Deferasirox for managing iron overload in people with thalassaemia (Review)

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[Intervention Review]

Deferasirox for managing iron overload in people with thalassaemia

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ABSTRACT

Background

Thalassemia is a hereditary anaemia due to ineffective erythropoiesis. In particular, people with thalassaemia major develop secondary iron overload resulting from regular red blood cell transfusion. Iron chelation therapy is needed to prevent long-term complications.

Both deferoxamine and deferiprone have been found to be efficacious. However, a systematic review of the effectiveness and safety of the new oral chelator deferasirox in people with thalassaemia is needed.

Objectives

To assess the effectiveness and safety of oral deferasirox in people with thalassaemia and secondary iron overload.

Search methods

We searched the Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register. We also searched MEDLINE, EMBASE, EBMR, Biosis Previews, Web of Science, Derwent Drug File, XTOXLINE and three trial registries: www.controlled-trials.com; www.clinicaltrials.gov; www.who.int./ictrp/en/. Date of the most recent searches of these databases: 24 June 2010.

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 03 November 2011.

Selection criteria

Randomised controlled trials comparing deferasirox with no therapy or placebo or with another iron chelating treatment.

Data collection and analysis

Two authors independently assessed risk of bias and extracted data. We contacted study authors for additional information.

Main results

Four studies met the inclusion criteria.

Two studies compared deferasirox to placebo or standard therapy of deferoxamine (n = 47). The placebo-controlled studies, a pharmacokinetic and a dose escalation study, showed that deferasirox leads to net iron excretion in transfusion-dependent thalassaemia patients. In these studies, safety was acceptable and further investigation in phase II and phase III trials was warranted.

Two studies, one phase II study (n = 71) and one phase III study (n = 586) compared deferasirox to standard treatment with deferoxamine. Data suggest that a similar efficacy can be achieved depending on the ratio of doses of deferoxamine and deferasirox being compared; in the phase III trial, similar or superior efficacy for surrogate parameters of ferritin and liver iron concentration could only be achieved in the highly iron-overloaded subgroup at a mean ratio of 1 mg of deferasirox to 1.8 mg of deferoxamine corresponding to a mean dose of 28.2 mg/d and 51.6 mg/d respectively. Data on safety at the presumably required doses for effective chelation therapy are limited. Patient satisfaction was significantly better with deferasirox, while rate of discontinuations was similar for both drugs.

Authors' conclusions

Deferasirox offers an important alternative line of treatment for people with thalassaemia and secondary iron overload. Based on the available data, deferasirox does not seem to be superior to deferoxamine at the usually recommended ratio of 1 mg of deferasirox to 2 mg of deferoxamine. However, similar efficacy seems to be achievable depending on the dose and ratio of deferasirox compared to deferoxamine. Whether this will result in similar efficacy in the long run and will translate to similar benefits as has been shown for deferoxamine, needs to be confirmed. Data on safety, particularly on rare toxicities and long-term safety, are still limited.

Therefore, we think that deferasirox should be offered as an alternative to all patients with thalassaemia who either show intolerance to deferoxamine or poor compliance with deferoxamine. In our opinion, data are still too limited to support the general recommendation of deferasirox as first-line treatment instead of deferoxamine. If a strong preference for deferasirox is expressed, it could be offered as first-line option to individual patients after a detailed discussion of the potential benefits and risks.

PLAIN LANGUAGE SUMMARY

Deferasirox for managing transfusional iron overload in people with thalassaemia

Thalassaemia is a hereditary anaemia due to a defect in the production of haemoglobin. Regular red blood cell transfusions are needed, particularly for the severe form of the disease, thalassaemia major. This results in secondary iron overload. Since the human body has no means of actively getting rid of excessive iron, drug treatment (iron chelators) is needed. Several years ago, a new oral iron chelator, deferasirox, was introduced. However, it is not known whether deferasirox offers advantages compared to deferoxamine or deferiprone with regard to effectiveness and safety.

Four studies are included in the review. Two studies comparing deferasirox with placebo showed effectiveness of deferasirox with regard to iron excretion. Two other studies compared deferasirox with standard treatment of deferoxamine. Similar effectiveness seems to be achievable depending of the doses and ratio of the two drugs compared. It needs to be confirmed whether this results in similar improvement of patient-important outcomes in the long run.

The safety of deferasirox was acceptable; however, rarer adverse events or long-term side effects could not be adequately investigated due to the limited number of patients and the short duration of the studies. Patient satisfaction was significantly better with deferasirox, while rate of discontinuations was similar for both drugs.

Deferasirox should be offered as an alternative to all patients who do not tolerate deferoxamine or who have poor compliance with deferoxamine. Ideally, further studies looking at patient-important, long-term outcomes as well as rarer adverse events should be conducted prior to routine recommendation of deferasirox as first line therapy in thalassaemia patients with iron overload.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Deferasirox compared to Deferoxamine for People with thalassaemia and secondary iron overload

Patient or population: People with thalassaemia and secondary iron overload
Settings:
Intervention: Deferasirox
Comparison: Deferoxamine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Deferoxamine	Deferasirox				
Mortality at any point in time Follow-up: mean 52 weeks	**10 per 1000**	**3 per 1000** (0 to 31)	**RR 0.33** (0.03 to 3.12)	622 (2 studies)	⊕⊕◯◯ **low**[1,2,3]	
Responder analysis (Responder: LIC: 1 to less than 7 mg Fe/g dw) Follow-up: mean 52 weeks	**664 per 1000**	**531 per 1000** (458 to 611)	**RR 0.8** (0.69 to 0.92)	553 (1 study)	⊕⊕◯◯ **low**[1,3,4,5]	
Mean change in serum ferritin (μg/l) Follow-up: mean 52 weeks		The mean change in serum ferritin (μg/l) in the deferasirox group was **521.82 lower** (387.78 to 655.87 lower) , i.e. ferritin reduction was higher in the deferoxamine group		563 (1 study)	⊕⊕⊕◯ **moderate**[1,3,4]	

Change in LIC (mg Fe/g dw) evaluated by biopsy or SQUID Follow-up: mean 52 weeks		The mean change in LIC (mg Fe/g dw) evaluated by biopsy or SQUID in the deferasirox group was **2.37 lower** (1.68 to 3.07 lower), i.e. LIC reduction was higher in the deferoxamine group		541 (1 study)	⊕⊕⊕◯ **moderate**[1,3,5]
Satisfaction with treatment (very satisfied or satisfied): Patients previously treated with DFO questionnaire Follow-up: mean 52 weeks	**387 per 1000**	**704 per 1000** (623 to 793)	**RR 1.82** (1.61 to 2.05)	571 (1 study)	⊕⊕⊕◯ **moderate**[1]
Discontinuations	**45 per 1000**	**54 per 1000** (28 to 103)	**RR 1.19** (0.62 to 2.29)	657 (1 study)	⊕⊕◯◯ **low**[1,6]
Adverse event: Isolated serum creatinine increase above upper limit of normal	**137 per 1000**	**352 per 1000** (258 to 481)	**RR 2.57** (1.88 to 3.51)	657 (2 studies)	⊕⊕◯◯ **low**[1,7]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No blinding; unclear whether free of selective reporting.
[2] Very wide confidence interval including both clinically relevant benefit as well as harm. Very low number of events.
[3] Dose-response gradient observed for both drugs. Effects therefore depending on ratio of drugs used in comparisons.
[4] Inconsistency due to differing ratio of drugs between subgroups.

[5] Surrogate of ferritin/LIC used for patient-important outcomes such as mortality or end-organ damage.
[6] Wide confidence interval, including less discontinuations with deferoxamine treatment.
[7] Surrogate of creatinine used for patient-important outcome of kidney failure.
CI: confidence interval
LIC: liver iron concentration
RR: risk ratio

BACKGROUND

Description of the condition

Thalassaemia, first described by Cooley and Lee in 1925 (Cooley 1925), is a hereditary anaemia resulting from a defect in haemoglobin production (Weatherall 2000). The disruption in the synthesis of either the α- or β-chains of haemoglobin, classified in α- and β-thalassaemia, leads to an ineffective erythropoiesis (i.e. the process by which red blood cells are produced) (Rund 2005). The worldwide birth rate for symptomatic thalassaemia is about 0.44 per 1000 births (Angastiniotis 1998) summing up to more than 40,000 newborns per year (Modell 2008). An estimated number of one to two million people with thalassaemia major, the severe form of thalassaemia, would need regular blood transfusions worldwide (Weatherall 2000; Modell 2008) of which only approximately 100,000 are treated as required (Modell 2008). The high frequency of thalassaemia genes can be explained by a protective effect against malaria (Weatherall 1998; Richer 2005).

Due to various mutations in the different genes for the α- and β-chain genes and other modifying factors, there is a broad spectrum of clinical symptoms ranging from intrauterine death, through to severe anaemia with the need for regular red blood cell transfusions to asymptomatic anaemia (Olivieri 1999). Diagnosis is usually confirmed by either using electrophoretic techniques or molecular analysis. According to the underlying mutations and clinical manifestations, the β-thalassaemia syndromes can be classified into thalassaemia major, thalassaemia intermedia and haemoglobin E thalassaemia.

To achieve sufficiently high haemoglobin levels for adequate growth and development, children with thalassaemia major usually require regular red blood cell transfusions, starting within their first year of life. Several studies have shown that a haemoglobin level above 9 to 10 g/dl is required to successfully suppress ineffective erythropoiesis and prevent hepatosplenomegaly as well as bone deformities due to extra-medullary haematopoiesis (Olivieri 1999; Weatherall 2000; Rund 2005).

Iron overload in people with thalassaemia is mainly the result of the additional iron load of up to 10 g per year by regular blood transfusions (Kushner 2001). Particularly in people with thalassaemia intermedia, iron overload is also due to increased intestinal iron absorption (Taher 2006). Since the human body has no means of effectively excreting excess iron apart from gastrointestinal mucosal shedding, loss via sweat or through any bleeding (e.g., menstrual loss), iron chelation therapy is essential for these people. Without iron chelation therapy, iron mediated free radical damage causes liver fibrosis, endocrine failure and myocardial damage (Borgna-Pignatti 2005).

Description of the intervention

Deferoxamine (DFO, Desferal®), which was reviewed in detail in a Cochrane Review (Roberts 2005), has been the treatment of choice for iron overload for the last 40 years. Due to its long availability it is the only chelating agent for which a profound effect on the long-term survival of a large cohort of people with thalassaemia has been shown (Zurlo 1989; Brittenham 1994; Gabutti 1996; Borgna-Pignatti 2004). To be clinically effective, deferoxamine has to be administered as a subcutaneous or less often an intravenous infusion over 8 to 12 hours, five to seven days per week. This regimen has been demonstrated to reduce the body iron load, prevent the onset of iron-induced complications and even reverse some of the organ-damage due to iron (Olivieri 1994; Davis 2004). But the arduous schedule of overnight subcutaneous infusions often leads to reduced compliance (Olivieri 1997; Modell 2000; Cappellini 2005a). Another problem concerns the toxicity of deferoxamine, particularly at higher doses. Toxicities beside local skin reactions include ophthalmologic (optic neuropathy, retinal pigmentation) and hearing problems (high frequency sensorineural hearing loss). Rare adverse effects like growth retardation, renal impairment (Koren 1991), anaphylactic reactions and pulmonary fibrosis (Freedman 1990) have been reported. The high cost (about $US 10,000 a year) of DFO (Delea 2008) and the consumables required (e.g., balloon infusers, which imply additional costs) as well as its complicated mode of administration limit its use in developing countries.

Oral preparations have been highly sought after for many years. In 1987 two studies showed that the orally active iron chelator deferiprone (1,2 dimethyl-3-hydroxypyrid-4-1, also known as L1, CP20, Ferriprox® or Kelfer) could achieve effective short-term iron chelation (Kontoghiorghes 1987a; Kontoghiorghes 1987b). However, doubts on the efficacy to reduce liver iron and prevent liver damage arose due to individuals with progression to overt liver fibrosis (Olivieri 1998). However, the hypothesis of direct liver toxicity of deferiprone could not be confirmed (Wanless 2002; Wu 2006). Several studies have shown in the meantime the efficacy of deferiprone for iron chelation (Ceci 2002; Maggio 2002) and in particular its benefit on cardiac iron and cardiac morbidity (Peng 2008). Use has been still quite limited though, mainly as second line therapy, due to its range of adverse effects (Hoffbrand 2003). These include gastrointestinal disturbances, arthropathy, neutropenia and agranulocytosis (Hoffbrand 1989). Recently, studies on combination therapy of deferoxamine and deferiprone have been performed, most of which showed additive rather than synergistic effects (Kattamis 2003; Origa 2005; Farmaki 2006; Galanello 2006; Tanner 2007; Kolnagou 2008). An extensive Cochrane Review on the effectiveness of deferiprone in people with thalassaemia was first published in 2007 (Roberts 2007).

How the intervention might work

Deferasirox (4-(3,5-bis-(2-hydroxyphenyl)-(1,2,4)-triazole-1-yl)benzoic acid) also known as CGP 72670, ICL670 or Exjade®) is a new oral chelator now available for routine use. It is approved for the treatment of secondary iron overload by the US Food and Drug Administration (FDA) (FDA 2005) and the European Medicines Agency (EMEA) (EMEA 2007). It is rapidly absorbed after administration and has a bioavailability of about 70%. Safety and tolerability was shown to be reasonable in a randomised dose escalation trial in people with β-thalassaemia in 2003 (Nisbet-Brown 2003). The elimination half-life of 8 to 16 hours allows a once daily administration after the tablets have been added to water or juice. Being a tridentate chelator two molecules of deferasirox are needed to bind one molecule of iron. The excretion of the bound iron is mainly via faeces.

Adverse effects known from experiences in people with thalassaemia include gastrointestinal disturbances (nausea, stomach pain or diarrhoea) that have generally been mild and a diffuse rash being more common at higher doses (Cappellini 2006). More rarely, fever, headache and cough have been encountered. The main adverse effect with the use of deferasirox seemed to be a mild to moderate elevation of the creatinine level in about a third of patients. Elevations of liver enzyme levels have also been described with a lower incidence (5.6%) (Cappellini 2006). As with standard therapy (DFO), hearing loss and ocular disturbances including cataracts and retinal disorders have been reported with a very low incidence (less than 1%).

Recently, with wider use outside of clinical studies, other more severe adverse effects have been reported, such as: cytopenias; Fanconi syndrome and renal failure (Rafat 2009; Grange 2010; Yew 2010); liver failure; and gastrointestinal bleeding, which resulted in a boxed warning by the FDA (FDA Boxed Warning 2010).

