



Canadian Agency for
Drugs and Technologies
in Health

RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL



TITLE: Ferumoxytol versus Other Intravenous Iron Therapies for Anemia: A Review of the Clinical and Cost-effectiveness and Guidelines – An Update

DATE: 21 November 2014

CONTEXT AND POLICY ISSUES

Anemia (a condition categorized by a deficiency of red blood cells or of hemoglobin in the blood) and iron deficiency anemia (IDA, characterized by iron deficiency) are associated with a wide range of adverse health conditions¹ (e.g. cardiovascular morbidity² fatigue, low energy, reduced tolerance to exercise, and decreased physical functioning³) along with issues relating to reduced quality of life (i.e. impaired cognitive functioning and development, lowered resistance to infection, and reduced work capacity).¹ In the United States, IDA is estimated to affect 1% to 2% of men and 2% to 5% of women.¹ In men and postmenopausal women, the most common cause of IDA occurs upon blood loss from chronic gastrointestinal bleeding.³ IDA is a common concern in patients with chronic kidney disease (CKD), either directly due to factors such as dietary iron intake, iron absorption issues, chronic iron loss as a result of intestinal bleeding, and chronic inflammation, or indirectly due to factors related to kidney dysfunction.⁴

The management of IDA is generally the same for patients with dialysis-dependent (DD) and non-dialysis-dependent (NDD) CKD or those with various underlying conditions.^{1,2} Treatment consists of iron supplementation and the use of erythropoiesis-stimulating agents (ESA).² First-line treatment of IDA is oral iron; however, many patients may not have a sufficient response, respond to, or be able to tolerate this treatment.¹⁻⁴ Subsequent treatment is intravenous (IV) iron administration which bypasses difficulties associated with iron absorption.⁴ IV iron is appropriate for patients unable to tolerate or are intolerant to oral iron therapy, in patients also receiving ESA therapy, and in patients undergoing hemodialysis.⁴ Numerous IV iron complexes are available, including iron sucrose (saccharated iron oxide), low-and-high-molecular weight dextrans, ferric gluconate, ferric citrate, ferric carboxymaltose, iron isomaltoside 1000, and ferumoxytol. The newer iron complexes (ferric carboxymaltose, iron isomaltoside 1000, and ferumoxytol) can be administered at much higher doses than the older complexes and do not require test doses.⁴ Due to potential iron toxicities, older iron complexes were administered in small doses at many visits (between five and 10, depending on the patient and treatment) thereby often reducing treatment adherence due to inconvenience.¹ These newer generation iron complexes can be administered at higher doses in fewer dosing sessions.

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Ferumoxytol (Feraheme) is a colloidal superparamagnetic iron-carbohydrate complex that was specifically designed to reduce immunological reactivity.^{1,5} It can be rapidly administered (IV rate of 30-60 seconds) as a 510 mg dose with the second IV injection administered two to eight days later.^{1,5} The federal Food and Drug Administration (FDA) in the United States has listed ferumoxytol for the treatment of IDA in adult patients with CKD.¹ Health Canada has recently placed restrictions on the use of ferumoxytol due to the potential for serious allergic reactions. Therefore, this review was performed to assess the clinical effectiveness and safety of ferumoxytol compared with other IV iron therapies for patients with IDA. In addition, cost-effectiveness and evidence-based guidelines were also investigated to determine the costs associated with ferumoxytol and its use in patients with IDA. This is an update to a previous review on ferumoxytol⁶ which found limited evidence that stated that it seemed to have comparable efficacy to other iron complexes but that it was associated with an increased adverse event profile.⁶

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of ferumoxytol compared with other intravenous iron therapies for adult patients with anemia resulting from chronic kidney disease or other types of anemia?
2. What is the cost-effectiveness of ferumoxytol compared with other intravenous iron therapies for adult patients with anemia?
3. What are the evidence-based guidelines regarding the use of ferumoxytol for adult patients with anemia?

KEY FINDINGS

Intravenous ferumoxytol appears to be noninferior to iron sucrose with regard to its efficacy in both dialysis-dependent and non-dialysis-dependent patients with or without chronic kidney disease who experienced iron deficiency anemia. In addition, the safety profiles of ferumoxytol and iron sucrose are similar, though careful observation for potential rare and severe anaphylactic reactions has been suggested post-infusion. Intravenous ferumoxytol appears to raise hemoglobin and ferritin saturation levels post-administration when administered twice (two to eight days apart) at a dose of 510 mg or once at a dose of 1.02 g with a 15 minute infusion rate. The latter results should, however, be interpreted with caution as these results came from an exploratory observational study with a small sample size. While the efficacy and safety results seem promising with IV ferumoxytol therapy for iron deficiency anemia (regardless of its cause) more good quality studies are required to further validate intravenous ferumoxytol use, particularly as a one dose option. This is especially relevant in those patients who have varying underlying conditions like abnormal uterine bleeding, postpartum bleeding, cancer, and gastrointestinal disorders.

No economic evaluations or evidence-based guidelines within the search date parameters were identified.

METHODS

Literature Search Strategy

This report makes use of a literature search conducted for a previous CADTH report. The original literature search was conducted September 19, 2014 on key resources including PubMed, The Cochrane Library (2014, Issue 9), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The initial search was also limited to English language documents published between January 1, 2013 and September 19, 2014. For the current report, a PubMed update search was rerun on October 23, 2014 to capture any articles published since the initial search date.

Selection Criteria and Methods

One reviewer screened the original search while a second reviewer screened the updated search and selected studies based on full-text review. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adults with anemia
Intervention	Ferumoxytol (Feraheme)
Comparator	Other intravenous iron products (e.g. iron sucrose, iron dextran, sodium ferric gluconate)
Outcomes	<ul style="list-style-type: none"> • Q1: Clinical benefits and harms • Q2: Cost-effectiveness • Q3: Any evidence-based guidelines that include ferumoxytol
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies (NRS), economic evaluations, evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to 2013.

