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CADTH COMMON DRUG REVIEW

Clinical Review Report

IRON ISOMALTOSIDE 1000 (MONOFERRIC)

(Pharmacosmos A/S)

Indication: For the treatment of iron deficiency anemia in adult patients who have intolerance or unresponsiveness to oral iron therapy.

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Abbreviations

ADR	adverse drug reaction
AE	adverse event
CCC	Crohn's and Colitis Canada
CDR	CADTH Common Drug Review
CH-RLSq	Cambridge–Hopkins Restless Legs Syndrome Questionnaire
CI	confidence interval
CKD	chronic kidney disease
CKD-5D	chronic kidney disease stage 5
ESA	fagent
FACIT	Functional Assessment of Chronic Illness Therapy
FACIT-FS	Functional Assessment of Chronic Illness Therapy–Fatigue Scale
FAS	full analysis set
Hb	hemoglobin
HRQoL	health-related quality of life
IBD	inflammatory bowel disease
ID	iron deficiency
IDA	iron deficiency anemia
ITT	intention-to-treat
KFOC	Kidney Foundation of Canada
LASA	Linear Analog Scale Assessment
LOCF	last observation carried forward
MCID	minimal clinically important difference
MCS	mental component summary
MMRM	mixed-effects model for repeated measures
NDD-CKD	non–dialysis-dependent chronic kidney disease
NIM	noninferiority margin
NMA	network meta-analysis
PCS	physical component summary
PP	per protocol

QoL	quality of life
RCT	randomized controlled trial
RLS	restless legs syndrome
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form (36) Health Survey
s-ferritin	serum ferritin
s-iron	serum iron
TEAE	treatment-emergent adverse event
TSAT	transferrin saturation
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

Drug	Iron isomaltoside 1000 (Monoferric)
Indication	Indicated for the treatment of iron deficiency anemia in adult patients who have intolerance or unresponsiveness to oral iron therapy. The diagnosis must be based on laboratory tests.
Reimbursement request	As per indication.
Dosage form(s) and route of administration and strength(s)	100 mg/mL administered intravenously
NOC date	June 22, 2018
Sponsor	Pharmacosmos A/S

Executive Summary

Introduction

Anemia is defined by a decrease in the quantity of red blood cells and reduced hemoglobin (Hb) levels with concomitant impaired capacity to transport oxygen and/or altered red blood cell morphology. Its etiology varies significantly by geography, age, sex, pregnancy, altitude, and smoking habits.[1,2] The Hb level thresholds recommended by WHO to diagnose anemia are less than 13 g/dL in men over 15 years of age, less than 12 g/dL in non-pregnant women over 15 years of age and less than 11 g/dL in pregnant women.[3] Iron deficiency anemia (IDA) is the most prevalent and treatable form of anemia worldwide.[1,4] Blood loss is the primary mechanism for developing IDA and is most often the result of either menstruation or gastrointestinal bleeding. Underlying disorders resulting in poor iron absorption and low dietary intake of iron are also common reasons for developing IDA.[4,5] Patients with chronic underlying diseases such as chronic kidney disease (CKD), inflammatory bowel disease (IBD), malignancies, and rheumatoid arthritis are also at increased risk of developing IDA.[2]

Iron isomaltoside 1000 for injection (Monoferric) is an IV iron product indicated for treatment of IDA in adult patients (≥ 18 years of age) with an intolerance or unresponsiveness to oral iron.[6] Iron isomaltoside 1000 consists of iron and a carbohydrate moiety in which iron is tightly bound within a matrix structure, consisting of iron (III) atoms and isomaltoside pentamers.[6-8] This structure permits a gradual release of iron to available iron-binding proteins to primarily form ferritin, the storage form of iron, or to a lesser extent, the transport molecule transferrin. The released iron replenishes Hb and iron stores, both of which are significantly diminished with IDA. Iron isomaltoside 1000 may be administered as an IV bolus injection, an IV drip infusion, or an injection into a dialyzer:[6]

- IV bolus injections of iron isomaltoside 1000 may be administered up to 500 mg up to once a week at a rate of up to 250 mg iron/minutes.
- IV drip infusions may be administered as a single iron isomaltoside 1000 dose of up to 20 mg iron/kg body weight or as weekly infusions until the cumulative iron dose is reached.
- Iron isomaltoside 1000 may be directly injected into the venous limb of a dialyzer following the same procedures of an IV bolus injection.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of iron isomaltoside 1000 injection (100 mg elemental iron/mL) for the

treatment of IDA in adults (≥ 18 years of age) who have an intolerance or unresponsiveness to oral iron.