Why it is important to do this review

Deferoxamine necessitates serious commitment from the user and due to its adverse effects, deferiprone is only approved as second line therapy in some countries. Thus, much hope is being placed in the new oral chelator deferasirox which apparently offers a promising line of treatment due to its iron chelation properties and safety and tolerability profile (Cappellini 2007). Therefore, a systematic review of the effectiveness and safety of deferasirox according to Cochrane standards is urgently needed.

OBJECTIVES

To evaluate the effectiveness and safety of oral deferasirox for management of iron overload in people with thalassaemia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were considered for this review.

Types of participants

People with thalassaemia regardless of age, type of thalassaemia (e.g. thalassaemia major, thalassaemia intermedia) and setting (e.g. country, primary or secondary care), who have received repeated red blood cell transfusions in the past or who are receiving regular red blood cell transfusions currently which have resulted in iron overload (defined as ferritin levels of over 1000 ng/ml on at least two occasions).

Types of interventions

For oral deferasirox (all schedules and doses) the following comparisons were considered:

1. deferasirox compared with no therapy or placebo;
2. deferasirox compared with another iron chelating treatment (i.e. deferoxamine or deferiprone or any combination thereof).

These comparisons constitute two separate groups and were analysed separately. However, the necessity of chelation therapy in iron-overloaded people is well-established and, if at all, only short-term, e.g. pharmacokinetic, studies would be ethically justifiable. Longer-term studies with no therapy or placebo would not suffice the paradigm of equipoise and we did not expect to find and in fact did not find any longer-term studies comparing deferasirox to no therapy or placebo.

Types of outcome measures

Primary outcomes

1. Overall mortality measured at any point in time

Secondary outcomes

1. Reduced end-organ damage due to iron deposition
   - i) cardiac failure (necessitating medical treatment)
   - ii) endocrine disease (necessitating substitution hormone therapy or treatment of diabetes)
   - iii) histological evidence of hepatic fibrosis
   - iv) pathological surrogate markers of end-organ damage (i.e. elevated liver enzymes, elevated fasting glucose or pathological oral glucose tolerance test (OGTT), pathological measures (e.g. ejection fraction in echocardiography)

2. Measures of iron overload
   i) serum ferritin (ng/ml)
   ii) iron levels in biopsies of liver and other tissue (mg/g liver dry weight)
   iii) tissue iron assessment by SQUID (superconducting quantum interference device) (mg/g liver wet weight)
   iv) tissue iron assessment by MRI (magnetic resonance imaging) (ms)
3. Measures of iron excretion (urine and faeces) over 24 hours (mg/kg/d)
4. Any adverse events
   i) raised levels of creatinine or kidney failure (above upper normal limit or rise of more than 20% above baseline level)
   ii) skin rash
   iii) gastrointestinal disturbances
   iv) neutropenia or agranulocytosis (absolute neutrophil count (ANC) less than 1000/µl or less than 500/µl)
   v) raised levels of liver enzymes (above upper normal limit or rise of more than 20% above baseline level) or progression to liver fibrosis
   vi) hearing loss
   vii) eye problems (e.g. retinal toxicity)
   viii) unanticipated adverse events as reported in the primary studies
5. Participant satisfaction (measured e.g. by a validated questionnaire) and compliance with chelation treatment (measured by the number of people in each arm that show adequate level of adherence to treatment (intake or application of iron chelator on five or more days per week)).
6. Cost of intervention per year.

Data from outcomes not defined *a priori* but which have arisen from the review were collected, if the outcome was considered to be of clinical relevance.

Search methods for identification of studies

No language restriction was applied.

Electronic searches

We identified relevant studies from the Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: (thalassaemia OR haemoglobinopathies general) AND ICL670(A).

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of *The Cochrane Library*) and quarterly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group Module.

Date of most recent search of the Group's Haemoglobinopathies Trials Register: 03 November 2011.

We searched for relevant trials in the following databases:

via OvidSP: Embase 1980 to 2010 Week 24 (searched: 24 June 2010), Medline 1950 to June Week 3 2010, Medline in Process and Other Non-Indexed Citations to June 25, 2010 (searched: 28 June 2010), Biosis Previews 1969 to 2010 Week 29 (searched: 28 June 2010);

via Wiley Interscience: The Cochrane Library: Cochrane Database of Systematic Reviews 2010, Issue 6; other Cochrane Library Databases 2010 Issue 2 (searched: 29 June 2010);

via Thomson Reuters: Web of Science 1945 to 26.06.2010 (searched: 30 June 2010);

via DIMDI: XTOXLINE 01.01.1965 - 29.06.2010, Derwent Drug File 01.01.1983 - 23 June 2010 (searched: 01 July 2010).

The searches were performed from 24 June to 1 July 2010. For details of the search strategies see the appendices (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6). Given there is much ongoing research into deferasirox treatment, the following three trial registries were searched on 28 June 2010 for all years available in all possible fields using the basic search function (using separately the following keyword terms: "deferasirox", "ICL670", "ICL 670" and "exjade"):

1. Current Controlled Trials: www.controlled-trials.com (all available registers were searched).
2. ClinicalTrials.gov: www.clinicaltrials.gov
3. ICTRP: www.who.int/ictrp/en/

One ongoing study is currently listed and if possible, will be included in the next update of this review.

Searching other resources

Additionally, reference lists of all identified papers were screened to identify other potentially relevant citations.

Contact was made with selected experts in the field as well as the manufacturer of deferasirox (Novartis) to request information on any unpublished studies that involved deferasirox.

Data collection and analysis

Selection of studies

One author (JM) screened all titles and abstracts of papers identified by the search strategies for relevance. We only excluded citations which were clearly irrelevant at this stage. We obtained

full copies of all potentially relevant papers. At this stage two review authors (JM and DB) independently screened the full papers, identified relevant studies and assessed eligibility of studies for inclusion. We resolved any disagreement on the eligibility of studies through discussion and consensus or if necessary through a third party (GA). We excluded all irrelevant records and recorded details of the studies and the reasons for exclusion.

Data extraction and management

In addition to details relating to the risk of bias of the included studies, we extracted two sets of data.

1. Study characteristics: place of publication; date of publication; population characteristics; setting; detailed nature of intervention; detailed nature of comparator; and detailed nature of outcomes. A key purpose of this data was to define unexpected clinical heterogeneity in included studies independently from the analysis of the results.
2. Results of included studies with respect to each of the main outcomes indicated in the review question. We carefully recorded reasons why an included study did not contribute data on a particular outcome and considered the possibility of selective reporting of results on particular outcomes.

Two review authors (JM, DB) independently undertook data extraction using a data extraction form developed by the authors. The review authors resolved any disagreements by consensus or through discussion with a third review author (GA). Once we had resolved disagreements, we recorded the extracted data on the final data extraction form. One review author (JM) transcribed these into RevMan 5.1 (Review Manager 2011). Another review author (DB) verified all data entry for discrepancies. We only extracted data from full publications of studies.

Assessment of risk of bias in included studies

Two review authors (JM, DB) assessed every study using a simple form and following the domain-based evaluation as described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1 (Higgins 2011).

We assessed the following domains as having either a low, unclear, or high risk of bias:

1. randomisation;
2. concealment of allocation;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data;
5. selective outcome reporting;
6. other sources of bias.

We reviewed the assessments and discussed any inconsistencies between the review authors in the interpretation of inclusion criteria and their significance to the selected studies. We resolved any disagreements through discussion with a third author (GA). We did not automatically exclude any study as a result of a rating of 'unclear risk of bias' or a 'high risk of bias'. We presented the evaluation of the risk of bias in included studies in tabular form in the Results section of the review.

Measures of treatment effect

We analysed extracted data using the most up-to-date version of RevMan available at the time of analysis (Review Manager 2011). We planned to extract hazard ratios with their 95% confidence intervals for the time-to-event outcomes mortality and end-organ damage. If reports did not provide hazard ratios, we planned to use indirect estimation methods described by Parmar (Parmar 1998) and Williamson (Williamson 2002) to calculate them.

If we were unable to either extract these data from the study reports or receive the necessary information from the primary investigators, alternatively we used, where appropriate, the proportions of participants with the respective outcomes measured at certain time points (i.e. three months, six months, then six-monthly intervals) to be able to calculate risk ratios (RR). We also extracted data from other time points if available.

We expressed any results for binary outcomes as risk ratios (RR) with 95% confidence intervals as measures of uncertainty. Continuous outcomes were expressed as mean differences (MD) with 95% confidence intervals as measures of uncertainty.

Unit of analysis issues

We did not include any cross-over studies in this review. However, for future updates, we plan to use the methods recommended by Elbourne for combining results from such studies (Elbourne 2002). We will use the methods described by Curtin to combine results from parallel and cross-over studies (Curtin 2002a; Curtin 2002b; Curtin 2002c).

For some outcomes, a possible perception of the comparison might be whether deferasirox is not inferior to standard treatment with deferoxamine. Therefore, for these outcomes a per-protocol analysis might be chosen.

The investigators planned that the included phase III trial would be a non-inferiority trial (Cappellini 2005b). Therefore, they did not report efficacy outcomes based on ITT analysis. For our review, we used the data as presented (per protocol).

Currently, there are only two studies included in this review comparing deferasirox and deferoxamine. Pooling of data between the Piga and Cappellini trials was only possible for the following outcomes: mortality (Analysis 2.1); mean change in serum ferritin (Analysis 2.4); isolated creatinine increase (Analysis 2.9); agranulocytosis (Analysis 2.16); hearing loss (Analysis 2.19); lens abnormalities (Analysis 2.20); and discontinuations (Analysis 2.38) (Piga 2002; Cappellini 2005b).

Therefore, we did not use any of the below mentioned strategies outlined by Witte (Witte 2004) in this version of the review. However, for future updates we will consider applying one of these strategies according to the data available.

1. If all studies report only an ITT analysis (or all studies report only a PP analysis), we will perform a non-inferiority meta-analysis based on Witte's 'perfect case' proposal.

2. If some studies report only an ITT analysis and others only a PP analysis (exclusively), we will perform meta-regression with analysis type as a covariate.

3. If some studies report only an ITT analysis and others only a PP analysis, whilst others report both, we will undertake a sensitivity analysis.

4. If all studies give enough information to do both analyses, we will analyse data using a bivariate model.

To interpret results according to a non-inferiority scenario, we will use the following definitions:

For time-to-event data, non-inferiority is given, if the relative difference in hazard ratios is less than 10%. For RRs, non-inferiority is defined as a relative RR difference of less than 10% in treatment failures compared to standard therapy. For the continuous outcomes of "measures of iron overload and iron excretion" as well as "costs", a relative difference of less than 10% is considered equivalent.

Dealing with missing data

We contacted the original investigators to clarify some methodological issues and to request additional data; we are currently in contact with investigators from two studies (Galanello 1999: Nisbet-Brown 2001). However, to date, we have not received any additional data to that presented in the primary reports. If we subsequently receive additional information, we plan to incorporate these data in the next update of this review. We are also in contact with the manufacturer of deferasirox (Novartis), who may be able to provide additional data for future updates of this review.

Assessment of heterogeneity

Where feasible, we considered clinical heterogeneity by presenting results of subgroups according to differences in dose of intervention and baseline measures of iron overload. We examined statistical heterogeneity in the results of studies using the I^2 and Chi^2 statistics (Higgins 2002; Higgins 2003).

Assessment of reporting biases

We made a great effort to identify unpublished studies and minimise the impact of possible publication bias by using a comprehensive search strategy and contacting the manufacturer of deferasirox. We did not plan to use funnel plots to assess publication bias, since asymmetry is difficult to detect with a small number of studies (i.e. less than 10) and we could only include four studies in this review. If in future we are able to include more than 10 studies in the review, we will use funnel plots to graphically assess the likelihood of publication bias. We took care in translating the results of the included studies into recommendations for action by involving all review authors in drawing conclusions.

Data synthesis

While extracting data, we realized that we had to take the following decisions. Although we would have preferred to consistently present data separately for the different dose groups, we decided to pool safety data of the different dose groups from the Nisbet-Brown study, since splitting of the placebo group (N = 5) did not seem reasonable due to the small size (Nisbet-Brown 2001). However, safety data from the Piga study were presented by dose group since the placebo group seemed large enough to split (Piga 2002). Since there is a clear dose-effect relation, efficacy data are presented for the different dose groups, if enough information was available from the original reports.

We conducted meta-analyses of pooled data from all contributing studies using a fixed-effect model. We took heterogeneity arising from different doses of intervention or different baseline iron measure into account by providing results by respective subgroups. Therefore, we did not use a random-effects model as a secondary analysis. For future updates, if we find marked clinical or statistical heterogeneity (I^2 more than 50%) we will also use a random-effects model and report results from both models.

Subgroup analysis and investigation of heterogeneity

If data were available, we presented subgroups according to baseline measures of iron overload or doses of intervention. For future updates of this review, we will assess clinical heterogeneity, if possible, in addition by examining differences due to:

- age of participants (e.g., 0 to 2 years, 3 to 5 years, 6 to 11 years; 12 to 17 years, 18 years or older);
- age at commencement of the intervention (e.g., 0 to 2 years, 3 to 5 years, 6 to 11 years, 12 to 17 years, 18 years or older).

Additional subgroup analyses are planned for different:

- subtypes of thalassaemia (e.g., thalassaemia major, thalassaemia intermedia, haemoglobin E thalassaemia).

Sensitivity analysis

We only included two studies for each of our comparisons and no additional unpublished studies were identified. Therefore, no sensitivity analyses were performed. For future updates of this review, we plan to perform sensitivity analyses based on assessment of risk of bias (evaluating only studies of low risk of bias) and publication status (unpublished and published studies).