Critical Appraisal of Individual Studies

The quality of all included reports was assessed using a validated instrument specific to the study design. The Downs and Black checklist⁷ was used to guide the assessment of the included randomized controlled trials and observational studies. Numerical scores were not calculated; instead, the strengths and limitations of individual studies as identified through use of the checklist are summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 195 citations were identified in the original⁸ and updated literature searches. Following screening of titles and abstracts, 189 citations were excluded and 6 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, two publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in the Appendix 2.

Summary of Study Characteristics

Three RCTs^{1,3,9} and two NRSs^{2,10} were included in this review. No health technology assessments, systematic reviews, meta-analyses, economic evaluations or evidence-based guidelines were identified. Detailed characteristics of the included studies are summarized in Table 2, Appendix 3.

All three RCTs were multinational studies^{1,3,9} while both NRSs originated in the United States.^{2,10} The RCTs were set up as either open label noninferiority trials with an active comparator (one Phase III trial [N=605]¹ and one Phase II trial [N=162]⁹) or as a double-blind superiority trial with placebo as the comparator (N=808).³ The NRSs were single armed trials. The Schiller et al. study² examined IV ferumoxytol treatment in dialysis centres (specifically three Chains) in a retrospective manner (N=8666). These Chains used the standard dose of 2 x 510 mg IV ferumoxytol (Chains A and B) or either standard IV ferumoxytol dosing or 1 x 510 mg IV ferumoxytol.² The other NRS was an exploratory longitudinal observational study examining an alternate ferumoxytol administration regimen (N=60).¹⁰ Patient characteristics in all trials^{1-3,9,10} were similar in that patients had a history of either oral iron intolerance or unsatisfactory response to oral iron therapy in addition to IDA (of which the underlying IDA causes differed). Patient populations between trials differed with regard to dialysis as one trial included a mixed population of DD and NDD patients,⁹ another included DD patients only,² another included NDD patients only,³ and two did not comment on dialysis treatment.^{1,10} Four of the included studies were open label trials^{1,2,9,10} while the other one used a double blind design.³

Four of the primary studies implemented a two dose regimen of 510 mg IV ferumoxytol (cumulative ferumoxytol dose of 1.02 g) given anywhere between two and eight days apart with an IV injection rate of under 1 minute (approximately 17 seconds).^{1-3,9} The final included study examined a larger IV injection of 1.020 g ferumoxytol extending over a 15 minute time frame.¹⁰ Two of the studies used iron sucrose (1 g total dose with either five visits spread out over 14 days^{1,9} or ten visits spread out over three weeks⁹) as their comparator, one compared ferumoxytol with placebo,³ and the other studies were observational in nature with no comparators.^{2,10} Similar outcomes of interest examined in multiple studies included the following:

- proportion of patients achieving a greater than 2 g/dl increase in hemoglobin^{1,3}
- change in hemoglobin levels from baseline^{1,3,9,10}

- proportion of patients achieving and hemoglobin (Hgb) level of greater than or equal to 12 g/dl or within a target range of 10 to 12 g/dl¹⁻³
- time to a hemoglobin increase of greater than or equal to 2.0 g/dl (or ≥ 1.0 g/dl)^{9,10} or hemoglobin reaching greater than or equal to 12 g/dl from baseline^{1,3,9}
- changes in total iron saturation (TSAT)^{1-3,9,10}
- changes in various patient reported outcomes^{1,3}
- harms.^{1-3,9,10}

Summary of Critical Appraisal

Details of the critical appraisal are provided in Table 3, Appendix 4.

All of the included studies had clearly defined objectives, interventions, and outcomes,^{1-3,9,10} with all of the RCTs^{1,3,9} also detailing baseline patient characteristics. The RCTs all had large enough sample sizes to provide the power to determine non-inferiority (margin of 15%) to^{1,9} or superiority³ over their respective comparators and they examined the ITT population. It appeared that the results from each trial were generalizable for their respective populations of patients with IDA (not sufficiently controlled on oral iron therapy or for those who could not take oral iron) with regard to dialysis treatment; however, results may not be generalizable to the full population of patients with IDA. All of the studies were open label^{1,2,9,10} with the exception of the Vadhan-Raj RCT³ which incorporated a double blind design. While the dosing was generally comparable between trials, dosing within one trial was both the same as other trials included in this review yet also had one Chain that used a different lower dose (with these different dosings perhaps reflecting a more real world scenario).² Conflicts of interest were declared in all^{1-3,9} but one study,¹⁰ while all studies were industry funded by the same manufacturer.^{1-3,9,10} Losses to follow-up in the Schiller et al study² were noted but not accounted for in the analysis population. These patients simply met their iron targets, were followed for 90 days after the last-ferumoxytol dose, and then were not followed. The Macdougall et al. RCT treated patients lost to follow-up as nonresponders.⁹

Summary of Findings

Detailed study results are presented in Table 4, Appendix 5. In addition, the author's conclusions are presented in Table 5, Appendix 5.

What is the clinical effectiveness and safety of ferumoxytol compared with other intravenous iron therapies for adult patients with anemia resulting from chronic kidney disease or other types of anemia?

Efficacy

In patients with IDA who were intolerant to oral iron or for whom oral iron therapy was insufficient, IV ferumoxytol (total cumulative dose of 1.02 g) displayed noninferiority compared with IV iron sucrose (total cumulative dose of 1 g) at five weeks post-administration the following outcomes: mean hemoglobin increases (2.7 g/dl and 2.4 g/dl, respectively; P=0.0124), mean changes in hemoglobin (0.8 g/dl and 0.7 g/dl, respectively; P=0.52), increases in TSAT (14.5% and 10.6%, respectively; P=0.0048), and in improvements in patient reported outcomes such as increases in the Functional Assessment of Chronic Illness therapy (FACIT)-Fatigue score (41.7 [standard deviation (SD) of 10.05] and 41.5 [SD of 9.51], respectively), the 36-Item Short-Form General Health Survey (SF-36) Vitality score (13.0 and 12.5, respectively; P=0.05), and the