Stakeholder Engagement

Patient Input

Two patient groups — Crohn's and Colitis Canada (CCC) and the Kidney Foundation of Canada (KFOC) — provided input for this review. The patients indicated that in a patient with IBD, blood loss due to gastrointestinal bleeding and malabsorption of iron from nutritional sources can cause anemia. Most people with moderate-to-severe CKD develop anemia. Patients described that the most common symptoms of IDA are weakness, fatigue, low energy, shortness of breath, and poor concentration and compromised quality of life (QoL). It was indicated that patients with IBD are often prescribed oral iron supplements or, in serious cases, iron IV infusion.

Patients indicated that when choosing iron supplementation therapies, they faced trade-offs between slower response (oral tablets) and the convenience of taking the treatment at home compared to iron infusions in a clinical setting, which requires an appointment and potentially missing school or work. Two patients who had experience using iron isomaltoside 1000 (Monoferric) expressed that it worked well (effective) and quickly (noticed effect within a few days) and was easy to take (single treatment instead of the previous requirement of an infusion every six to eight weeks). Although one patient did not experience adverse effects on Monoferric, another patient reported some reactions when the infusion first started (including burning sensation in body, red face and ears, and heart palpitations). Additionally, patients expressed concern over their ability to cover the cost of Monoferric in the absence of drug insurance or employment.

Clinician Input[1]

One clinical specialist with expertise in the diagnosis and management of adults with IDA (≥ 18 years of age), who have an intolerance or unresponsiveness to oral iron, was consulted and provided their clinical input for this review. The clinical expert indicated that IDA is a common clinical problem most typically due to chronic blood loss (i.e., menses, gastrointestinal bleeding from hemorrhoids, polyps, or tumours) and that frequently reported symptoms include fatigue, decreased exercise tolerance, decreased mental concentration, and shortness of breath, particularly upon exertion.

Treatment of IDA, according to the clinical expert, focuses on correcting anemia and replenishing iron stores with either oral or IV iron supplementation, as well as addressing the underlying cause of blood loss, with the overall goal to improve clinical symptoms and a patient's QoL. However, IV iron supplementation is normally reserved for patients who respond poorly to or do not tolerate oral iron therapy. IV iron may also be used when rapid iron repletion and correction of anemia is desired.

The clinical expert identified a practical limitation associated with iron sucrose, the most commonly used IV iron product in clinical practice. Iron sucrose requires two hours per infusion (300 mg/dose) and thus imposes practical limitations associated with the availability of chair time in infusion clinics. An IV iron formulation that delivers a higher iron

[1] This information is based on information provided in draft form by clinical experts consulted by CADTH Common Drug Review (CDR) reviewers for the purpose of this review.

dose over a shorter infusion time would improve delivery convenience and use of resources. As well, the clinical expert noted that the ability to deliver a larger amount of iron in a single dose would benefit patients with significant ongoing blood loss (i.e., severe menorrhagia) that is difficult to offset with iron sucrose due to practical limitations on frequency of dosing and administration.

The clinical expert expects that iron isomaltoside 1000 would be used for the same clinical indications as iron sucrose (i.e., treatment of IDA in patients who cannot tolerate or do not respond well to oral iron supplements).

Patients with IDA are easily diagnosed in a clinical setting with complete blood counts and serum ferritin (s-ferritin). Hb and s-ferritin are the two key laboratory parameters used to assess whether a patient is responding to IV iron therapy. The clinical expert indicated that a good response would entail a rise in Hb level and once Hb is normalized, a rise in ferritin level reflecting improved iron stores. The expected rise in Hb is roughly 10 g/L for every 300 mg iron; thus, one dose of iron sucrose of 300 mg should give 10 g/L and one dose of iron isomaltoside 1000 of 1,000 mg should give about 30 g/L.

The clinical expert noted that although patients with uncomplicated IDA may be diagnosed, treated, and monitored by any physician or nurse practitioner, the use of IV iron for the treatment of IDA will be limited to specialists (e.g., an internist or hematologist) as family doctors do not have access to hospital infusion clinics. Additionally, the clinical expert indicated that outpatient patients will most likely be the patient population with the most use of iron isomaltoside 1000 as it can be administered in an infusion clinic or a hospital day unit. Preoperative patients may be considered for iron isomaltoside 1000 if rapid correction of anemia is desired.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Four phase III, randomized controlled trials (RCTs) were identified and included in this systematic review (PROPOSE, FERWON-NEPHRO, PROVIDE, and FERWON-IDA).[9-17] PROPOSE[9] and PROVIDE[11] were the pivotal studies identified by the sponsor and FERWON-NEPHRO[14] and FERWON-IDA[16] were identified with the CADTH Common Drug Review (CDR) systematic search strategy.