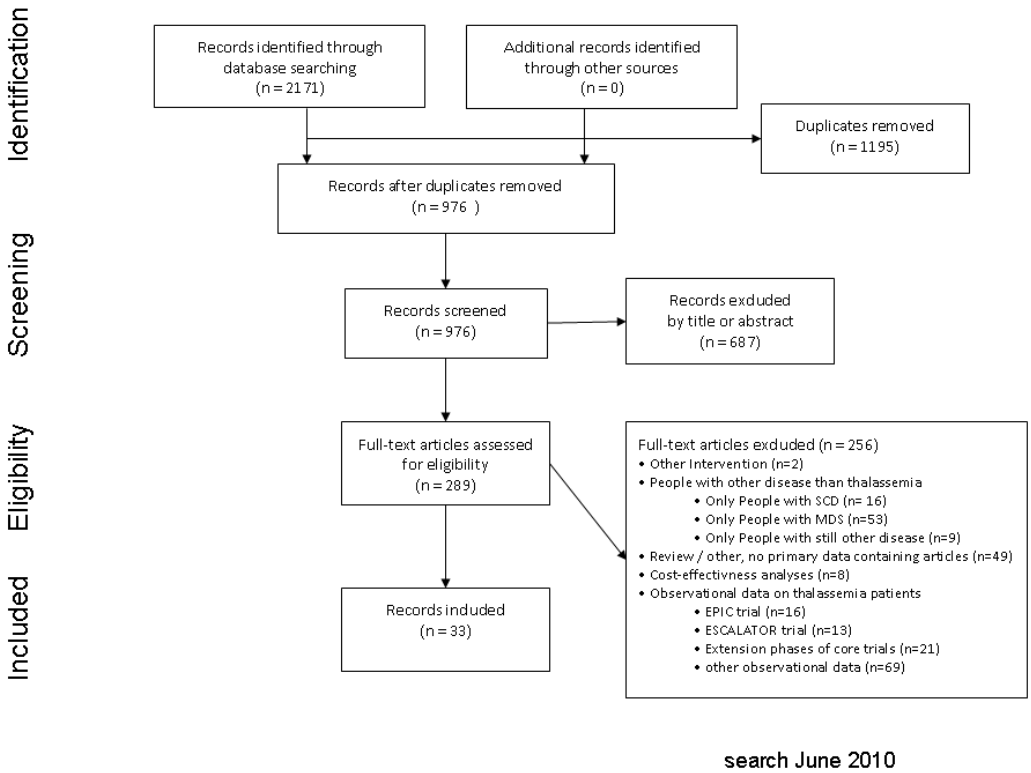
RESULTS

Description of studies

Results of the search

The searches were run in August 2008, June 2009, June 2010 and lastly (for the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register only) November 2011 (see also Figure 1). Altogether, 2171 citations, including 1195 duplicates, were identified. After title and abstract screening of the 976 unique citations, 687 citations could be excluded. A total of 289 full texts were screened of which 256 reports were excluded; reasons for exclusion are as follows:

Figure 1. Identification of eligible reports



- included people with disease other than thalassaemia
  - only sickle cell disease (n = 16)
  - only myelodysplastic syndrome (n = 53)
  - other condition (n = 9)
- review article or editorial/comment (n = 49)
- intervention other than deferasirox (n = 2)
- cost-effectiveness analysis (n = 8)
- non-randomised data on patients with thalassaemia (n = 119) (for selected references see Characteristics of excluded studies)
  - EPIC trial (n = 16)
  - ESCALATOR trial (n = 13)
  - Extension phases of core trials (n = 21)
  - other observational data (n = 69)

Four randomised studies were identified; two comparing deferasirox to placebo and two comparing deferasirox with deferoxamine. Altogether, 33 reports could be assigned to these four studies: two to Galanello 1999, three to Nisbet-Brown 2001, five to Piga 2002 and 23 plus two published responses to letters to Cappellini 2005b.

The search of the three trial registers (last run on 30 June 2010) identified 49 unique references to trials. One ongoing randomised trial was identified (Thalassaemia 2007).

Included studies

Four studies, two each comparing deferasirox to placebo (Galanello 1999; Nisbet-Brown 2001) or deferoxamine (Cappellini 2005b; Piga 2002), met the inclusion criteria (Characteristics of included studies).

The two studies comparing deferasirox to placebo are short-term studies examining mainly safety and pharmacokinetic outcomes of deferasirox (Galanello 1999; Nisbet-Brown 2001). This is not surprising since long-term studies comparing deferasirox to placebo would be ethically unjustifiable, given that the benefit and therefore also the necessity of iron chelation therapy in regularly transfused thalassaemia patients, has been shown. Consequently, studies of new iron-chelating drugs, such as deferasirox, should compare their effects against standard treatment of deferoxamine.

The first study was reported in one full article and one abstract (Galanello 1999). Twenty-four patients were allocated to three groups: all groups received two single doses of deferasirox at an interval of at least seven weeks. Group 1 received single doses of 2.5 mg/kg and 20 mg/kg, group 2 single doses of 5 and 40 mg/kg and group 3 single doses of 10 and 80 mg/kg. In each treatment period, two of eight patients received placebo in such a way that a given patient did not receive placebo more than once. Usual deferoxamine and transfusion therapy was given in the interval between the two doses. This study by Galanello on deferasirox focused on safety, tolerability and pharmacokinetics. Safety data were presented descriptively, so that quantitative data extraction was not easily feasible. In addition, it was not clear whether patients contributed more than one episode to the count of one adverse event such as headache since safety parameters were assessed after each dose. So, a single patient could theoretically contribute more than one episode of an event such as headache. For this reason, we do not present these data in a forest plot. We have contacted the authors but have not yet been able to clarify all details.

The second study was reported in one full article and two abstracts (Nisbet-Brown 2001). It was designed as a dose-escalation trial focusing on effectiveness and safety; treatment duration was 12 days. A total of 23 patients were randomly assigned to placebo (n = 5), 10 mg/kg/d of deferasirox (n = 5), 20 mg/kg/d of deferasirox (n = 6) and 40 mg/kg/d of deferasirox (n = 7). Primary objectives included assessment of safety and tolerability (measured by adverse events and clinical laboratory monitoring), pharmacokinetics (measured as drug and drug-iron complex), and cumulative net iron excretion (measured by faecal and urine output minus food input).

The third study was reported in one full article and four abstracts (Piga 2002). This is a randomised open-label phase II trial including 71 β-thalassaemia patients aged >18 years from four centres in Italy (Table 1). The primary objective was to determine the safety and tolerability of deferasirox at daily doses of 10 and 20 mg/kg in comparison with a standard dose of deferoxamine 40 mg/kg in patients with transfusional haemosiderosis (Table 2). Secondary objectives included evaluation of the effects of deferasirox on liver iron concentration (LIC), serum ferritin, serum iron, transferrin and transferrin saturation. The Intention-to-treat principle was used for analyses.

Results from the fourth study were reported in four full articles, 19 abstracts (and two responses to letters) (Cappellini 2005b). This phase three open-label randomised trial was planned as a non-inferiority trial with a predefined delta of 15% (two-sided 95% CI). There were 591 patients actually randomised, but five withdrew consent prior to any study medication; 586 patients were included in the trial, of which 541 completed one year of therapy (Table 3). After randomisation, stratified by three age groups, people were assigned to a treatment dose of either deferasirox or deferoxamine according to baseline LIC (Table 4); the mean ratio of doses between deferasirox and deferoxamine varied from 1:5.5 to 1:1.8. The primary endpoint was maintenance or reduction of LIC (see Table 5). Secondary criteria for response included evaluation of the change in serum ferritin levels over time and evaluation of net body iron balance.

Excluded studies

No randomised trials were excluded. However, several reports of the extension phases of trials, particularly of the Cappellini trial, were not included, since after completion of the core first year, cross-over of deferoxamine patients to deferasirox treatment was done during the extension phase (Cappellini 2005b). Therefore, data collected during the extension phase represent observational data on a large cohort of deferasirox treated patients; there is no longer a comparison group and patients were not analysed according to their initially assigned group.

Furthermore, observational studies such as the EPIC or ESCALATOR studies are listed as Excluded studies (references of full text articles reporting on these studies are given).

Risk of bias in included studies

The risk of bias for the four included studies in this review was classified as previously described (Assessment of risk of bias in included studies).

The two blinded trials comparing deferasirox to placebo were judged overall as having an 'unclear' risk of bias (Galanello 1999; Nisbet-Brown 2001). These assessments were mainly based on the

inadequate reporting of several of the criteria that are considered to be important in the evaluation of methodological rigour in terms of trial design and conduct.

The two open trials comparing deferasirox to standard therapy of deferoxamine were also classified as having an overall 'unclear' risk of bias (Piga 2002; Cappellini 2005b). Again, these assessments were due to inadequate reporting of several of the pre-defined criteria used for evaluation of the risk of bias.

For further details see the risk of bias tables in Characteristics of included studies, the risk of bias graph (Figure 2) and the risk of bias summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

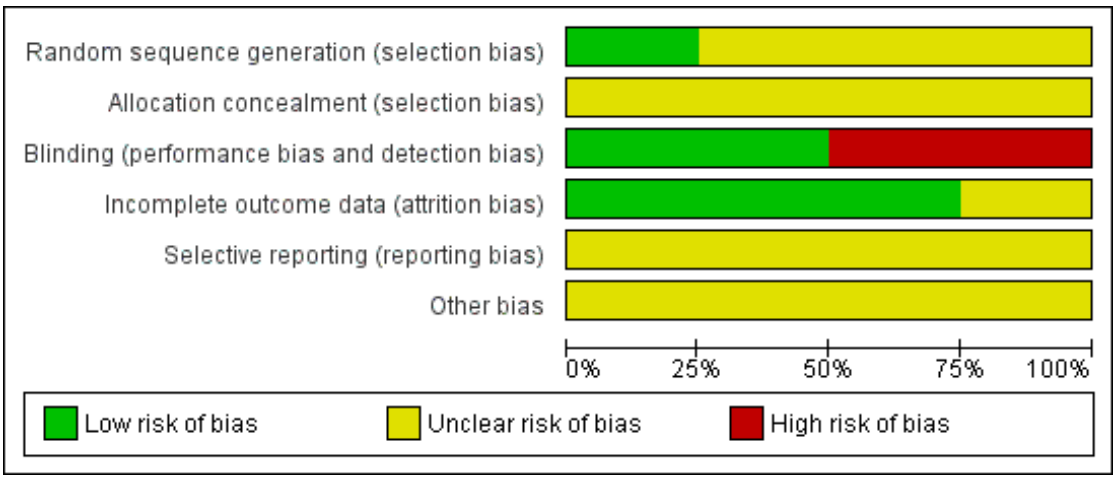
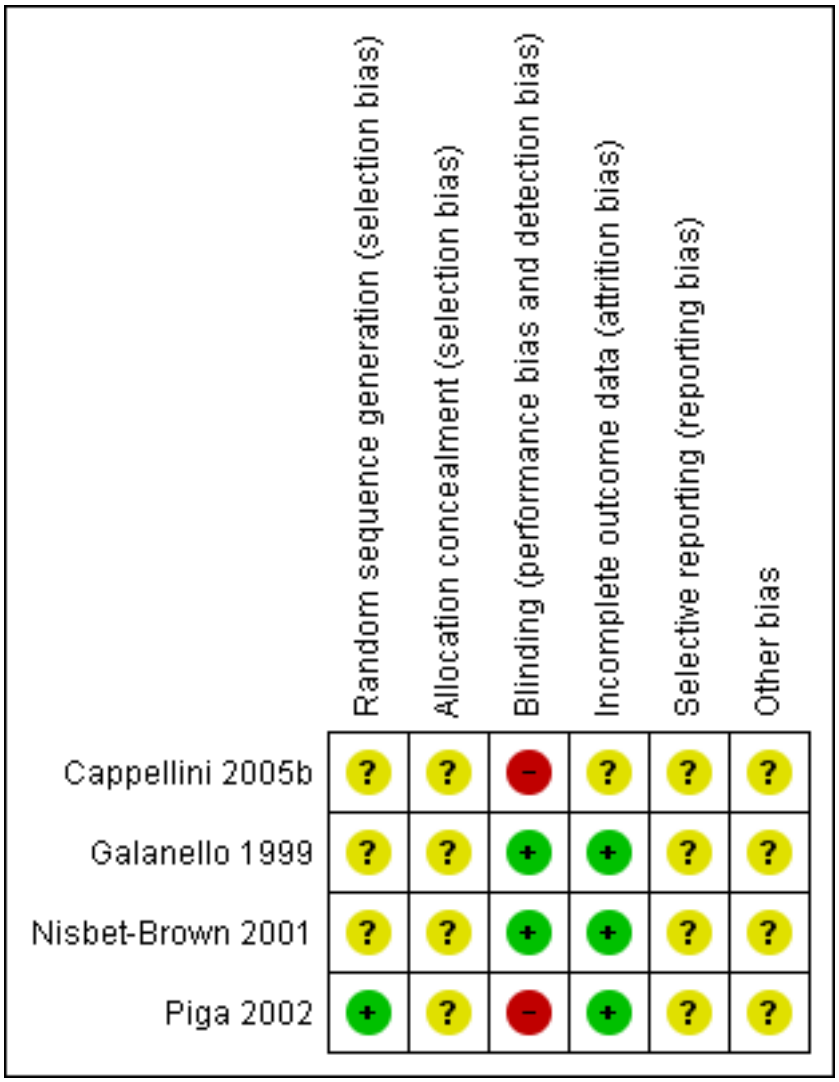


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The methods to generate the allocation sequence were not described in three studies (Galanello 1999; Nisbet-Brown 2001; Cappellini 2005b). In only one trial was the use of a "validated system that generates an automated random assignment of numbers to treatment groups" mentioned (Piga 2002).

Since no details were given in the reports with regard to allocation concealment, it remains unclear whether allocation concealment was achieved. One study reported using sealed envelopes but it was unclear if these were opaque and numbered (Nisbet-Brown 2001).

Blinding

Blinding was done in the two placebo-controlled trials (Galanello 1999; Nisbet-Brown 2001). However, these trials provided only limited data on safety because of their small sample sizes; efficacy parameters are difficult, if not impossible to estimate, particularly with regard to patient-relevant outcomes due to the short study period.

Two studies comparing deferasirox and deferoxamine were open-label, the reason being the obvious difference in application mode, deferasirox being an orally taken tablet, while deferoxamine needs to be applied subcutaneously over several hours. Blinding was not

deemed critical by the primary investigators, since efficacy endpoints were rather objective, e.g. ferritin levels, LIC measurements. However, blinding of the data assessors would have been feasible.

Incomplete outcome data

Since the Cappellini study was planned as a non-inferiority study, efficacy data were not consistently reported on an ITT basis (Cappellini 2005b). The remaining three studies adequately reported or addressed outcome data (Galanello 1999; Nisbet-Brown 2001; Piga 2002).

Selective reporting

For all four studies selective reporting can not be excluded. Data on a broad spectrum of adverse events were collected. However, only limited adverse event data were reported, usually only quantitatively. Also, efficacy parameters were collected at several time points during some of the studies, but results from all time points were not reported (Cappellini 2005b; Piga 2002). However, end of study results for the primary outcome were reported in all studies.

Other potential sources of bias

All studies were conducted with support and involvement of the producer of deferasirox (Novartis). Also, many authors were affiliated with Novartis. Conflicts of interest were reported. The relevance of these conflicts is open to interpretation. Evidence of publication bias could not be detected.

Effects of interventions

See: **Summary of findings for the main comparison** Deferasirox compared to Deferoxamine for People with thalassaemia and secondary iron overload

Deferasirox compared to placebo

Two studies compared deferasirox to placebo (Galanello 1999; Nisbet-Brown 2001). Due to both its design and the presentation of results in the paper, data could not be extracted quantitatively from the Galanello study (Galanello 1999) (for detailed reasons see also description of Included studies). Therefore, we decided to report important information in a narrative manner as done by Galanello (Galanello 1999). For details on safety in this study see directly quoted text under "4. Any adverse events" (Galanello 1999). Some data reported by Nisbet-Brown regarding discontinuations (Analysis 1.2) and adverse events (Analysis 1.3) could be extracted; other information, however, could only be presented narratively (Nisbet-Brown 2001).