QOL Linear Analog Scale Assessment (LASA)-Energy score (21.9 and 21.3, respectively; $P > 0.05$).¹ Ferumoxytol noninferiority to iron sucrose was further substantiated by the proportion of patients achieving an equal to or greater than 2 g/dl increase in hemoglobin at any time during the study (84% and 81.4%, respectively), in the proportion of patients achieving a hemoglobin level of equal to or greater than 12 g/dl at any time during the study (66.7% and 48.2%, respectively),¹ in peak TSAT levels (33.0 g/dl [SD of 13.1] and 26.0 g/dl [SD of 17.2], respectively), and in peak ferritin levels (854 ng/ml and 546 ng/ml, respectively).⁹ The mean time to hemoglobin response [defined as an equal to or greater 2 g/dl hemoglobin increase or a hemoglobin level of equal to or greater than 12 g/dl] when comparing ferumoxytol with iron sucrose^{1,9} or placebo³ ranged anywhere from 16 to 28.8 days in patients treated with ferumoxytol^{1,3,9} and 22 to 33.4 days in patients treated with iron sucrose.^{1,9} The time to hemoglobin response was measured at 42.5 days in patients in the placebo group.³ The Auerbach et al. study,¹⁰ whereby patients with IDA were administered one dose of 1.02 g of IV ferumoxytol at a 15 minute infusion rate, reported similar results to the aforementioned studies^{1,9} in that mean increases in hemoglobin were 2.1 g/dl at week four and 2.6 g/dl at week eight and the proportion of patients who had at least a 2 g/dl increase in hemoglobin was 58% at week four and 86% at week eight.

The Schiller et.al. study,² whereby DD patients with CKD were being treated for IDA, included 8666 patients who were observed for 12 months post-ferumoxytol administration. Mean hemoglobin levels at month 12 were 11.23 g/dl, 11.04 g/dl, and 11.37 g/dl in Chains A, B, and C, respectively (the majority of patients in Chain C only received 510 mg of ferumoxytol (Table 2, Appendix 3). In addition, upon IV ferumoxytol treatment, the proportion of patients able to maintain target hemoglobin levels (10 to 12 g/dl) after 12 months ranged from 61% to 72%.² The proportion of patients able to reach stable TSAT levels ranged in month 12 from 28% to 34%, while mean month 12 ferritin levels ranged from 753 ng/ml to 834 ng/ml.² Only one study reported on ESA therapy, and in that study 91% of patients had no change to their ESA regimen.⁹

The effects of underlying conditions on hemoglobin increases were examined as subgroup analyses in two studies.^{1,3} With regard to the proportion of patients achieving an equal to or greater than 2 g/dl increase in hemoglobin at any time, superiority of ferumoxytol over placebo³ and noninferiority of ferumoxytol to iron sucrose¹ was observed when patients were subgrouped according to various underlying conditions at baseline (abnormal uterine bleeding, gastrointestinal disorders, or in the 'Other' subgroup). While there was also a positive trend for ferumoxytol in the cancer subgroup, this difference was not statistically significant in either study.^{1,3}

Safety

All of the studies reported adverse events.^{1-3,9,10} Most of the adverse events experienced after either ferumoxytol or iron sucrose were reported as mild and transient and many were associated with the IV iron infusion process. In two of the RCTs^{1,9}, the proportion of patients experiencing adverse events associated with ferumoxytol treatment ranged between 14.3% and 48% while those associated with iron sucrose range between 16.1% and 65%. A similar proportion of 43.3% was observed in the Auerbach et al. study where 1.02 g ferumoxytol was administered in one sitting.¹⁰ The most common adverse events in patients treated with both ferumoxytol and iron sucrose were headache,^{3,9,10} nausea,^{2,3,9,10} and urinary tract infections.^{2,3,9} Protocol-defined adverse events of special interest (including hypotension and hypersensitivity)

were reported in 2.7%,¹ 1.3%,⁹ and 3.6%³ of patients treated with ferumoxytol and in 5.0%,¹ 6.1%⁹ and 1.0%³ of patients treated with iron sucrose.

All studies, with the exception of Auerbach et al.,¹⁰ reported serious adverse events.^{1-3,9} Hypotension and hypersensitivity occurred in 0.12% and 0.06%, respectively, in IDA patients with DD-CKD treated with ferumoxytol² whereas 6.1% of IDA patients with either DD-CKD or NDD-CKD who were treated with iron sucrose experienced hypotension.⁹ Hypersensitivity was also observed 0.5% of patients with IDA treated with ferumoxytol.³ All studies^{1-3,9} reported between one and two anaphylactic responses associated with iron infusion, (although one did not term this anaphylaxis; however, the patient was treated with diphenhydramine and steroids, with symptoms resolving within minutes¹⁰) which seems to correlate with most other studies that examine IV infusions with iron or a derivative thereof.⁴ The anaphylactic reaction frequency ranged between 0.02% to 1.3% of patients treated with ferumoxytol.^{1-3,9} No patients experienced anaphylaxis with iron sucrose treatment. Deaths were reported in two of the RCTs^{1,3} but were thought to be unrelated to the study treatments.

What is the cost-effectiveness of ferumoxytol compared with other intravenous iron therapies for adult patients with anemia?

No literature was identified on the cost-effectiveness of ferumoxytol compared with other intravenous iron therapies for adult patients with anemia; therefore, no summary can be provided.

What are the evidence-based guidelines regarding the use of ferumoxytol for adult patients with anemia?

No evidence-based guidelines were identified regarding the use of ferumoxytol for adult patients with anemia; therefore, no summary can be provided.

Limitations

Study design appeared to be a limitation in two of the included RCTs^{1,9} as both conducted their study in an open label and non-blinded manner which could have introduced bias. One study appropriately dealt with losses to follow-up statistically,² while the others either did not mention how losses to follow-up were handled.^{1,3,9} In addition, the length of follow up may not have been sufficient to capture all of the adverse events.

While in-depth baseline characteristics were provided in most of the studies, the Auerbach et al. study¹⁰ only mentioned a few characteristics (e.g. age, gender, ethnicity) and nothing regarding disease characteristics. This may be problematic for result interpretation in specific populations as these patients were being tested with a new IV ferumoxytol dosing regimen.

