analysis and the non-comparative nature of the manufacturer's meta-analyses, results for Fisher et al. and Kuo et al. will be summarized in this section.

Deferiprone compared with deferoxamine

Comparative results between DFP and DFO are summarized in Table 25.

Mortality

Kuo et al.[29] meta-analyzed the results of two studies and reported one case of death in DFP patients and none in DFO groups; the estimated risk ratio of 3.43 was not statistically significant.

Left ventricular ejection fraction

Fisher et al.[31] used data from three RCTs to estimate the difference in mean change of LVEF between DFP and DFO after one year of treatment. The inclusion of 245 patients showed that the two treatments did not differ with statistical significance in improving LVEF. Kuo et al.[29] included the results of one RCT (N = 61) and reported a statistically significant difference of 2.88% (95% confidence interval [CI], 1.12 to 4.64) showing more improvement if LVEF with DFP.

Serum ferritin (mg/L)

Kuo et al.[29] reported that 218 patients from three RCTs showed that the mean difference between DFP and DFO in change of serum ferritin of 0.09 mg/L favouring DFO, but the difference was not statistically significant.

Liver fibrosis

One included study by Kuo et al.[29] reported that DFP and DFO did not significantly differ in the incidence of liver fibrosis; the risk ratio was 1.25 (95% CI, 0.44 to 3.52) favouring DFO.

Liver iron concentration (mg/g dry weight)

Both Kuo et al.[29] and Fisher et al.[31] reported that DFP and DFO did not differ with statistical significance in terms of their effect on LIC after one year of treatment.

Safety

Fisher et al. reported that DFP was associated with a statistically significantly higher rate of adverse events (AEs) than DFO; the risk ratio was 2.24 (95% CI, 1.19 to 4.23). However, the two treatments did not statistically differ in terms of the incidence of leukopenia, neutropenia, or agranulocytosis (risk ratio 2.51; 95% CI, 0.66 to 9.55).

TABLE 25: RESULTS OF RANDOMIZED CONTROLLED TRIALS COMPARING DEFERIPRONE WITH DEFEROXAMINE

Outcomes	LA36[66]	Fisher et al.[31]	Xia et al.[30]	Kuo et al.[29]
RCTs that compared DFP vs. DFO				
Mortality				
Number of studies				2
Number of patients				157
Risk ratio (95% CI)				3.43 (0.16 to 71.36)[a]
Cardiac outcomes: LVEF, mean change from baseline (%)				
Number of studies		3 (at 12 months)	3 (at 12 months)	1
Number of patients		245	229	61
MD (95% CI)		1.76 (–1.42 to 4.93)[b]	–0.31 (–0.57 to –0.05)[a]	2.88 (1.12 to 4.64)[b]
Cardiac outcomes: MRI for myocardial iron concentration, mean				
Number of studies			3 (at 12 months)	
Number of patients			187	
MD (95% CI)			–0.29 (–0.58 to 0.00)[a]	
Serum ferritin, mg/L				
Number of studies			4 (at 12 months)	3 (at 12 months)
Number of patients			258	218
MD (95% CI)			–0.06 (–0.31 to 0.19)[a]	0.09 (–0.11 to 0.28)[a]
Liver fibrosis				
Number of studies				1
Number of patients				36
Risk ratio (95% CI)				1.25 (0.44 to 3.52)[a]
LIC: mean at end point (mg/g dry weight)				
Number of studies		2	3 (at 12 months)	4
Number of patients		53	227	144
MD (95% CI)		1.45 (–0.91 to 3.82)[b]	0.08 (–0.18 to 0.34)[a]	1.46 (-1.06 to 3.98)[a]
Endocrine disorders: mean end–of–study bone mineral density at lumbar level (z score)				
Number of studies				1
Number of patients				22
Risk ratio (95% CI)				0.09 (0.08 to 0.10)[b]
AE				
Number of studies		1		
Number of patients		144		
Risk ratio (95% CI)		2.24 (1.19 to 4.23)[a]		
Leukopenia, neutropenia, and/or agranulocytosis				
Number of studies		5		
Number of patients		323		
Risk ratio (95% CI)		2.51 (0.66 to 9.55)[a]		

AE = adverse event; CI = confidence interval; DFO = deferoxamine; DFP = deferiprone; LIC = liver iron concentration; LVEF = left ventricular ejection fraction; MD = mean difference; MRI = magnetic resonance imaging; RCT = randomized controlled trial; vs. = versus.

[a] Risk ratio < 1 or negative mean difference indicates results favouring DFP.

[b] Risk ratio > 1 or positive mean difference indicates results favouring DFP.

Deferiprone compared with the combination of deferiprone and deferoxamine

Comparative results between DFP and DFO are summarized in Table 26.

Kuo et al.[29] reported results comparing change in serum ferritin between DFP and DFP-DFO, while Fisher et al.[31] reported on LIC. Both reviews reported that DFP and DFP-DFO did not statistically differ in terms of change in serum ferritin or LIC.

Fisher et al.[31] reported that DFP did not differ from DFP-DFO in rates of AEs or leukopenia, neutropenia, or agranulocytosis.

TABLE 26: RANDOMIZED CONTROLLED TRIALS COMPARING DEFERIPRONE WITH DEFERIPRONE-DEFEROXAMINE

Outcomes	LA36[66]	Fisher et al.[31]	Xia et al.[30]	Kuo et al.[29]
RCTs that compared DFP vs. DFP-DFO				
Serum ferritin				
Number of studies				3
Number of patients				154
Mean difference (95% CI)				–0.58 (–1.11 to –0.04)[a]
LIC: mean at end point (mg/g dry weight)				
Number of studies		2		
Number of patients		53		
MD (95% CI)		1.45 (–0.91 to 3.82)[a]		
AE				
Number of studies		3		
Number of patients		217		
Risk ratio (95% CI)		1.03 (0.53 to 2.01)[a]		
Leukopenia, neutropenia, and/or agranulocytosis				
Number of studies		3		
Number of patients		217		
Risk ratio (95% CI)		0.71 (0.38 to 1.32)[a]		

AE = adverse event; CI = confidence interval; DFO = deferoxamine; DFP = deferiprone; LIC = liver iron concentration; MD = mean difference; MRI = magnetic resonance imaging; RCT = randomized controlled trial; vs. = versus.

[a] Risk ratio > 1 or positive mean difference indicates results favouring DFP.

[b] Risk ratio < 1 or negative mean difference indicates results favouring DFP.

5. Conclusion

A total of four meta-analyses were reviewed in this section. Results of two meta-analyses could not be used because one did not include any comparative results and the other had double-counting. Results of two meta-analyses showed that DFP did not differ with statistical significance from DFO in terms of mortality, liver fibrosis rates, LVEF, serum ferritin, or LIC. However, the reviewed evidence showed that DFP was associated with higher rates of AEs compared with DFO.

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