Primary outcomes

1. Overall mortality measured at any point in time

No deaths were observed during these two short-term studies.

Secondary outcomes

1. Reduced end-organ damage due to iron deposition

No data on end-organ damage were available from either study.

2. Measures of iron overload

Efficacy was not a focus of the Galanello study and no consistent trend on serum iron and transferrin could be observed (as expected after single-dose administration) (Galanello 1999). Other measures of efficacy were not reported.

For the Nisbet-Brown study, ferritin levels were reported at baseline and end of study for each group (Nisbet-Brown 2001). However, since no standard deviation was given for mean change of ferritin and since we were unable to obtain these data from the authors, the mean ferritin levels (µg/l) and standard deviations at baseline and end of study are presented here (as reported in the primary study):

Baseline: placebo 4265 (3882), 10 mg/d 2452 (869), 20 mg/d 4753 (3168), 40 mg/d 2644 (1320)

End of study: placebo 5215 (5430), 10 mg/d 2344 (1606), 20 mg/d 4872 (2511), 40 mg/d 1756 (793)

We decided against estimating SDs because imputation from another study would require studies similar in design and conduct which are not available (due to the fact that we are dealing here with an early phase dose escalation study). We decided against use of post-treatment values only, since there were large, clinically relevant differences between groups at baseline due to small sample size despite randomization. In conclusions, we felt that efficacy measures in these early, dose-finding studies with a focus on pharmacokinetics or dynamics were, in our opinion, of limited value. However, since they fulfilled our inclusion criteria and were relevant in particular for safety issues, we included them. They showed a dose-response effect as expected, but conclusions regarding efficacy when taken continuously were not really appropriate.

3. Measures of iron excretion (urine and faeces) over 24 hours (mg/kg/d)

In the Galanello study, the authors note that the majority of iron is excreted in the faeces; however, data are only given for urinary iron excretion (Galanello 1999). These data are presented as urinary iron excretion over 24 h intervals for each dose. To minimize the influence of outliers, medians and ranges are given:

Placebo: 0.017 mg/kg/24h; range 0.006 to 0.629;
2.5 mg deferasirox: 0.009 mg/kg/24h; range 0.005 to 0.031;
5 mg deferasirox: 0.010 mg/kg/24h; range 0.006 to 0.028;
10 mg deferasirox: 0.010 mg/kg/24h; range 0.004 to 0.014;
20 mg deferasirox: 0.016 mg/kg/24h; range 0.006 to 0.119;
40 mg deferasirox: 0.193 mg/kg/24h; range 0.053 to 0.508;
80 mg deferasirox: 0.391 mg/kg/24h; range 0.121 to 0.842.
Therefore, we were unable to extract these data to include them in the RevMan graphs. We are trying to obtain additional data on fecal iron excretion.

The Nisbet-Brown study measured net iron excretion (Nisbet-Brown 2001). Since the actual data were not given in the publications and we have not received these from the authors, we estimated the values from the figures of the paper and performed an analysis of variance for the three dose groups using the placebo group as reference (Software: R). The mean (mg Fe/kg/d) and respective standard errors are 0.03 (0.10), 0.12 (0.14), 0.31 (0.14) and 0.47 (0.13) for placebo, 10 mg/d, 20 mg/d and 40 mg/d of deferasirox respectively.

4. Any adverse events

Galanello reported that "Adverse events were infrequent and of mild intensity. The most frequently reported adverse event was headache, with no association to the dose level (four patients at 2.5 mg/kg, one patient at 20 mg/kg, and one patient at placebo). Nausea and diarrhoea occurred in the 80-mg/kg group only (3 of 8 patients, all from one centre), suggesting that these symptoms were either drug related or possibly related to the dense oral suspension administered. Single occurrences of influenza, joint pain, and vertigo were not dose associated and were not suspected to be drug related. No consistent effect on individual laboratory values was observed. In single cases, hematological, biochemical, and special kidney parameters were outside the normal range, including at baseline, but no correlation with treatment could be observed. Notable parameters outside the normal ranges (and order of magnitude) were as follows: bilirubin, alanine aminotransferase, and aspartate aminotransferase (up to 1.5- to 3-fold increase); alkaline phosphatase (up to 1.5-fold increase); and creatinine kinase (0.3- to 0.6-fold decrease). A couple of creatinine values were just below the normal ranges (with the exception of a single value observed at screening, which was below the lower limit by a factor of 0.8). Abnormally low hematocrit, haemoglobin, and erythrocytes were frequent but had no association to the dose level, while other hematological parameters were abnormally high, such as platelet, eosinophils, lymphocytes, monocytes, and neutrophils, with an order of magnitude of 1.2 to 1.5. These findings are suspected to be caused by the underlying disease and by frequent blood sampling during the study. As expected in this study population, all patients had elevated ferritin values prior to the study, ranging from 1422 to 4780 ng/ml. No notable change in the levels of the trace elements was observed (zinc, copper, magnesium, and calcium). Among the special kidney function parameters, values of α-glutathione-S-transferase and β2- microglobulin were in single instances above the range of the normal values by a factor of 2- to 5-fold (including at baseline) and, in the extreme case, by a factor of more than 10- and 30-fold, respectively, for each parameter. The urinalysis sometimes showed pH values up to 6.5 to 7, as well as traces of urine bilirubin, glucose, ketones, leukocytes, and protein." (Galanello 1999).

Nisbet-Brown reported that nine patients in total discontinued treatment for serious adverse events, eight of which where receiving deferasirox (Nisbet-Brown 2001). However, two patients did not complete a single treatment day and only three discontinuations due to rash were deemed to be drug-related. Other safety and tolerability data are only available descriptively.

"No clinically relevant changes in any safety variable were seen between ICL670 and placebo groups. Specifically, no relevant changes were reported in haematological variables, mean concentrations of serum calcium, phosphorus, magnesium, uric acid, creatinine, urea nitrogen, albumin, creatine kinase, triglycerides, or total cholesterol. No abnormalities of renal sediment were noted. Further, no relevant changes from baseline in electrocardiographic, audiometric, or ophthalmologic examinations were noted, with the exception of one patient in whom a myelinated fibre bundle or retinal infarct was seen after seven days of treatment with ICL670 at 20 $mg\,kg^{-1}\,day^{-1}$. This patient was reviewed by an independent ophthalmologist, and the change was thought to be secondary to his underlying diabetes mellitus. No significant changes between ICL670 and placebo were seen in copper or zinc concentrations in blood over the study period, indicating thus that ICL670 was highly selective for iron." (Nisbet-Brown 2001).

5. Participant satisfaction

No data on participant satisfaction were available from either study (Galanello 1999; Nisbet-Brown 2001).

6. Cost of intervention per year

No data on costs of intervention were available from either study (Galanello 1999; Nisbet-Brown 2001).

In summary, the two pharmacokinetic, dose-finding studies comparing deferasirox to placebo showed that deferasirox lead to dose-dependent iron excretion mainly via faeces (Galanello 1999, Nisbet-Brown 2001). There were no statistically significant differences in the rates of discontinuations or adverse events found (based on n < 25 in each of both studies) (Analysis 1.2; Analysis 1.3). In conclusion, pharmacodynamic efficacy and acceptable safety could be confirmed justifying further clinical testing in phase II and phase III studies based on an estimated equivalence ratio of deferasirox to deferoxamine of approximately 1 mg: 2 mg.

Deferasirox compared to deferoxamine

Two studies compared deferasirox to deferoxamine (Cappellini 2005b; Piga 2002).

Primary outcomes

1. Overall mortality measured at any point in time

There was no significant difference in mortality observed; data were pooled despite slightly different study durations of 48 and 52 weeks (Analysis 2.1). However, the number of patients and in particular the number of events was very limited.

Secondary outcomes

1. Reduced end-organ damage due to iron deposition

No data on end-organ damage were available from any study.

2. Measures of iron overload

Responder-definition varied between the studies (decrease in LIC > 10% in the study by Piga and LIC 1 to less than 7 mg Fe/g dw in the Cappellini study) (Analysis 2.2; Analysis 2.3). Results for mean change in serum ferritin and LIC could not be extracted from the Piga study due to missing standard deviations (Piga 2002). In the Cappellini study the mean ratio of deferasirox to deferoxamine varied between the predefined subgroup according to iron overload measures at baseline (Table 4) and different effects were seen in the different subgroups accordingly (Cappellini 2005b). Data from Cappellini showed a clear dose-response effect for serum ferritin levels (Analysis 2.4). At a ratio of less than 1:2.2 of deferasirox to deferoxamine, the latter was statistically more effective; similar efficacy was achieved only in the highly iron-overloaded subgroup at a mean ratio of 1:1.8 (Table 4). Both for change in LIC and iron excretion-intake ratio, results from Cappellini reflect the dose-response and ratio effect seen for ferritin (Analysis 2.5, Analysis 2.6). At a ratio of 1:1.8 deferasirox showed a significantly higher efficacy than deferoxamine in the subgroup of highly iron-overloaded people, while deferoxamine showed higher efficacy in the other three subgroups at ratios of 1:2.2, 1:3.6 and 1:5.5.

3. Measures of iron excretion (urine and faeces) over 24 hours (mg/kg/d)

No data on iron excretion were available from either study.

4. Adverse events

No statistically significant differences were found between deferasirox and deferoxamine with regard to the frequencies of "any adverse events" or "any serious adverse events" (Analysis 2.7; Analysis 2.8). Only isolated increases of creatinine occurred significantly more often while on deferasirox treatment compared to deferoxamine (Analysis 2.9); all other reported adverse events such as gastrointestinal problems (Analysis 2.10; Analysis 2.11; Analysis 2.12; Analysis 2.13; Analysis 2.14), cytopenias (Analysis 2.15; Analysis 2.16; Analysis 2.17), liver toxicity (Analysis 2.18), hearing or eye problems (Analysis 2.19; Analysis 2.20; Analysis 2.21), cardiac events (Analysis 2.22), other general symptoms (Analysis 2.23; Analysis 2.24; Analysis 2.25; Analysis 2.26; Analysis 2.27; Analysis 2.28; Analysis 2.29) or infectious complications (Analysis 2.30; Analysis 2.31; Analysis 2.32; Analysis 2.33; Analysis 2.34; Analysis 2.35; Analysis 2.36; Analysis 2.37) were either not observed at all or at frequencies that were not statistically different between both treatments.

5. Participant satisfaction

Discontinuations and dose adjustments or dose interruptions were not significantly different between both treatments (Analysis 2.38; Analysis 2.39); approximately 5% of people discontinued, while dose adjustments were required in approximately one third of people.
Satisfaction with, convenience of and willingness to continue treatment was significantly higher in the group receiving deferasirox who had previously been treated with deferoxamine (Analysis 2.40; Analysis 2.42; Analysis 2.44), although differences were not as marked in the small group of deferoxamine-naive patients (Analysis 2.41; Analysis 2.43; Analysis 2.45) (even when those who did not respond to the questionnaire were counted as not satisfied or unwilling to continue treatment). Time lost from normal activities due to treatment was significantly less with deferasirox (Analysis 2.46; Analysis 2.47).

6. Cost of intervention per year

No data on costs of intervention were available from either study.

Further information on outcomes (information that could not be extracted quantitatively and information on outcomes not defined *a priori* but which have arisen from the review)

Further remarks and partly descriptive information on results of the two studies comparing deferasirox and deferoxamine (Cappellini 2005b; Piga 2002) can be found below.

Piga study

From the Piga phase II study reports, some safety data could be extracted by dose group (Piga 2002). We decided to split the control group to retain the information of reporting of adverse events for the different dose groups of deferasirox (see Analysis 2.7; Analysis 2.9; Analysis 2.10; Analysis 2.11; Analysis 2.12; Analysis 2.13; Analysis 2.14; Analysis 2.15; Analysis 2.16; Analysis 2.17; Analysis 2.19; Analysis 2.20; Analysis 2.21; Analysis 2.23; Analysis 2.24; Analysis 2.25; Analysis 2.26; Analysis 2.27; Analysis 2.28; Analysis 2.29; Analysis 2.30; Analysis 2.31; Analysis 2.32; Analysis 2.33; Analysis 2.34; Analysis 2.35; Analysis 2.36; Analysis 2.37; Analysis 2.38;).

"Four patients (two each in the deferasirox 20 mg/kg/day and DFO groups) were withdrawn prematurely from the study (Analysis 2.38), three due to adverse events and one due to an unsatisfactory therapeutic effect. In one patient receiving DFO, the adverse events leading to discontinuation (arthralgia, headache and fever) were suspected by the investigator to be study drug-related (Piga 2002). The other adverse events resulting in withdrawal from the study comprised arrhythmia and cardiac failure in a patient receiving DFO, and trauma due to a road traffic accident in a patient on deferasirox 20 mg/kg/day; neither was considered study drug-related. The patient withdrawn due to unsatisfactory therapeutic effect was randomised to deferasirox 20 mg/kg/day but the dose was reduced to 10 mg/kg/day on day 85 when a fall in LIC from 5.2 to 2.6 mg Fe/g dw was detected. On day 250, the LIC had increased again to 4.5 mg Fe/g dw. The patient was also noted to have QTc prolongation. Since this was an exclusion criterion for study participation, and given the limited clinical experience with deferasirox available at that time, dose re-escalation to 20 mg/kg/day was considered inappropriate and the study drug was therefore discontinued."

Other safety data are reported only descriptively: "Elevations of urinary b-2 microglobulin were detected in all treatment groups but were more frequent in patients receiving deferasirox 20 mg/kg/day. The elevations were transient and low-grade (<10-fold above the upper limit of normal) and tended to normalize despite continuation of the study drug. In three patients receiving deferasirox, treatment was temporarily interrupted and elevated values normalized within 7 to 10 days. In the two patients treated with deferasirox 20 mg/kg/day who experienced the highest elevations of b-2 microglobulin, the dose of study drug was reduced to 10 mg/kg/day as a precautionary measure, and this was followed by prompt normalization of the b-2 microglobulin levels. There were no consistent changes in levels of urinary N-acetyl-beta-glucosaminidase. Most patients had normal AST levels at baseline, though a relevant proportion (32%) had increased ALT, presumably reflecting liver damage due to chronic viral hepatitis and/or iron overload. No patient developed consistent or progressive elevations in transaminase levels. Serum copper and zinc levels fluctuated considerably during the study but no patient developed progressive decreases in these trace elements."