Each observational study^{2,10} had one single treatment arm. While this is often necessary in this type of study, especially when performing an exploratory analysis,¹⁰ it can hinder the interpretation of the treatment in the context of other, competing treatments. In addition, in the large retrospective study by Schiller et al.,² there was a mixture of ferumoxytol dosing regimens (2 x 510 mg ferumoxytol or 1 x 510 mg ferumoxytol). These differences in dosing regimens are practiced in real world clinical settings; however, it does introduce some uncertainty with regard to result interpretation.

Finally, all of the included studies were funded by industry. In addition, it was the same manufacturer who also funded each of these studies. This potential leads to result bias as studies (and subsequent results) are less likely to be reported with older agents.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

As it pertains to the studies included in this review, it appears that IV ferumoxytol is noninferior to IV iron sucrose in its ability to correct IDA in DD and NDD patients with or without CKD. The safety profiles of these two agents were also observed to be similar, with the exception of hypotension and hypersensitivity which were increased in patients administered iron sucrose. However, caution should be used in any interpretation of such safety results as there was only one study that appropriately dealt with patients lost to follow-up² or studies had insufficient follow-up time to capture such events.

With regard to all IV iron infusions, there is still the possibility of serious adverse events like hypotension, hypersensitivity, and anaphylaxis due to the toxic nature of iron. IV ferumoxytol is no different in this respect, except that it was designed to decrease potential immunological reactivity. It has been suggested that ferumoxytol might increase adherence to IV iron infusion therapy as patients are only required to go for infusions twice, regardless of their reason for the iron deficiency anemia or whether they have DD-CKD or NDD-CKD. In addition, the safety and efficacy of ferumoxytol appears to be similar to that of IV iron sucrose and the treatment with ferumoxytol does not require an additional testing dose. The 1.02 g ferumoxytol single dosing regimen appears to have similar results associated with the current two dose regimen; however, the results were obtained from an exploratory observational study with a small sample size. Observations from such study designs and sample sizes require caution when interpreting any efficacy and safety data.

While the studies included in this review provide evidence into the clinical effectiveness and acceptable safety profile of ferumoxytol, randomized controlled trials are required to verify the true effectiveness and safety of a one-time IV ferumoxytol dosing regimen for patients with IDA and in patients with various underlying causes of IDA at baseline. While the former CADTH review reported on increased adverse events associated with IV ferumoxytol use, the evidence identified for this review seems to provide an acceptable safety profile. While this and the former review differed their safety assessments, both reported comparative clinical effectiveness of IV ferumoxytol with other IV iron formulations.

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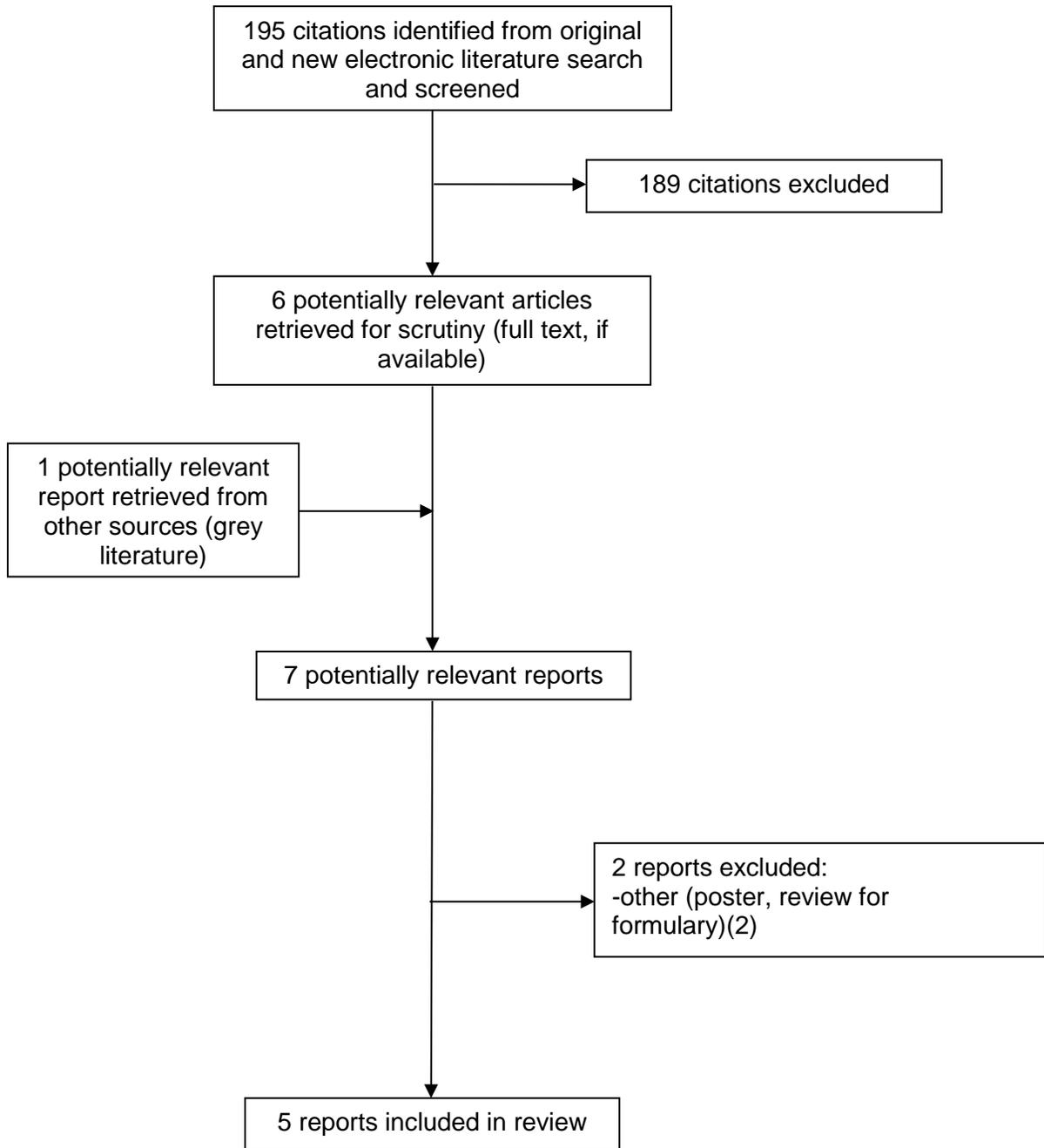
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional References of Potential Interest