Efficacy was assessed by measuring LIC by biomagnetic susceptometry. In addition, markers of iron metabolism (serum ferritin, serum iron, serum transferrin and transferrin saturation) were analysed. Ferritin levels remained stable in the 20 mg/kg/d deferasirox and DFO group, while there was a tendency for ferritin levels to increase modestly in the 10 mg/kg/d deferasirox group. These data are presented only in a figure giving means and standard deviations at various time points; since no information was given with regard to change in mean serum ferritin with respective standard deviations, we were unable to extract data on ferritin. Regarding mean change in LIC, actual results are reported: -0.4 mg Fe/g dw for the 10 mg/kg/d DFX dose group, -2.1 mg Fe/g dw for the 20 mg/kg/d DFX dose group and -2.0 mg Fe/g dw for the 40 mg/kg/d DFO group. However, again we were unable to include these results in the analysis (Analysis 2.5), since no standard deviations for change in LIC are reported. To date, we were unable to obtain these additional data from either the primary investigators or Novartis.

Cappellini study

For the Cappellini study, discrepancies between patients who discontinued (n = 29) or those who died (n = 4), who were not included in the primary efficacy population (n = 33) and those who did not complete one year of study (n = 45 according to the primary report and n = 29 according to the report on patient-reported outcomes) were not clearly addressed (Cappellini 2005b). The success rate analysis (Analysis 2.3) was based on the primary efficacy population (n = 553), while changes in ferritin were based on n = 563 (Analysis 2.4), and both changes in LIC and iron excretion to iron intake ratio were based on those only who completed one year of study (n = 541) (per protocol analysis) (Analysis 2.5; Analysis 2.6).

In most patients, the LIC was measured by biopsy (n = 454) and only in a minority by SQUID (n = 87) (Cappellini 2005b). According to the authors, SQUID measurement underestimated LIC; however, since this applies to both groups and data were not completely given for all relevant outcomes, we did not examine these data for the subgroups separately, but rather decided to extract the data on LIC for the combined group measured by either biopsy or SQUID (Analysis 2.3; Analysis 2.5).

For both drugs a clear dose-effect relation was shown. Data on LIC and ferritin levels which were only given in figures showed that doses of 5 to 10 mg/kg/d of deferasirox most likely resulted in an increase of iron overload, 20 mg/kg/d maintained levels of iron overload and 30mg/kg/d of deferasirox resulted in a decrease of iron overload for most but not all patients. For deferoxamine, doses of up to 35 mg/kg/d appeared to maintain stable ferritin levels, while doses above 35 mg/kg/d resulted in an dose-dependent reduction of iron overload levels over the course of the study.

Regarding safety, it is not clearly stated whether all 586 patients were included in this analysis; however, since discontinuations are

reported, we assume that all 586 patients were included. Neither discontinuations nor dose adjustments/interruptions were significantly different between deferasirox and deferoxamine (Analysis 2.38; Analysis 2.39). Four deaths occurred during the study, one in the deferasirox group and three in the deferoxamine group; all were felt to be unrelated to the administration of the study drug by the independent Program Safety Board (Analysis 2.1).

Other safety information was given mainly descriptively or reported only for the deferasirox group, so that extraction was rarely possible; we contacted Novartis to request further details, but were unable to obtain any additional data to date.

"The most common adverse events with an apparent relationship to deferasirox were transient gastrointestinal events in 15.2% of patients that included abdominal pain, nausea and vomiting, diarrhoea, and constipation, as well as skin rash in 10.8% of patients. The gastrointestinal events lasted a median of eight days or less. These symptoms rarely required dose adjustment or discontinuation of deferasirox. Mild, dose-dependent increases in serum creatinine were observed in 38% of patients receiving deferasirox, most frequently at doses of 20 and 30 mg/kg in the population of patients having the most dramatic decrease in LIC and serum ferritin. These increases were sometimes transient and generally within the normal range, and they never exceeded two times the ULN. Similar increases in serum creatinine occurred in 14% of patients receiving deferoxamine. A dose reduction of 33% to 50% was undertaken for those 15 years or older with at least 2 consecutive increases in serum creatinine greater than 33% above baseline and for those younger than 15 years with at least 2 consecutive increases in serum creatinine greater than 33% that were also above the upper limit of age-appropriate normal. As the creatinine spontaneously normalized in a number of patients, dose reductions were instituted in only 13% of patients receiving deferasirox. In about 25% of patients the creatinine then returned to baseline, and in the remainder of the patients it remained stable or fluctuated between baseline and the maximum increase observed prior to dose reduction. Two patients developed elevated ALT values greater than twice the ULN while receiving deferasirox, which was felt by the investigator to be related to its administration. In one case, the ALT values were still elevated to 3 times ULN 4 months after drug discontinuation, and in the other theALT value returned to baseline within 1 month. In neither case was the alkaline phosphatase or bilirubin elevated significantly above baseline. Deafness, neurosensory deafness, or hypoacusis were reported as adverse events irrespective of drug relationship in 8 patients on deferasirox and 7 on deferoxamine. These symptoms were considered related to the study drug in 1 patient on deferasirox (0.3%) and 5 patients on deferoxamine (1.7%). Cataracts or lenticular opacities were reported as adverse events regardless of drug relationship in 2 patients on deferasirox and 5 on deferoxamine. These symptoms were considered related to the study drug in 1 (0.3%) patient on deferasirox and 4 (1.4%) patients on deferoxamine. No drug-related agranulocytosis was observed during this trial. Zinc and copper levels at the end of the study with deferasirox were comparable with those observed in patients receiving deferoxamine. The electrocardiograms performed at baseline and every 3 months during the study were analysed in a central laboratory for 258 patients receiving deferasirox and 245 patients receiving deferoxamine (86% of the overall population). No cardiac safety concerns specific to deferasirox were identified. A similar percentage of patients receiving deferasirox and deferoxamine experienced cardiac adverse events (deferasirox 5.1%, deferoxamine 6.9%) and serious adverse events (deferasirox 0.7%, deferoxamine 1.0%). Evaluation of paediatric patients revealed that growth and development proceeded normally while patients were receiving deferasirox." (Cappellini 2005b).

Patient-reported outcomes of this phase III trial were reported in a separate publication (Cappellini 2005b). Data were available regarding satisfaction (Analysis 2.40) and convenience (Analysis 2.42); however, only information of those patients who completed the questionnaire were available. For the outcomes "time lost from normal activities" (Analysis 2.46) and "willingness to continue" (Analysis 2.44) the number of patients who responded at end of study were not given; however, to incorporate these data, we assumed that all patients provided this information.

DISCUSSION

Summary of main results

In the two pharmacokinetic, dose-finding studies iron eliminating efficacy could be shown. Safety was acceptable to warrant further clinical testing in phase II and phase III trials. The phase II study (n = 71) focusing on safety did not find any statistically significant differences in the rate of common adverse events (> 16%) between deferasirox or deferoxamine (Piga 2002). Efficacy was judged to be comparable for 20 mg/kg/d of deferasirox and 40 mg/kg/d of deferoxamine supporting the assumed 1:2 equivalence ratio. The phase III study showed that depending on the actual dose of deferasirox, sufficient efficacy could be achieved to lower both serum ferritin level and LIC in iron overloaded thalassaemia patients (Cappellini 2005b). In comparison to deferoxamine, at a ratio of more than 2:1, deferoxamine showed a higher efficacy compared to deferasirox; however, similar efficacy of deferasirox could be achieved at a mean ratio of 1.8:1 of deferoxamine to deferasirox.

Adverse effects, particularly rare adverse effects, are difficult to investigate in randomised clinical trials with a limited number of patients. Accordingly, with the exception of "increase in creatinine" no significant differences in frequencies were observed. However, from the data it seems that gastrointestinal problems are more common while on deferasirox. With a total of 657 patients included in these two trials, frequencies of rare adverse events can

not be judged. Also, data on patient-relevant outcomes such as mortality or end-organ damage are either sparse (low number of events for mortality) or not available at all (end-organ damage) to adequately evaluate the efficacy of deferasirox. Due to study duration of maximum one year, long-term effects of deferasirox can not be judged.

Satisfaction with and convenience of deferasirox was judged significantly better resulting in higher willingness to continue treatment; time lost from normal activities was also reported to be less with deferasirox. The proportion of people who discontinued treatment for any reason or who required dose interruptions or adjustments was similar for both drugs.

Overall completeness and applicability of evidence

Because of our comprehensive search strategy and contact with Novartis, we are confident that we have identified all randomised trials comparing deferasirox with either placebo or deferoxamine. However, evidence on deferasirox for treatment of iron overload in people with thalassaemia is still limited due to the low number of studies and the limited number of patients included in trials comparing deferasirox with deferoxamine (n = 657).

Pooling of data from different trials was only feasible for a few outcomes, so that for most outcomes data from only one trial were available. Results from the ongoing trial will hopefully add information regarding some of these outcomes in the near future (Thalassaemia 2007).

Although these results are directly applicable to other people with thalassaemia major (since these studies only included this group of people), the applicability is hampered by the use of surrogate endpoints and the short duration of studies. Since the value of iron chelation therapy with deferoxamine in thalassaemia patients is well established (Roberts 2005), change in surrogate parameters such as serum ferritin or LIC would be acceptable to deduce changes in patient-relevant endpoints such as mortality or end-organ damage for studies comparing deferasirox to placebo. However, to adequately compare the efficacy of two iron chelating drugs such as deferasirox and deferoxamine, information on patient relevant endpoints such as mortality or end-organ damage should be available. In particular, there is a lack of data from randomized trials regarding removal of cardiac iron and prevention of cardiac complications.

Although studies with longer duration investigating these patient-important endpoints would be important to adequately weigh benefits and adverse effects of deferasirox compared to standard treatment with deferoxamine, it has to be taken into account that this kind of study takes a long time to conduct and is very cost-intensive. Therefore, it is not surprising that the producer of deferasirox has no particular interest in this kind of study after approval by FDA and EMA. However, for a comprehensive evaluation of effects of deferasirox and comparison with deferoxamine, such studies would be necessary.

Some additional data including longer-term effects of on deferasirox were available from observational studies. However, these studies were not systematically searched for nor critically evaluated within this review. Also, due to a higher risk of bias and potential confounding, these kind of data are not as well-suited for comparison of two interventions as are data from high quality randomised trials.

It is important to note, however, that recently, with wider use of deferasirox outside of clinical studies, other more severe adverse effects have been reported, such as: cytopenias; Fanconi syndrome and renal failure (Rafat 2009; Grange 2010; Yew 2010); liver failure; and gastrointestinal bleeding, which resulted in a boxed warning by the FDA (FDA Boxed Warning 2010). These potential severe adverse effects have to be taken into consideration when prescribing or using deferasirox.

Also, recent studies have shown that higher doses of deferasirox than those evaluated in the included trials are often needed to achieve adequate reduction of iron overload or prevent further iron accumulation in heavily transfused patients (Chirnomas 2009; Taher 2009).

Finally, the oral mode of application of deferasirox presents a very important advantage of deferasirox over deferoxamine, which is of high relevance to patients (Taher 2010). Whether this advantage will translate into better long-term adherence and improved patient-relevant outcomes still has to be shown (Trachtenberg 2011).

Quality of the evidence

Overall, the quality of evidence on deferasirox for treatment of iron overload in thalassaemia is still limited. The risk of bias of the two studies comparing deferasirox to deferoxamine is moderate. Due to different modes of application, both trials were not blinded. While publication bias seems not to be an issue, it is unclear whether selective reporting of results may have occurred.

Since all studies were designed and conducted with support or involvement from Novartis (or both), independent, investigator-initiated trials confirming these results would further increase the confidence in the body of evidence.

Potential biases in the review process

A very comprehensive search strategy was applied to identify all potential studies and their reports. However, although 31 reports plus two responses to letters on four RCTs were identified, information on several relevant outcome data prespecified in our protocol were not reported. Several of these outcome measures are, however, important to make an informed and balanced decision on which chelator to choose. Some of these outcome measures were most likely not ascertained during the trial, however, others

could have well been collected but not reported. Unfortunately, even after contacting the primary investigators, to date we have not been able to obtain any additional data.

We followed the rigid methodology for systematic reviews outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), e.g. extracting data independently in duplicate to minimize errors and reduce bias in the process of doing this systematic review.

Agreements and disagreements with other studies or reviews

Vanorden and Hagemann published the first review based on a systematic literature search in 2006 focusing on deferasirox (Vanorden 2006). Besides data from the phase III trial, this review includes evidence from phase I and phase II as well as pharmacokinetic studies in both humans and non-humans. The authors made no attempt to pool the data; so findings are presented narratively (including observational data). The authors concluded that their findings suggest that deferasirox is as safe and effective as deferoxamine.

Lindsey and co-authors summarized the available data from five phase I/II and the one phase III trial in their systematic review published in 2007 (Lindsey 2007). All six studies are critically discussed, but no pooling of data was performed and data are synthesized qualitatively. Based on the only trial looking at efficacy as a primary endpoint (Cappellini 2006), the authors come to the conclusion that the two agents have similar efficacy although, overall the non-inferiority of deferasirox could not be shown by the primary phase III study investigators. Tolerability is assessed as good, even though deferasirox is associated with a higher incidence of adverse effects. The authors conclude that long-term efficacy and safety remain to be established.

In 2009, McLeod and co-authors published a comprehensive health technology assessment on deferasirox for secondary iron overload in patients with chronic anaemia, such as thalassaemia and SCD (McLeod 2009). They identified 14 randomised trials looking at various iron chelation regimens with a high degree of heterogeneity between trials in terms of trial design and outcome reporting. Only three of these compared deferasirox to deferoxamine, but data were not included in a meta-analysis. Furthermore, eight economic evaluations were included in their report. The authors conclude that it appears that there is little difference between agents in terms of reducing serum ferritin. The economic evaluations appear to demonstrate the cost-effectiveness of deferasirox compared to deferoxamine. However, the authors state that both their clinical and economic analyses were restricted by the available evidence and should only be considered exploratory. Cochrane Reviews on the effects of deferasirox in people with sickle cell disease and myelodysplastic syndrome have recently been published; both conclude that data on deferasirox in these groups of patients are still limited and therefore evidence is insufficient to recommend first-line use of deferasirox in sickle cell disease or myelodysplastic syndrome. Several narrative reviews on deferasirox have also been published of late. These have usually concluded that efficacy is given and the profile of adverse events manageable and therefore acceptable (Cappellini 2008; Cappellini 2009; Porter 2009).

A clinical practice guideline by the Italian Society of Hematology for the management of iron overload in thalassaemia major and related disorders support our findings and conclusions by recommending deferoxamine for children who start iron chelation therapy before six years of age and in whom the goal of chelation therapy is the prophylactic maintenance of iron balance; while oral chelators (such as deferasirox) should be considered investigational and be used primarily within clinical trials or registries or for patients with poor compliance to, or experiencing adverse events from deferoxamine (Angelucci 2008). Due to the limited evidence, these recommendations were given a level D according to the Scottish Intercollegiate Guidelines Network (SIGN) grading system reflecting consensus of the experts (SIGN 2008).