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APPENDIX 3: Characteristics of Included Publications

Table 2: Study and Patient Characteristics of Included Clinical Studies

First Author, Year, Country	Study & Patient Characteristics	Interventions	Comparators	Clinical Outcomes
<i>Randomized Controlled Trials</i>				
Hetzel, ¹ 2014, Multinational	<p>Study</p> <ul style="list-style-type: none"> N = 605 OL, active-controlled, multicentre, Phase III, noninferiority Randomized 2:1 5 week follow-up <p>Patients</p> <ul style="list-style-type: none"> ≥ 18 yrs Baseline Hgb > 7 to < 10 g/dl TSAT < 20% and history of unsatisfactory oral Fe therapy or intolerance to oral Fe 	<ul style="list-style-type: none"> 2 x 510 mg FCM injections over 30-60s (given 5 days apart) 	<ul style="list-style-type: none"> 5 IV infusions or injections of 200 mg iron sucrose (1 g cumulative) on 5 consecutive days (over 14-day period) <p><i>Note</i></p> <ul style="list-style-type: none"> 20 mg test dose injection or 25 mg infusion of iron sucrose to iron sucrose-naïve pts^b 	<p>Primary</p> <ul style="list-style-type: none"> Pts achieving > 2 g/dl increase in Hgb (anytime from baseline to Week 5) Change in Hgb in from baseline to Week 5^c (from baseline to Week 5) <p>Secondary</p> <p><i>Anytime from baseline to Week 5</i></p> <ul style="list-style-type: none"> Pts achieving Hgb ≥ 12 g/dl Time to Hgb increase of ≥ 2 g/dl or to Hgb ≥ 12 g/dl <p><i>From baseline to Week 5</i></p> <ul style="list-style-type: none"> Change in TSAT <p><i>PRO from baseline to Week 5</i></p> <ul style="list-style-type: none"> Change in FACIT-Fatigue Change in energy domain of LASA-Energy Change in vitality domain of SF-36 <p>Safety</p> <ul style="list-style-type: none"> TEAE incidence SAEs AEs WDAEs
Macdougall, ⁹ 2014, Multinational	<p>Study</p> <ul style="list-style-type: none"> N = 162 OL, randomized, active-controlled, Phase II, designed 	<ul style="list-style-type: none"> Cumulative FCM dose of 1.02 g (as 2 x 510 mg [17 ml; no faster than over 	<p><i>Hemodialysis pts</i></p> <ul style="list-style-type: none"> Cumulative dose of 1.0g iron sucrose (as 100 	<p>Primary</p> <ul style="list-style-type: none"> Descriptive review of AEs associated with FCM compared with iron sucrose (incidence, severity, and relationship to

Table 2: Study and Patient Characteristics of Included Clinical Studies

First Author, Year, Country	Study & Patient Characteristics	Interventions	Comparators	Clinical Outcomes
	<p>as noninferiority study</p> <ul style="list-style-type: none"> 5 week follow-up Randomized 1:1 <p>Patients</p> <ul style="list-style-type: none"> ≥ 18 yrs eGFR = < 60 ml/min per 1.73 m² or diagnosis of CKD (e.g. nephropathy, nephritis) Hgb < 11.0 and ≥ 7 g/dl TSAT < 30% Hemodialysis pts on maintenance dialysis ≥ 3 months prior to screening or currently receiving dialysis 3 times/week 	<p>17 s] within 5 ± 3 days); IV injections</p>	<p>mg doses at 10 consecutive dialysis sessions within 3 weeks); IV infusion</p> <p><i>Nondialysis pts</i></p> <ul style="list-style-type: none"> Cumulative dose of 1.0 g iron sucrose (as 200 mg doses at 5 visits within ~ 14 days); IV infusion <p><i>Note</i></p> <ul style="list-style-type: none"> First exposure to iron sucrose was administered as test dose 	<p>drug)</p> <p>Secondary Efficacy <i>From Baseline to Week 5</i></p> <ul style="list-style-type: none"> Change in Hgb (adjusted for covariates of baseline Hgb and dialysis status) Pts with increase in Hgb ≥ 1 g/dl TSAT and ferritin Time to 1 g/dl increase from baseline or Hgb ≥ 12 g/dl Pts who initiated, ceased, or adjusted dose of ESA use by ≥ 20% over course of study
Vadhan-Raj, ³ 2014, Multinational	<p>Study</p> <ul style="list-style-type: none"> N = 808 DB, placebo-controlled, multicentre (182 sites), Phase III 5 week follow-up Randomized 3:1 <p>Patients</p> <ul style="list-style-type: none"> ≥ 18 yrs IDA (defined as Hgb < 10.0 g/dl; TSAT < 20%; history or unsatisfactory or who could not take oral Fe therapy) 	<ul style="list-style-type: none"> 2 x 510 mg (17 ml under 1 min.) rapid FCM IV injection (second dose 2-8 days later) 	<ul style="list-style-type: none"> Placebo (normal saline) 	<p>Primary <i>Baseline to Week 5</i></p> <ul style="list-style-type: none"> Pts achieving Hgb increase of ≥ 2.0 g/dl Change in Hgb (alternate efficacy analysis) <p>Secondary</p> <ul style="list-style-type: none"> Pts achieving Hgb ≥ 12 g/dl any time from baseline to Week 5 Change in TSAT from baseline to Week 5 Time to Hgb increase of ≥ 2.0 g/dl or ≥ 12 g/dl from baseline <p><i>PROs from baseline to Week 5</i></p>

Table 2: Study and Patient Characteristics of Included Clinical Studies

First Author, Year, Country	Study & Patient Characteristics	Interventions	Comparators	Clinical Outcomes
				<ul style="list-style-type: none"> Change in FACIT-Fatigue Change in energy domain of LASA-Energy Change in vitality domain of SF-36 <p><i>Safety</i></p> <ul style="list-style-type: none"> AEs SAEs TEAEs
<i>Non-Randomized Studies</i>				
Auerbach, ¹⁰ 2013, US	<p>Study</p> <ul style="list-style-type: none"> N = 60 Single arm, OL, single centre 4 and 8 week follow-up <p>Patients</p> <ul style="list-style-type: none"> ≥ 18 yrs; mean age = 53.4 (range 22-89) Mean weight = 84.5 kg Mean BMI = 30.8 Hgb < 11 ID = serum ferritin ≤ 100 ng/ml or ID = TSAT < 20% with normal or elevated TIBC History of oral Fe intolerance or post gastric bypass surgery, hereditary hemorrhagic telangiectasia 	<ul style="list-style-type: none"> 1,020 g (34 mL) IV FCM over 15 min 125 mg prophylactic MEP^a 	<ul style="list-style-type: none"> NA 	<p>Primary</p> <ul style="list-style-type: none"> AEs associated with 15 min. FCM infusion <p>Secondary</p> <ul style="list-style-type: none"> Change in Hgb from baseline^d to Week 4 and Week 8 Change in TSAT from baseline to Week 4 and Week 8 Patients with increase in Hgb of ≥ 1.0 g/dL from baseline to Week 4 and Week 8 Change in RDW at Week 4 and Week 8 <p><i>Safety</i></p> <ul style="list-style-type: none"> SAEs AEs
Schiller, ² 2014, US	<p>Study</p> <ul style="list-style-type: none"> N = 8666, mean age ~64 yrs Retrospective observation study of 3 dialysis chains (160 clinics) 12-month period 	<p><i>Chains A & B FCM dosing paradigms:</i></p> <ul style="list-style-type: none"> 2 x 510 mg rapid FCM IV injection (max rate 1ml – 30 mg Fe – per s over 	<ul style="list-style-type: none"> NA 	<p>Efficacy</p> <ul style="list-style-type: none"> Monthly Hgb levels relative to baseline Pts maintaining Hgb within target range of 10-12 g/dl Monthly TSAT levels Monthly ferritin levels

Table 2: Study and Patient Characteristics of Included Clinical Studies

First Author, Year, Country	Study & Patient Characteristics	Interventions	Comparators	Clinical Outcomes
	<p>Patients</p> <ul style="list-style-type: none"> • DD-CKD pts with IDA • Chain A (N=1250) <ul style="list-style-type: none"> ○ Hgb < 13.0 g/dl (Chain A) ○ TSAT 30%-50% or ferritin 300-500 ng/ml • Chain B (N=3359) & C (N=3398) <ul style="list-style-type: none"> ○ Hgb < 12.5 g/dl ○ TSAT < 30% or ferritin < 500 ng/ml 	<p>17s) within 3-8 days</p> <p><i>Chain C FCM dosing paradigm:</i></p> <ul style="list-style-type: none"> • Majority received 1 x 510 mg IV FCM IV injection (max rate 1ml – 30 mg Fe – per s over 17s) (N=3164) or, • 2 x 510 mg rapid FCM IV injection (max rate 1ml – 30 mg Fe – per s over 17s) (N=234) within 3-8 days 		<p>Safety</p> <ul style="list-style-type: none"> • AEs • SAEs • AEs leading to drug discontinuation or AEs leading to hospitalization

AE = adverse event; AUB = abnormal uterine bleeding; BMI = body mass index; CKD = chronic kidney disease; DD-CKD = dialysis-dependent chronic kidney disease; FACIT-Fatigue = Functional Assessment of Chronic Illness therapy Fatigue; FCM = ferumoxytol; Fe = iron; eGFR = estimated glomerular filtration rate; ESA = erythropoiesis-stimulating agent; GI = gastrointestinal; Hgb = hemoglobin; hr = hour; ID = iron deficiency; IDA = iron deficiency anemia; IV = intravenous; LASA-Energy = QOL Linear Analogue Scale Assessment; MEP = methylprednisolone; min = minute(s); NA = not applicable; OL = open label; RPO = patient reported outcomes; pts = patients; RDW = red cell distribution width; s = seconds; SAE = serious adverse events; SF-36 = 36-Item Short-Form General Health Survey; TEAE = treatment-emergent adverse event; TIBC = total iron binding capacity/transferrin saturation; TSAT = total iron binding capacity/ferritin saturation; US = United States; WDAE = withdrawal due to adverse event; yrs = years.

^a Only administered to patients with a history of 2 or more drug allergies or asthma (n=15).

^b Given prior to their first dose as per labeling requirements.

^c Alternate prespecified primary endpoint analysis.

^d Defined as the hemoglobin level immediately prior to the ferumoxytol treatment course.

APPENDIX 4: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Primary Studies ^a		
First Author, Year	Strengths	Limitations
<i>Randomized Controlled Studies</i>		
Hetzel, ¹ 2014	<ul style="list-style-type: none"> Clearly stated objectives, interventions, and outcomes. <i>A priori</i> criteria for noninferiority (specific noninferiority margin). Specified ITT analysis. Baseline characteristics provided in depth. Sample size large enough to provide 94% power for the assessment of the noninferiority of FCM and iron sucrose; noninferiority margin calculated. Generalizable to patients with IDA who have a history of unsatisfactory oral iron therapy or who cannot take oral iron. Conflicts of interest declared. 	<ul style="list-style-type: none"> OL study design; potential to introduce bias even with active comparator. Study not powered to detect significant differences between treatments in predefined subgroup analyses. Dosing regimens were different between groups (could lead to differences in both efficacy and tolerability); however, they are the ones used in clinical practice. Industry funded.
Macdougall, ⁹ 2014	<ul style="list-style-type: none"> Clearly stated objectives, interventions, and outcomes. <i>A priori</i> criteria for noninferiority (specific noninferiority margin). Specified ITT analysis. Baseline characteristics provided in depth. Sample size large enough to provide 81% power for the assessment of the noninferiority of FCM and iron sucrose; noninferiority margin calculated. Generalizable to pts with every stage CKD, on or not on dialysis, who have a history of unsatisfactory oral iron therapy or who cannot take oral iron. Conflicts of interest declared. 	<ul style="list-style-type: none"> OL study design. Small sample size. Descriptive review of AEs; could not perform statistics due to small N. Industry funded.
Vadhan-Raj, ³ 2014	<ul style="list-style-type: none"> Clearly stated objectives, interventions, and outcomes. DB RCT; specified ITT analysis. 	<ul style="list-style-type: none"> Not generalizable to patients undergoing dialysis, which represent a large proportion of patients with IDA. Industry funded.