AUTHORS' CONCLUSIONS

Implications for practice

Deferasirox offers an important alternative line of treatment for people with thalassaemia and secondary iron overload. Based on the available data from randomized trials, deferasirox does not seem to be superior to deferoxamine. Similar efficacy seems to be achievable depending on the dose and ratio of deferasirox compared to deferoxamine. However, whether this will result in similar efficacy in the long run and will translate to similar benefits as has been shown for deferoxamine, needs to be confirmed.

Therefore, we believe that deferasirox should be offered as alternative to all patients with thalassaemia who either show intolerance to deferoxamine or poor compliance with deferoxamine. However, in our opinion, data are still too limited to support a general recommendation of deferasirox as first line treatment instead of deferoxamine. If people show a strong preference for deferasirox, it could be offered as first line option in individual patients after detailed explanation of benefits and potential risks.

Implications for research

Although the efficacy of deferasirox to reduce iron overload has been shown, data for a comprehensive comparison with the standard treatment of deferoxamine are still insufficient. Therefore, patients should ideally be included in further, investigator-initiated clinical trials independent from the producer Novartis assessing patient-relevant outcomes and long-term effects of deferasirox. In addition, assessment of rarer adverse effects as well as assessment of long-term compliance would be reasonable.

Since this review only included evidence from randomised trials and additional evidence is available from non-randomised, uncontrolled trials, a systematic review also considering this observational evidence would most likely shed some additional light on this topic. Taking into account that there is a third chelator, deferiprone, available and approved in some countries for treatment of iron overload in people with thalassaemia, a network analysis comparing these three interventions would seem useful.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cappellini 2005b

Methods	Open-label, multinational, multicenter, randomised, phase III, non-inferiority study
Participants	"Eligible patients included those at least 2 years of age with a diagnosis of -thalassaemia and chronic iron overload from blood transfusions as indicated by an LIC value of 2 mg Fe/g dw or higher. Patients needed to be receiving at least 8 blood transfusions per year, and could be enrolled irrespective of prior chelation therapy. Female patients were required to use double-barrier contraception. Patients were excluded from this trial if they had one of the following conditions: an ALT level greater than 250 U/L during the year prior to enrolment, chronic hepatitis B infection, active hepatitis C infection, a history of a positive HIV test, serum creatinine above the ULN, a urinary protein/creatinine ratio of greater than 0.5 mg/mg, nephrotic syndrome, uncontrolled systemic hypertension, a prolonged corrected QT interval, or systemic infection within the 10 days prior to entry. Additionally, patients were excluded if they had gastrointestinal conditions preventing absorption of an oral medication, concomitant conditions preventing therapy with deferasirox or deferoxamine, a history of ocular toxicity related to iron chelation therapy, a poor response to deferoxamine, or noncompliance with prescribed therapy."
Interventions	"Once-daily treatment with deferasirox at the assigned dose was administered as a suspension in water half an hour prior to breakfast 7 days a week. Deferoxamine was administered as a slow subcutaneous infusion using electronic Microject Chrono infusion pumps (Canè Medical Technology, Torino, Italy) over 8 to 12 hours, 5 days a week. Exceptions were permitted to the number of days of administration, which ranged from 3 to 7 days a week (to facilitate comparison, all deferoxamine doses reported are normalized to administration for 5 days a week; i.e., 50 mg/kg administered 7 days a week would be reported as 70 mg/kg) Treatment with either therapy was continued for 1 year, and was only interrupted at the discretion of the investigator for intercurrent illness or adverse events. Dose modifications were mainly permitted for safety reasons after consultation with Study Monitoring Committee or Program Safety Board members. Drug administration was recorded on the case report form." (see also Table 4)
Outcomes	"Assessments for safety and efficacy performed at monthly intervals at a central laboratory (B.A.R.C. Laboratories, Gent, Belgium) included complete blood count/differential, electrolytes, liver function tests, trace element analysis, urinary protein/creatinine and serum ferritin, iron, and transferrin. ECGs and ophthalmologic and auditory examinations were performed every 3 months. For patients younger than 16 years of age, additional evaluations included assessment of growth rate and sexual development. Growth was monitored by measuring standing height and sitting height using a Harpenden (Holtain, Crosswell, United Kingdom) stadiometer with an approximation to within 0.1 cm. This assessment was performed every 3 months during the trial in order to calculate growth velocity. At the end of the 1-year period, all patients underwent a repeat LIC determination using the same methodology as the initial determination performed (liver biopsy or SQUID)

	Net iron balance (total body iron excretion) was calculated based on the amount of RBCs transfused (iron intake in milligrams = *Kin*) and on the changes in total body iron from baseline to the end of the study: net body iron balance = (*Kin* + [*Us(t0) - Us(t)*])/*(t - t0))*; iron intake in milligrams of iron was calculated as *Kin* = (total amount of RBCs transfused) x 1.08. The total amount of RBCs transfused is calculated as the total amount of blood in milliliters multiplied by the hematocrit of each unit in percentage divided by 100. Complete datasets (volume and hematocrit) were available for all transfusions in three quarters of the patients. If an individual hematocrit was missing, the average hematocrit of the blood given as transfusions at the respective centre was used, and if this was not available the value was assumed to be 65%. If the amount of blood transfused was given only as units, instead of in milliliters with the hematocrit, the volume of RBCs was assumed to be 185 mL and thus 200 mg iron was assumed to be given per unit. *Us (t)* is the total body iron extrapolated from the LIC (in mg Fe/g dw) at time *t* (*t0* = 0, for baseline measurement) *Us(t)* = 10.6 x LIC (x [body weight in kg]). Both the iron intake *Kin* and the changes in total body iron *Us(to) - Us(t)* are expressed in milligrams of iron; therefore, the net body iron balance is expressed in milligrams of iron per day The**primary response criterion** for this trial was nonparametric and consisted of maintenance or reduction of LIC (Table 3). As LIC values greater than 7 mg Fe/g dw have been reported in the literature to be associated with an increased morbidity and mortality, maintenance or reduction of LIC values to below this level was desirable as an endpoint. However, because it was considered unrealistic to expect to reach values below 7 mg Fe/g dw after 1 year in heavily iron-overloaded individuals (LIC 10 mg Fe/g dw), a decrease of at least 3 mg Fe/g dw was selected as a reasonable target to be accomplished in 1 year, since in most patients such an annual reduction would lead to safe body iron levels within a few years. Reduction of LIC to less than 1 mg Fe/g dw was considered undesirable, potentially exposing patients to the risk of overchelation, and such patients were to be considered failures in the analysis of success. **Secondary criteria for response** included evaluation of the change in serum ferritin levels over time and evaluation of net body iron balance. "
Notes	Non-inferiority trial (65 centres in 12 countries; enrolment period: March to November 2003): "The percentage of successes for each treatment was calculated in the population representing all patients who completed both LIC assessments or who discontinued due to safety concerns (considered as failures). Deferasirox was to be declared non-inferior to deferoxamine if the lower limit of the 95% confidence interval (2-sided) for the difference in the percentage of treatment successes of deferasirox and deferoxamine was above -15%. This margin was chosen based on statistical consideration used for other agents. The sample size was calculated to demonstrate non-inferiority at a 2-sided alpha level of 5% if the success rates of deferasirox and deferoxamine were both 50%. Thus, 468 patients (234 per arm) would have been required to achieve a power of 90%. Although intended to recruit only 500 patients, a greater number of patients than expected entered into screening met the enrolment criteria. The confidence intervals for the success rates and differences in success rates were calculated using the normal approximation Reported *P* values for the investigation of secondary endpoints are based on 1- or 2-sided significance tests (Student *t*-test)."
Risk of bias	

Cappellini 2005b (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given with regard to sequence generation. "Randomisation was stratified by age groups: 2 to younger than 12 years, 12 to younger than 18 years, and 18 years or older. After randomizations, patients were assigned by the investigator to a dose dependent on their baseline LIC according to the algorithm noted in Table 2."
Allocation concealment (selection bias)	Unclear risk	No details given with regard to concealment of allocation. "Randomisation was stratified by age groups: 2 to younger than 12 years, 12 to younger than 18 years, and 18 years or older. After randomisation, patients were assigned by the investigator to a dose dependent on their baseline LIC according to the algorithm noted in Table 2."
Blinding (performance bias and detection bias) All outcomes	High risk	This was an open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No flowchart according to CONSORT available. 586 patients were randomised of which 29 discontinued and 4 died. The primary efficacy population consists of 553 patients. However, it is stated that 541 patients completed one year of therapy. It remains unclear, what happened to the remaining 12 patients "Most patients completed 1 year of therapy on this study: 541 (92.3%) of 586 underwent both baseline and 1-year LIC assessments. Discontinuations were relatively similar in the groups receiving deferasirox (n = 17) and deferoxamine (n = 12)." "The primary efficacy population in this study consisted of 553 patients with LIC evaluations at baseline and after 52 weeks and those who discontinued due to safety reasons (adverse event, abnormal laboratory value or test procedure result, or iron overload-related death)."

Cappellini 2005b (*Continued*)

Selective reporting (reporting bias)	Unclear risk	see also "Outcomes" in "Characteristics of included studies" table Cappellini 2005b above. Not all time points nor all parameters (secondary: e.g. trace elements)) reported. However, EOS primary results are reported and secondary as outlined in methods section. However, it remains unclear whether any others were measured.
Other bias	Unclear risk	Involvement of Novartis in design, conduct and analysis of the trial "Supported in part by research funding from Novartis Pharma to Y.A., A.C., S.P., A.P., T.C., A.K., Y.K., G.J.-S., C.M., M.V., A.K.-S., M.D.C., P.G., R.G., G.D., J.P., I. T., C.V., and N.O. Two authors (P.M. and D.A.) have declared a financial interest in a company whose product was studied in the present work. Several of the authors (H.O. , C.R.-D., P.M., D.A.) are employed by a company (Novartis Pharma) whose product was studied in the present work."

Galanello 1999

Methods	Two-period, randomised, double-blind, placebo-controlled, sequential parallel-group design
Participants	"Male Caucasian patients age $\geq$ 18 years with transfusion-dependent β-thalassaemia were included in the study. The patients had serum ferritin values between $\geq$ 1500 ng/ mL and $\leq$ 5000 ng/mL, as well as posttransfusion haemoglobin levels of at least 13 ± 0. 5 g/ dL. All patients had previously been treated with a mean daily dose of 20 to 50 mg/ kg/day deferoxamine for at least 4 weeks before screening Excluded were those patients with a history of systemic reactions to treatment with deferoxamine, a history of systemic disease, or any medical condition that might have significantly altered the absorption, distribution, metabolism, or excretion of the study drug."
Interventions	"Following a 16-day run-in period, 24 patients were allocated to one of three study groups, with each group consisting of 8 patients. Each group was administered two single oral doses of ICL670 at an interval of at least 7 weeks, first a lower dose and later a higher dose. Group 1 received 2.5 and 20 mg/kg, group 2 received 5 and 40 mg/kg, and group 3 received 10 and 80 mg/kg ICL670, in all cases given as an oral suspension of 100 mL prepared from dispersible tablets. Before proceeding to a higher dose, the safety and tolerability of the preceding dose had to be assessed as satisfactory. In each treatment period, 2 of 8 patients received placebo in such a way that a given patient did not receive placebo more than once. Patients went back to their usual deferoxamine therapy and transfusion scheme in the interval between study periods."

Galanello 1999 (*Continued*)

Outcomes	"Safety assessments included physical examination, vital signs, ECG, audiometry, clinical laboratory evaluations, and adverse event monitoring. Safety laboratory evaluations included hematology (including transferrin and serum iron), biochemistry (including routine renal and liver function parameters, zinc, copper, and vitamin C), special kidney function parameters (α-glutathione-S-transferase, N-acetyl-β-Dglucosaminidase, β2-microglobulin, and retinol-binding protein), and urinalysis. Safety assessments were performed up to 10 days post dose Efficacy was assessed by urinary iron excretion. Iron in serum and urine was analysed by atomic absorption spectrometry and transferrin in serum by nephelometry."
Notes	"One patient discontinued before the second period due to gastrointestinal tract surgery and was replaced for the second period only, resulting in 25 patients actually randomized."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given with regard to sequence generation. From information given in paper, unclear, whether randomisation took place both in group assignment and in allocating patients to placebo. Author confirmed that randomisation was used to allocate placebo "Randomization was used to assign both drug (all treatment groups) and placebo. Hope to have clarified."
Allocation concealment (selection bias)	Unclear risk	No details given with regards to concealment of allocation.
Blinding (performance bias and detection bias) All outcomes	Low risk	"The study employed a two-period, randomised, double-blind, placebo-controlled, sequential parallel group design." However, no definition of double-blind. Unclear whether e.g. outcome assessors and data analysts were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not applicable. Data from all patients are presented.
Selective reporting (reporting bias)	Unclear risk	Only general information with regard to safety issues. No clear-cut comparison of placebo vs verum groups. Unclear, whether other parameters were evaluated than those reported

Galanello 1999 (*Continued*)

Other bias	Unclear risk	Novartis involved in trial. No details given and no information available with regard to potential conflicts of interest "From the Ospedale Regionale Microcitemie, Dipartimento di Scienze Biomediche e Biotecnologie, Università di Cagliari, Italy; Ospedale Regina Margherita, Dipartimento di Scienze Pediatriche, Centro Microcitemie, Torino, Italy; and Novartis Pharma AG, Origgio (Italy), Rueil-Malmaison (France), and Basel (Switzerland). Submitted for publication May 12, 2002; revised version accepted February 22, 2003. Address for reprints: Dr. Romain Séchaud, Novartis Pharma AG, Exploratory Clinical Development, WSJ-27.3.086, CH-4002 Basel, Switzerland."

Nisbet-Brown 2001

Methods	Randomized, double-blind, placebo-controlled dose-escalation trial
Participants	24 participants with transfusion-dependent beta-thalassaemia of age 16 years and older with serum ferritin values between 1000 and 8000 ng/ml and liver biopsies done in the previous 3 months with greater than or equal to 3.5 mg iron per g dry weight. All patients required treatment with deferoxamine at 20 mg/kg/day (mean daily dose) for at least 4 weeks before screening and a post-transfusion haemoglobin concentration of at least 130 g/L
Interventions	"Dose-escalation study of 10 mg/kg (n = 5) , 20 mg/kg (n = 6), and 40 mg/kg (n = 7) ICL670 given daily to patients with thalassaemia and transfusional iron overload; placebo group (n = 5)."
Outcomes	"Primary objectives included assessment of safety, tolerability, pharmacokinetics, and cumulative iron balance." 1. Dietary, urine and faecal iron measured by atomic absorption spectrometry 2. Net faecal iron excretion calculated by individual iron content in faeces minus individual iron content in the diet (the NIE for each patient in mg Fe kg-1 day-1 was derived from the sum of the daily measurements of net faecal iron excretion and urinary iron excretion) 3. UIBC calculated from serum iron concentration and total iron binding capacity
Notes	"128 patients were assessed for entry into the study; 104 were excluded. Thus, a total of 24 patients with transfusion-dependent thalassaemia were randomly allocated, including three replacements for patients who were withdrawn for serious adverse events during the study."