Table 3: Strengths and Limitations of Primary Studies^a

First Author, Year	Strengths	Limitations
	<ul style="list-style-type: none"> • Baseline characteristics provided in depth. • Sample size large enough to provide 99% power for superiority assessment; sample size sufficient to identify possible safety concerns. • Conflicts of interest declared. 	
<i>Non-Randomized Studies</i>		
Auerbach, ¹⁰ 2013	<ul style="list-style-type: none"> • Clearly stated objective, intervention, and outcomes. • Representative of overweight or obese population specifically. • Outcome measures were valid and reliable. 	<ul style="list-style-type: none"> • No blinding, OL study. • Baseline patient characteristics not provided. • Only exploratory descriptive and inferential analyses performed; no pre-specified sample sizes. • No comparators; only one treatment arm. • Representative of mostly an overweight population only and not generalizable to overall population (78% were either overweight or obese). • Conflicts of interest not declared.
Schiller, ² 2014	<ul style="list-style-type: none"> • Clearly stated objective, intervention, and outcomes. • Generalizable to DD-CKD patients with IDA in real-world clinical setting. • Large sample size that appeared generalizable to dialysis-dependent patients with IDA. • Conflicts of interests declared. 	<ul style="list-style-type: none"> • Non-blind retrospective observational study. • No comparators. • Differences in FCM dosing paradigms and requirements for monthly IV iron between Chains. • Pts who met target range earlier than the year were not followed for the full year. • Losses to follow-up unaccounted for. • Industry funded.

CKD = chronic kidney disease; DB = double blind; DD-CKD = dialysis-dependent chronic kidney disease; FCM = ferumoxytol; IDA = iron deficiency anemia; ITT = intention to treat; IV = intravenous; OL = open label; RCT = randomized controlled trial.

^a Downs and Black⁷ used to guide critical appraisal.

APPENDIX 5: Main Study Findings and Author's Conclusions

Table 4: Detailed Findings of Included Studies										
	Primary Studies									
	Hetzel, ¹ 2014 RCT		Macdougall, ⁹ 2014 RCT		Vadhan-Raj, ³ 2014 RCT		Auerbach, ¹⁰ 2013 NRS	Schiller, ² 2014 ^e NRS		
	FCM	IS	FCM	IS	FCM	PL	FCM	FCM		
								Chain A	Chain B	Chain C
From Baseline to Week 5										
Hgb										
Increase in Hgb (g/dl), mean	2.7	2.4	-	-	-	-	2.1 (week 4) 2.6 (week 8)	-	-	-
Treatment difference (g/dl)	0.3		-	-	-	-	-	-	-	-
P-value	0.0124		-	-	-	-	-	-	-	-
Change in Hgb (g/dl), mean (SD)	0.8 (0.1)	0.7 (0.1)	-	-	2.6 (1.5)	0.1 (0.9)	-	-	-	-
P-value	0.52		-	-	< 0.0001		-	-	-	-
Achieving ≥ 1 g/dl increase (%)	50	42	-	-	-	-	-	-	-	-
P-value	0.29		-	-	-	-	-	-	-	-
Week 4										
≥ 1 g/dl increase, ^a %	-	-	-	-	-	-	85	-	-	-
> 2 g/dl increase, ^a %	-	-	-	-	-	-	58	-	-	-
Mean increase (g/dl)	-	-	-	-	-	-	2.1	-	-	-
Week 8										
≥ 1 g/dl increase, ^a %	-	-	-	-	-	-	92	-	-	-
> 2 g/dl increase, ^a %	-	-	-	-	-	-	86	-	-	-
TSAT										
Change (increase) in TSAT, (%)	14.5	10.6	-	-	11.4 (15.1)	0.4 (5.8)	-	-	-	-
P-value	0.0048		-	-	< 0.0001		-	-	-	-
PRO										
Improvement in FACIT-Fatigue, mean (SD)	41.7 (10.05)	41.5 (9.51)	-	-	11.7 (11.7)	6.8 (9.5)	-	-	-	-
P-value	-		-	-	<0.0001		-	-	-	-
SF-36-Vitality score increase	13.0	12.5	-	-	10.6	5.4	-	-	-	-
P-value	0.05		-	-	<0.0001		-	-	-	-

Table 4: Detailed Findings of Included Studies

	Primary Studies									
	Hetzel, ¹ 2014 RCT		Macdougall, ⁹ 2014 RCT		Vadhan-Raj, ³ 2014 RCT		Auerbach, ¹⁰ 2013 NRS	Schiller, ² 2014 ^e NRS		
	FCM	IS	FCM	IS	FCM	PL	FCM	FCM		
								Chain A	Chain B	Chain C
LASA-Energy score increase	21.9	21.3	-	-	19.7	10.3	-	-	-	-
P-value	> 0.05		-		<0.0001		-	-	-	-
Any Time Between Baseline and Week 5										
Increase of Hgb ≥ 2 g/dl, %	84	81.4	-	-	81.1	5.5	-	-	-	-
P-value	-		-		<0.0001		-	-	-	-
Achieving Hgb ≥ 12 g/dl, %	66.7	48.2	-	-	50.5	3.0	-	-	-	-
From Baseline to Month 12										
Baseline Hgb (g/dl), mean (SD)	-	-	-	-	-	-	-	10.54 (1.38)	10.83 (1.29)	11.24 (1.36)
Month 12 Hgb (g/dl), mean (SD)	-	-	-	-	-	-	-	11.23 (1.33)	11.04 (1.32)	11.37 (1.02)
Target Hgb (10-12 g/dl) maintained, %	-	-	-	-	-	-	-	61	72	65
Other										
Mean time to response (≥ 2 g/dl Hgb increase or Hgb level of ≥ 12 g/dl), days	16	22	28.8 ^c	33.4 ^c	23.5	42.5	-	-	-	-
P-value	< 0.0001		NA		< 0.0001		-	-	-	-
TSAT										
Peak, week	-	-	2	2	-	-	4	-	-	-
Value (g/dl), mean (SD)	-	-	33.0 (13.1)	26.0 (17.2)	-	-	23.1% of pts	-	-	-
Reaching stable levels at month 12 (%), mean (SD)	-	-	-	-	-	-	-	30 (13)	34 (17)	28 (14)
Ferritin										
Peak, week	-	-	2	3	-	-	4	-	-	-
Mean value (ng/ml)	-	-	854	546	-	-	214	-	-	-
Reaching Month 12 levels (ng/ml), mean (SD)	-	-	-	-	-	-	-	490 (283) ^f	834 (325)	753 (238)
No change in EAS therapy (%)	-	-	91		-	-	-	-	-	-

Table 4: Detailed Findings of Included Studies

	Primary Studies									
	Hetzel, ¹ 2014 RCT		Macdougall, ⁹ 2014 RCT		Vadhan-Raj, ³ 2014 RCT		Auerbach, ¹⁰ 2013 NRS	Schiller, ² 2014 ^e NRS		
	FCM	IS	FCM	IS	FCM	PL	FCM	FCM		
								Chain A	Chain B	Chain C
Safety										
AEs (%)	14.3	16.1	48 ^d	65 ^d	-	-	43.3	1.25		
Most common AEs (%)										
Arthralgia/myalgia/ (muscle spasms)	-	-	(5.0)	(7.3)	-	-	23	-		
Edema (peripheral)	-	-	(2.5)	(7.3)	-	-	2	-		
Chest pain/tightness	-	-	-	-	-	-	7	-		
Cough	-	-	2.8	0	-	-	5	-		
Dizziness	-	-	-	-	-	-	5	0.15		
Flushing	-	-	1.3	0	-	-	5	0.07		
Headache	-	-	3.8	2.4	5.8	6.0	13	-		
Hypotension	-	-	2.5	9.8	-	-	-	0.21		
Nausea	-	-	7.5	3.7	4.6	2.5	5	0.37		
Pruritis/rash	-	-	-	-	-	-	5	0.29		
Urinary tract infection	-	-	3.8	7.3	2.8	3.0	-	0.07		
Protocol-defined AEs of special interest, ^b (%)	2.7	5.0	1.3	6.1	3.6	1.0	-	-	-	-
SAEs (%)	4.2	2.5	9	7	2.6	3.0	0	0.21		
Most Common SAEs, %										
Hypotension	-	-	-	6.1	-	-	-	0.12		
Hypersensitivity	-	-	-	-	0.5	0	-	0.06		
Anaphylactoid reactions	(n = 1)	0	1.3	-	0.2	0	-	0.02		
Deaths, n (%)	1 (0.2)	0	0	0	2 (0.3)	1 (0.5)	0	-	-	-
TEAEs (%)	41.1	44.2	-	-	49.2	43.0	-	-	-	-
WDAEs, (%)	0.7	1.0	1	5	0.5	0.5	-	-	-	-

FACT-Fatigue = Functional Assessment of Chronic Illness therapy Fatigue; FCM = ferumoxytol; EAS = erythropoiesis-stimulating agents; Hgb = hemoglobin; IS = iron sucrose; LASA-Energy = QOL Linear Analogue Scale Assessment; NA = not applicable; NR = not reported; NRS = non-randomized stud; PL = placebo; PRO = patient reported outcome; pts = patients; RCT = randomized controlled trial; SF-36 = 36-Item Short-Form General Health Survey; TSAT = total iron binding capacity/ferritin saturation; WDAE = withdrawal due to adverse events.

^a Results were obtained at Week 4.

^b AEs of special interest include hypotension and hypersensitivity.

^c Reponse defined as ≥ 1 g/dl or achieved Hgb ≥ 12 g/dl.

^d AEs occurring in $\geq 2\%$ of patients.

^e Analysis of pooled data, n = 8666.

^f Month 11 levels as opposed to Month 12 levels.

N=1Note: Anything with (-) denoted that this was not observed anywhere throughout the article.

Table 5: Author’s Conclusions From Included Studies

First Author, Year	Author’s Conclusions
<i>Randomized Controlled Trials</i>	
Hetzl, ¹ 2014	<ul style="list-style-type: none"> “...the results of this randomized, active-controlled, multicenter study suggest that the therapeutic usefulness of ferumoxytol may extend beyond its currently approved indication (i.e., the treatment of IDA in adult patients with CKD) to a broader population of IDA patients with a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used.” page 650 “In this study, ferumoxytol administered as two IV doses of 510 mg each was shown to be well tolerated and effective in treating IDA.” page 650
Macdougall, ⁹ 2014	<ul style="list-style-type: none"> “The efficacy results show that ferumoxytol was noninferior to iron sucrose.” page 6 “Data from this study show that both ferumoxytol and iron sucrose are safe and effective in this patient population and that no major differences were observed.” page 6
Vadhan-Raj, ³ 2014	<ul style="list-style-type: none"> “...ferumoxytol was shown to be well tolerated and effective in patients with IDA of any underlying cause, increasing Hgb, reducing fatigue, increasing energy and vitality, and could provide an important treatment option and help meet the unmet medical need for patients with IDA and a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used.” page 11
<i>Non-Randomized Studies</i>	
Auerbach, ¹⁰ 2013	<ul style="list-style-type: none"> “Ferumoxytol also demonstrated excellent efficacy in this population with a diverse group of etiologies for IDA.” page 946 “This study of 60 IDA patients demonstrates the ease of administering a complete replacement dose of IV iron with ferumoxytol in 15 min.” page 946
Schiller, ² 2014	<ul style="list-style-type: none"> “...ferumoxytol was broadly effective at raising and maintaining iron parameters and Hb values as an adjunct therapy to ESA administration for anemia therapy in dialysis patients in a real-world setting.” page 82 “...confirmation that the safety profile for ferumoxytol is both predictable and manageable when used to treat IDA in patients with CKD.” page 82

CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agents; Hgb = hemoglobin; IV = intravenous; IDA = iron deficiency anemia; IV = intravenous.