Nisbet-Brown 2001 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation process not stated. "The randomisation sequence was generated by Novartis Pharmaceuticals and delivered to the research pharmacy in duplicate sealed envelopes."
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes were used. However, unclear whether opaque and numbered "The randomisation sequence was generated by Novartis Pharmaceuticals and delivered to the research pharmacy in duplicate sealed envelopes."
Blinding (performance bias and detection bias) All outcomes	Low risk	This was a placebo-controlled trial, in which investigators and those responsible for administering study drug were blinded with regard to treatment allocation. However, it remains unclear whether outcome assessors and data analysts were blinded as well "The investigators and those responsible for administering study drug were unaware of treatment allocation." "Placebo and ICL670 were prepared as dispersible tablets with standard excipients. Tablets were suspended in water, and patients ingested the drug or placebo on an empty stomach."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Therefore, all patients who began either placebo or drug were included in the data analysis, whether they completed the 12-day course or withdrew prematurely."
Selective reporting (reporting bias)	Unclear risk	"We did clinical, laboratory, and other safety assessments regularly throughout the study." However, only a limited amount of data are presented in the publication
Other bias	Unclear risk	Conflicts of interest are stated; Novartis was involved in design and conduct of this study (see below)

Nisbet-Brown 2001 (*Continued*)

		"The design of the study was shared equally by the academic participants and Novartis. The study was monitored by Novartis in accordance with good clinical practice requirements and all data were entered into a validated clinical trial database. Final data were made available to all investigators, and interpretations of data were made by all collaborators." "Full financial support for this study was provided by Novartis Pharmaceuticals Corporation under contracts with Children's Hospital Boston and New York Presbyterian Hospital."

Piga 2002

Methods	Open label, randomised, multicenter, phase II trial
Participants	People with thalassaemia and transfusional iron overload: Inclusion: • should have been regularly transfused • should have received a mean daily dose of DFO ≥30 mg/kg for 5 days/week for at least 4 weeks prior to entering the screening period • Serum ferritin between 2000-8000ng/ml on at least two evaluations in the last 12 months or • LIC of 5-15 mg Fe/g dry weight measured in the last 12 months by SQUID • Average post-transfusion haemoglobin level between 10.5-13.5 g/dl during last 12 months Exclusion: • AST or ALT >250 U/l • Creatinine clearance <80 ml/minute • People with hypertension • People with any degree of A-V block, clinically relevant QT prolongation • Treatment with digoxin or any other drug that could induce prolongation of A-V conduction • People with diagnosis of cataract or a previous history of clinically relevant ocular toxicity related to iron chelation
Interventions	"Patients were randomised in a 1:1:1 ratio (24 patients : 24 patients : 23 patients) to receive either once-daily deferasirox (10 or 20 mg/kg) or DFO (40 mg/kg on 5 consecutive days per week). Daily doses of deferasirox were prepared using 250 mg tablets which were divisible into four parts. The correct number of tablets was dispersed in a glass of non-carbonated mineral water, stirred and ingested 30 minutes before breakfast. DFO doses were prepared as a 10% solution using commercially available vials of 500 or 2000mg dry powder. Subcutaneous infusion was performed using a Microject Crono® pump over 8-12 hours for 5 consecutive days each week. The study protocol allowed for dose adjustment within the range of 5-40 mg/kg/day in the deferasirox groups and 20-

	50 mg/kg in the DFO group." "Depending on the response of each patient, assessed primarily using the change in LIC at three consecutive determinations, dose increases or decreases were made by ±5 or ±10mg/kg in the deferasirox groups and by ±10mg/kg in the DFO group. Dose reductions were performed if the decrease in LIC was extrapolated to fall below 2 mg Fe/g dw within the next 12 weeks and dose increases were prescribed if an increasing trend in LIC was noted. Dose adjustments were decided on a case-by-case basis in joint consultation between the Study Monitoring Committee and the sponsor."
Outcomes	Safety assessment: • Laboratory testing at baseline and at 2-weekly intervals including blood indices, liver and renal function, serum electrolytes, copper and zinc. • Second void urine samples with measurement of N-acetyl-beta-glucosaminidase and beta2-miroglobulin • Ophthalmological examination every 2 weeks including slit lamp examination of the lens and retinal fundoscopy • Audiometry, ECG and liver ultrasonography every 3 months Efficacy assessment: • Liver iron concentration measured by SQUID at screening and then every 12 weeks and at end of study • Markers of iron metabolism (serum ferritin, serum iron, serum transferrin, transferrin saturation)
Notes	"During the 14-day run-in period, eligible patients had their usual DFO therapy adjusted to 40 mg/kg given on 5 consecutive days each week. Baseline LIC values were determined towards the end of the screening period. On day -5, patients were admitted to the study site to receive a blood transfusion to achieve a target haemoglobin level of ≥13g/dL prior to commencing study treatment followed by a DFO washout period of 5 days."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed using a validated system that generates an automated random assignment of numbers to treatment groups." We expect that using this system resulted in an adequate sequence generation
Allocation concealment (selection bias)	Unclear risk	"Randomization was performed using a validated system that generates an automated random assignment of numbers to treatment groups." No information is given with regard to allocation concealment

Piga 2002 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	It is classified as an open-label trial. There is no mentioning of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients are included in safety analysis (primary objective). Few patients only are not included in efficacy analysis (secondary objective)
Selective reporting (reporting bias)	Unclear risk	"Laboratory tests, including evaluation of blood indices, liver and renal function, serum electrolytes, copper and zinc, were performed at baseline and at 2-weekly intervals throughout the study. All laboratory parameters were measured at a central laboratory (EXACTA Clinical Trials Services, Verona, Italy). Second void urine samples were collected for measurement of N-acetyl-b-glucosaminidase and an aliquot of urine was alkalinized for measurement of b-2 microglobulin. An ophthalmology examination, including a slit lamp examination of the lens and retinal fundoscopy, was performed every 2 weeks. Audiometry, ECG and liver ultrasonography were carried out every 3 months. Adverse events were recorded at each study visit and the severity of each adverse event was graded as mild, moderate or severe. A serious adverse event was defined as a medically significant event that was either fatal or life threatening, required surgical intervention, prolonged hospitalization or resulted in persistent disability. All adverse events and serious adverse events were assessed by the investigator for a possible relationship to the study drug. Adverse events were ranked according to incidence in the deferasirox 20 mg/kg/day treatment group." "All biomagnetic liver susceptometry evaluations were performed at the Ospedale Regina Margherita, University of Turin, Italy. LIC was determined at screening and then every 12 weeks during treatment and at the end of the study..... During the study, markers of iron metabolism (serum ferritin, serum iron, serum transferrin and transferrin saturation) were analyzed by a central

		laboratory (EXACTA Clinical Trials Services, Verona, Italy). The transferrin saturation was calculated from the serum iron and the transferrin concentrations. Urinary iron excretion was determined in 24-hour urine collections in ten patients taking deferasirox (five in each dose group) who also underwent blood sampling for pharmacokinetic analyses. Urinary iron excretion was measured using atomic absorption spectrometry." Only selected parameters at selected time points are reported
Other bias	Unclear risk	Conflicts of interest are reported in the publication (Piga 2002): "AP, HO, RS and DA designed the study. AP, RG, GLF, MDC, RO, AZ, GD, EB, AL, and LZ collected data. RS, NH, JF, HO and DA analysed data. AP, RG, GF, MDC, RS, JF, HO and DA interpreted the results and jointly contributed to the first draft of the article. All authors reviewed and contributed revisions to the article and all authors gave final approval of the version to be published. Editorial assistance was provided by Drs Ruth Tidey and Matthew Lewis. RS, NH, JMF, HO, DA are employed by Novartis Pharma, whose product was studied in the present work. AP, RG, GLF, MDC received institutional research support, participated in scientific meetings and received lecture fees from Novartis Pharma. Although the authors do not own the data, they had full access to all data in this study and take complete responsibility for the integrity of the data, the accuracy of the data analysis and the final report Interim analyses of this study have been reported at the 44th American Society of Hematology Annual Meeting, Philadelphia, USA, 2002; BioIron World Congress on Iron Metabolism, Bethesda, USA, 2003; European Haematology Association Annual Meeting, Lyon, France, 2003; and Thalassaemia International Federation Annual Meeting, Palermo, Italy 2003. Funding: This study was supported by Novartis Pharma AG, Switzerland."

ALT: alanine aminotransferase
AST: aspartate aminotransferase
A-V: atrio-ventricular
CONSORT: consolidated standards of reporting trials
DFO: deferoxamine
ECG: electrocardiogram
Fe: iron
LIC: liver iron concentration
NIE: net iron excretion
RBCs: red blood cells
SQUID: superconducting quantum interference device
UIBC: unsaturated iron binding capacity
ULN: upper limit of normal

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
EPIC 2008	Not randomised, no comparison group. Single-arm observational study
ESCALATOR 2005	Not randomised, no comparison group. Single-arm observational study

Characteristics of ongoing studies *[ordered by study ID]*

Thalassaemia 2007

Trial name or title	Evaluating use of deferasirox as compared to deferoxamine in treating cardiac iron overload
Methods	A multicenter, randomized, open-label phase II trial evaluating deferasirox compared with deferoxamine in patients with cardiac iron overload due to chronic blood transfusions Patients will be treated for 12 months (core study phase). Patients who complete the core study phase will be offered to continue their study treatment in a 12-months extension phase. During the core and extension, the effects of treatment on iron overload in the heart and the liver will be evaluated using specific MRI assessments
Participants	Estimated enrolment: 192 Inclusion criteria: • male or female patients, aged 10 years and above, with beta-thalassaemia major or DBA or sideroblastic anaemia on chronic transfusion therapy, having given written consent to participate in the study; • Patients with cardiac iron as measured by a myocardial T2* value that is $\geq$ 6 ms but not $\geq$ 20 ms; • Patients with a lifetime history of at least 50 units of red cell transfusions, and must be receiving at least $\geq$ 10 units/yr of red blood cells transfusions; • Patients with a LVEF $\geq$ 56 % as determined by CMR; • Patients with LIC value $\geq$ 3 mg Fe / g dw, as determined by liver MRI. Exclusion criteria: • Patients with clinical symptoms of cardiac dysfunction; • Patients unable to undergo study assessments including MRI;

	• Patients participating in another clinical trial or receiving an investigational drug. Other protocol-defined inclusion/exclusion criteria may apply
Interventions	Experimental: deferasirox Comparator: deferoxamine
Outcomes	Primary outcome measures • Relative change from baseline in myocardial T2* after 12 months treatment with deferasirox vs deferoxamine. [Time frame: 1 year] [Designated as safety issue: no] Secondary outcome measures • Cardiac function after 6 & 12 months of treatment with deferasirox vs. deferoxamine, by change in left ventricular ejection fraction, left ventricular systolic & diastolic volumes, and the proportion of patients dropping out due to cardiac dysfunction. [Time frame: 1 year] [Designated as safety issue: no] • Absolute and relative change from baseline in LIC by liver MRI, and serum ferritin after 6 and 12 months treatment with deferasirox vs deferoxamine. [Time frame: 1 year] [Designated as safety issue: no] • Safety and tolerability of deferasirox vs deferoxamine over the 12 months treatment period. [Time frame: 1 year] [Designated as safety issue: no] • Single and repeated dose pharmacokinetics of deferasirox. [Time frame: 1 year] [Designated as safety issue: no] • Additional safety and efficacy for deferasirox and deferoxamine for patients treated beyond 12 months in the extension phase. [Time frame: 1 year] [Designated as safety issue: no]
Starting date	Study start date: November 2007 Estimated primary completion date: December 2010 (Final data collection date for primary outcome measure)
Contact information	Novartis Pharmaceuticals: +1 800-340-6843
Notes	ClinicalTrials.gov identifier: NCT00600938 Study ID number: CICL670A2206

Information given in table according to www.clinicaltrials.gov. Data from Clinicaltrials.gov were extracted on 23.04.2010.
CMR: cardiovascular magnetic resonance
LIC: liver iron concentration
LVEF: left ventricular ejection fraction
MRI: magnetic resonance imaging

DATA AND ANALYSES

Comparison 1. Deferasirox vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at any time point	2	47	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Discontinuations	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Rash	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Abdominal pain	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 Extended QT interval, hypocalcaemia, hypoparathyroidism	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.6 Retinal infarct	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Deferasirox vs Deferoxamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at any time point	2	657	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.12]
1.1 Mortality at 48 weeks (deferasirox 10 mg/kg/d)	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Mortality at 48 weeks (deferasirox 20 mg/kg/d)	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Mortality at 1 year	1	586	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.12]
2 Responders analysis I (responder: fall in LIC >10%)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Response at 48 weeks (deferasirox 10 mg/kg/d)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Response at 48 weeks (deferasirox 20 mg/kg/d)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Responder analysis II (responder: LIC 1 to less than 7 mg Fe/g dw)	1	553	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.69, 0.92]
3.1 Response at 1 year (LIC below 7 mg Fe/g dw)	1	172	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.37, 0.64]
3.2 Response at 1 year (LIC at least 7 mg Fe/g dw)	1	381	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.84, 1.18]
4 Mean change in serum ferritin (µg/l)	1	563	Mean Difference (IV, Fixed, 95% CI)	521.82 [387.78, 655.87]

4.1 less than 3mg Fe/g dw (median 5mg Deferasirox / 30mg Deferoxamine)	1	28	Mean Difference (IV, Fixed, 95% CI)	978.0 [544.71, 1411.29]
4.2 more than 3 to 7mg Fe/g dw (10/35)	1	150	Mean Difference (IV, Fixed, 95% CI)	801.0 [572.53, 1029.47]
4.3 more than 7mg Fe/g dw (20/41)	1	169	Mean Difference (IV, Fixed, 95% CI)	328.0 [124.94, 531.06]
4.4 more than 14mg Fe/g dw (30/51)	1	216	Mean Difference (IV, Fixed, 95% CI)	77.0 [-303.18, 457.18]
5 Change in LIC (mg Fe/g dw) evaluated by biopsy or SQUID	1	541	Mean Difference (IV, Fixed, 95% CI)	2.37 [1.68, 3.07]
5.1 LIC 3 mg Fe/g dw or less (5/30)	1	28	Mean Difference (IV, Fixed, 95% CI)	4.3 [2.30, 6.30]
5.2 LIC more than 3 mg to 7 mg (10/35) Fe/g dw	1	143	Mean Difference (IV, Fixed, 95% CI)	3.80 [2.74, 4.86]
5.3 LIC more than 7 mg to 14 mg Fe/g dw (20/41)	1	164	Mean Difference (IV, Fixed, 95% CI)	1.5 [0.28, 2.72]
5.4 LIC more than 14 mg Fe/g dw (30/51)	1	206	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-4.55, -0.45]
6 Iron excretion-intake ratio	1	541	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.24, -0.12]
6.1 less than 3 mg Fe/g dw (median 5 mg deferasirox / 30 mg deferoxamine)	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.37 [-0.54, -0.20]
6.2 more than 3 to 7 mg Fe/g dw (10/35)	1	143	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.41, -0.21]
6.3 more than 7 mg Fe/g dw (20/41)	1	164	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.21, -0.01]
6.4 more than 14 mg Fe/g dw (30/51)	1	206	Mean Difference (IV, Fixed, 95% CI)	0.23 [0.05, 0.41]
7 Any adverse event (AE)	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.94, 1.25]
7.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.90, 1.40]
7.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.86, 1.26]
8 Any serious AE	1	586	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.11, 3.88]
9 AE: Isolated serum creatinine increase above upper limit of normal	2	657	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [1.88, 3.51]
9.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.16, 11.78]
9.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.03, 7.32]
9.3 Deferasirox - variable dosage	1	586	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [1.95, 3.68]
10 AE: Abdominal pain	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.73, 2.57]
10.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.68, 3.76]
10.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.43, 2.92]
11 AE: Dyspepsia	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.26, 5.77]
11.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.03, 6.67]
11.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.25, 15.99]
12 AE: Nausea	1	71	Risk Ratio (M-H, Fixed, 95% CI)	2.44 [0.58, 10.17]
12.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.09, 9.07]
12.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.56, 28.40]
13 AE: Vomiting	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.44, 6.38]
13.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 3.64]

13.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.56, 28.40]
14 AE: Diarrhoea	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.45, 2.37]
14.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.34, 3.37]
14.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.30, 3.32]
15 AE: Neutropenia	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 AE: Agranulocytosis	2	657	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Deferasirox - variable dosage	1	586	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 AE: Thrombocytopenia	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 AE: Elevated ALT (> 2 UNL)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
19 AE: Hearing loss	2	657	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.41, 3.05]
19.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.3 Deferasriox - variable dosage	1	586	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.41, 3.05]
20 AE: Lens abnormality	2	657	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 2.00]
20.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.3 Deferasirox - variable dosage	1	586	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 2.00]
21 AE: Retinal abnormality	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 AE: Cardiac adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
23 AE: Asthenia	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.43, 3.44]
23.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.13, 3.55]
23.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.43, 7.17]
24 AE: Vertigo	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.31, 3.99]
24.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [0.30, 17.36]
24.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.08, 3.13]
25 AE: Headache	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.72, 5.07]
25.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.53, 8.00]
25.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.43, 7.17]
26 AE: Allergic conjunctivitis	1	83	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.51, 158.52]
26.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.2 Deferasirox 20 mg/kg/d	1	48	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.51, 158.52]
27 AE: Back pain	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.55, 2.11]
27.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.35, 2.41]
27.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.49, 3.17]
28 AE: Arthralgia	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.26, 3.54]
28.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.23, 14.56]
28.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.08, 3.13]
29 AE: Pyrexia	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.62, 2.99]
29.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.34, 3.37]
29.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.56, 4.95]
30 AE: Rhinitis	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.58, 2.84]

30.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.34, 3.37]
30.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.50, 4.54]
31 AE: Cough	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.68, 4.84]
31.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.26, 5.02]
31.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.65, 9.65]
32 AE: Pharyngolaryngeal pain	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.37, 2.08]
32.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.22, 2.64]
32.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.30, 3.32]
33 AE: Pharyngitis	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.51, 1.99]
33.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.46, 2.86]
33.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.32, 2.41]
34 AE: Bronchitis	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.31, 7.12]
34.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	5.28 [0.32, 87.88]
34.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 3.96]
35 AE: Influenza	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.20, 1.69]
35.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.02, 2.27]
35.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.24, 2.92]
36 AE: Influenza-like illness	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.41, 3.38]
36.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.40, 6.51]
36.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.14, 3.90]
37 AE: Urinary tract infection	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.31, 10.37]
37.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	4.32 [0.25, 73.90]
37.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.03, 7.32]
38 Discontinuations	2	657	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.62, 2.29]
38.1 Deferasirox 10 mg/kg/d	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 3.64]
38.2 Deferasirox 20 mg/kg/d	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.10, 9.96]
38.3 Deferasirox - variable dosage	1	586	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.67, 2.85]
39 Dose adjustments and dose interruptions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
40 Satisfaction with treatment (very satisfied or satisfied): patients previously treated with DFO	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
40.1 week 4	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
40.2 week 24	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
40.3 end of study (1 year)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
41 Satisfaction with treatment (very satisfied or satisfied): DFO-naive patients	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
41.1 week 4	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
41.2 week 24	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
41.3 end of study (1 year)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
42 Convenience (good or very good): patients previously treated with DFO	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
42.1 week 4	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
42.2 week 24	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
42.3 end of study (1 year)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
43 Convenience (good or very good): DFO-naive patients	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
43.1 week 4	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

43.2 week 24	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
43.3 end of study (1 year)	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
44 Willingness to continue treatment: patients treated previously with DFO	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
45 Willingness to continue treatment: DFO-naive patients	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
46 Time lost from normal activities due to treatment (hours/month): patients treated previously with DFO	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
46.1 week 4	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
46.2 week 24	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
46.3 end of study (1 year)	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
47 Time lost from normal activities due to treatment (hours/month): DFO-naive patients	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
47.1 week 4	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
47.2 week 24	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
47.3 end of study (1 year)	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

ADDITIONAL TABLES

Table 1. Piga 2002: Baseline characteristics of included patients

	Deferasirox 10 mg/kg/day (n = 24)	**Deferasirox 20 mg/kg/day (n = 24)**	**Deferoxamine 40 mg/kg/day (n = 23)**
Mean age in years (range)	23.7 (17 - 33)	25.6 (19 - 50)	22.7 (18 - 29)
Male/Female	6 / 18	10 / 14	10 / 13
Mean height in cm (SD)	155.6 (8.5)	157.0 (9.1)	160.0 (9.3)
Mean weight in kg (SD)	52.4 (7.5)	50.7 (9.3)	54.3 (9.0)
Underlying disease			
beta-thalassemia major	23	23	23
beta-thalassemia intermedia[1]	1	1	0
Medical history			
Splenectomy	8	12	14
Hypogonadism (male or female)	10	12	10

Table 1. Piga 2002: Baseline characteristics of included patients (*Continued*)

Hypothyroidism (acquired)	0	5	6
Hepatitis B	0	3	2
Hepatitis C[2]	7	6	6
Cardiac disorder	4	5	5

[1] Transfusion-dependent; [2] Anti-HCV-positive or HCV RNA-positive

SD: standard deviation

Table 2. Piga 2002: Dosing details

	Deferasirox 10 mg/kg/day (n = 24)	**Deferasirox 20 mg/kg/day (n = 24)**	**Deferoxamine 40 mg/kg/day* (n = 23)**
Mean (SD) daily dose (range)	11.7 (2.12) mg/kg (8.5 - 14.7)	19.0 (4.10) mg/kg (10.4 - 25.6)	28.6 (1.06) mg/kg (26.6 - 31.6)
No. of patients with dose adjustments	13	14	4
No. of dose adjustments	13	16	6
No. of patients with dose interruptions due to an adverse event	5	11	5
Dose at week 48† (mg/kg/day)			
Discontinued	0	2	2
10	11	5	0
20	13	11	0
30	0	6	2
40	0	0	18
50	0	0	1
Mean duration of exposure in days (min - max)‡	345 (332 - 369)	332 (21 - 402)	318§ (13 - 392)

Table 2. Piga 2002: Dosing details (*Continued*)

* DFO dose administered on 5 consecutive days per week † Although adjustments of ± 5 mg/kg were made, all adjustments were further altered such that final doses were all in steps of 10 mg/kg only ‡ The availability of a LIC result by biomagnetic susceptometry marked the end of study and hence of the exposure period to the study drug. For patients for whom there was a delay in performing biomagnetic susceptometry, the duration of exposure to study drug was slightly longer than 48 weeks § Days of participation in the study, as DFO was administered for only 5 days per week

DFO: deferoxamine
SD: standard deviation

Table 3. Cappellini 2005b: Baseline characteristics of included patients

	Deferasirox	Deferoxamine	All patients
No. patients	296	290	586
Sex, no. (%)			
Male	140 (47.3)	142 (49)	282 (48.1)
Female	156 (52.7)	148 (51)	304 (51.9)
Race, no. (%)			
White	262 (88.9)	251 (86.6)	514 (87.7)
African-American	2 (0.7)	1 (0.3)	3 (0.5)
Asian	9 (3.0)	10 (3.4)	19 (3.2)
Other	22 (7.4)	28 (9.7)	50 (8.5)
Age (years)			
Mean (SD)	17 (9.47)	17.3 (9.96)	17.2 (9.71)
Median (range)	15 (2 - 49)	15.5 (2 - 53)	15 (2 - 53)
Age groups, no. (%)			
less than 6 years	30 (10.1)	28 (9.7)	58 (9.9)
6 years to less than 12 years	67 (22.6)	68 (23.4)	135 (23.0)
12 years to less than 16 years	57 (19.3)	49 (16.)	106 (18.1)

Table 3. Cappellini 2005b: Baseline characteristics of included patients (*Continued*)

16 years to less than 50 years	142 (48)	144 (49.7)	286 (48.8)
50 years to less than 65 years	0 (0)	1 (0.3)	1 (0.2)
LIC, mg Fe/g dw			
Mean (SD)	14.1 (10.0)	13.2 (9.4)	13.7 (9.7)
Median (range)	11.3 (2.1 - 48.1)	11.0 (2.1 - 55.1)	11.1 (2.1 - 55.1)
Serum ferritin, µg/l			
Mean (SD)	2765 (1897)	2597 (1835)	2682 (1867)
Median (range)	2212 (321 - 12646)	2091 (453 - 15283)	2682 (321 - 15283)

dw: dry weight
Fe: iron
LIC: liver iron concentration
SD: standard deviation

Table 4. Cappellini 2005b: Dosing algorithm according to baseline LIC and average daily doses by LIC category

	Baseline LIC, mg Fe/g dw (regardless of method)			
	LIC 3 mg Fe/g dw or less	**LIC above 3 mg Fe/g dw - 7 mg Fe/g dw**	**LIC above 7 mg Fe/g dw - 14 mg Fe/g dw**	**LIC above 14 mg Fe/g dw**
Deferasirox				
No. patients	15	78	84	119
Protocol assigned dose, mg/kg	5	10	20	30
Baseline LIC, mean (SD)	2.5 (0.21)	4.9 (1.08)	10.6 (2.08)	24.2 (7.82)
Average daily dose, mg/kg/d*				
Mean (SD)	6.2 (1.6)	10.2 (1.2)	19.4 (1.7)	28.2 (3.5)
Median (range)	5.0 (4.3 - 8.7)	10.0 (5.6 - 16.3)	20.0 (9.9 - 21.4)	30.0 (11.0 - 30.0)
Deferoxamine				

Table 4. Cappellini 2005b: Dosing algorithm according to baseline LIC and average daily doses by LIC category (*Continued*)

No. patients	14	79	91	106
Protocol assigned dose, mg/kg¥	20 - 30	25 - 35	35 - 50	≥ 50
Baseline LIC, mean (SD)	2.7 (0.28)	5.2 (1.22)	10.6 (2.03)	23.9 (8.06)
Average daily dose, mg/kg/d*				
Mean (SD)	33.9 (9.9)	36.7 (9.2)	42.4 (6.6)	51.6 (5.8)
Median (range)	30.0 (23.0 - 52.6)	35.0 (20.0 - 75.6)	40.8 (21.0 - 70.0)	51.0 (30.0 - 66.1)
Ratio of mean deferasirox dose to mean deferoxamine dose	1:5.5	1:3.6	1:2.2	1:1.8

dw: dry weight
Fe: iron
LIC: liver iron concentration
SD: standard deviation

Table 5. Cappellini 2005b: Success criteria for primary LIC endpoint

LIC at baseline mg FE/g dw	Success, LIC value after 1 year, mg Fe/g dw	Failure, LIC value after 1 year, mg Fe/g dw
2 to less than 7	1 to less than 7	Less than 1 or at least 7
7 to less than 10	1 to less than 7	Less than 1 or at least 7
10 ore more	Decrease in LIC of at least 3	Decrease in LIC below 3

dw: dry weight
Fe: iron
LIC: liver iron concentration

WHAT'S NEW

Last assessed as up-to-date: 25 November 2011.

Date	Event	Description
24 March 2014	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 2, 2012

Date	Event	Description
22 May 2012	Amended	Contact details updated.
12 August 2009	Amended	Contact details updated.
10 January 2008	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Joerg Meerpohl: Conception, design and coordination of the review. Data collection and data management as well as analysis and interpretation of the data. Writing of the review and approval of the final version.

Gerd Antes: Methodological support and general advice on the review. Methodological advice on interpretation of data. Approval of final version.

Gerta Rücker: Statistical advice and methodological support. General advice on the review and approval of the final version.

Nigel Fleeman: Co-author of the HTA report by McLeod (McLeod 2009). General advice on the review and approval of the final version.

Edith Motschall: Advice on search strategy and conduct of last search (June 2010).

Charlotte Niemeyer: Interpretation of the data and clinical expertise. General advice on the review and approval of the final version.

Dirk Bassler: Data collection and data management. Analysis and interpretation of data. Involvement in writing the review and approval of the final version.

DECLARATIONS OF INTEREST

Joerg Meerpohl enrolled two adolescents with thalassaemia and one with Diamond-Blackfan anaemia in a post-marketing surveillance study on deferasirox and participated once in a Novartis advisory board meeting on paediatric iron overload. None declared for other authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Benzoates [adverse effects; *therapeutic use]; Clinical Trials, Phase II as Topic; Clinical Trials, Phase III as Topic; Deferoxamine [therapeutic use]; Erythrocyte Transfusion [adverse effects]; Iron Chelating Agents [adverse effects; *therapeutic use]; Iron Overload [*drug therapy; etiology]; Randomized Controlled Trials as Topic; Thalassemia [*complications; therapy]; Triazoles [adverse effects; *therapeutic use]

MeSH check words

Humans