Each of the four included trials was a multi-centre, open-label, parallel group, active-controlled, noninferiority RCT that enrolled adult men and women aged 18 or older. Eligible participants for PROPOSE (N = 351),[9] FERWON-NEPHRO (N = 1,538),[14] PROVIDE (N = 511),[11] and FERWON-IDA (N = 1,512)[16] were randomized 2:1 into iron isomaltoside 1000 and iron sucrose. In PROPOSE, participants were required to have CKD stage 5 (CKD-5D), receiving hemodialysis and maintenance iron therapy for renal-related anemia, and FERWON-NEPHRO included patients with non–dialysis-dependent CKD (NDD-CKD) and IDA. In PROVIDE and FERWON-IDA, patients with IDA caused by various etiologies and who had a documented intolerance or unresponsiveness to oral iron therapy or a need for rapid iron repletion identified by the investigators were eligible for enrolment.[11,16] If a potential FERWON-IDA participant did not have documented oral intolerance, a run-in period was initiated (up to one month).[16]

PROPOSE was designed to assess whether iron isomaltoside 1000 was noninferior to iron sucrose for maintenance therapy of renal-related anemia in CKD-5D patients on dialysis and receiving iron maintenance therapy. The primary outcome measure was the proportion of participants who maintained an Hb level between 9.5 g/dL and 12.5 g/dL (both values included) at week 6.[9]

FERWON-NEPHRO, PROVIDE, and FERWON-IDA were designed to assess the efficacy and safety of iron isomaltoside 1000 compared with iron sucrose for treatment of IDA. As such, primary end points in these studies compared the IV iron products for noninferiority on their ability to raise Hb levels.[11,14-16] FERWON-NEPHRO and FERWON-IDA had the same co-primary end point that measured, first, the proportion of participants with serious or severe hypersensitivity reactions and, second, the change in Hb from baseline to week 8.[14-16] The primary end point of PROVIDE evaluated efficacy by comparing the proportion of participants who achieved an increase in Hb of 2 g/dL or more from baseline to any time between week 1 and week 5.[11]

Secondary end points in the included studies further compared the IV iron products' abilities to raise Hb (i.e., change in Hb levels at earlier time points and the time to achieve an increase ≥ 2 g/dL) and to replenish iron stores (i.e., change in *s*-ferritin levels).[9,11,14-16] The QoL of participants was evaluated in PROVIDE via the Short Form (36) Health Survey (SF-36)[11] and in PROPOSE via the Linear Analog Scale Assessment (LASA).[9] Fatigue symptoms were assessed in PROVIDE and FERWON-IDA via the Functional Assessment of Chronic Illness Therapy–Fatigue Scale (FACIT-FS)[11,16] while PROPOSE assessed restless legs syndrome (RLS) via the Cambridge–Hopkins-Restless Legs Syndrome Questionnaire (CH-RLSq).[9]

Efficacy Results

The pivotal trials PROPOSE and PROVIDE showed iron isomaltoside 1000 to be noninferior to iron sucrose for their respective primary end points of maintaining Hb levels and raising Hb levels.[9,11] In PROPOSE, the proportion of participants who were able to maintain Hb between 9.5 g/dL and 12.5 g/dL (both values included) in the iron isomaltoside 1000 group (83.9%) and iron sucrose group (82.2%) were similar at six weeks and the adjusted risk difference in the per-protocol (PP) dataset of 2.2% points (95% confidence interval [CI], –6.4 to 10.9) concluded the treatments were noninferior as the lower limit of 95% CI was higher than –10% noninferiority margin (NIM). The finding of noninferiority was consistent across full analysis set (FAS) and PP datasets as well as various data imputation methods, with the exception of the FAS unadjusted analysis with missing values imputed as failures, signalling a potential source of bias.[9] In PROVIDE, more iron isomaltoside 1000 participants (FAS: 68.5%; PP: 70.1%) compared with iron sucrose (FAS: 51.5%; PP: 53.8%) achieved larger Hb response (i.e., ≥ 2 g/dL) from baseline to any time within one week to five weeks and the risk difference in the PP dataset of 15.9% (95% CI, 6.3 to 25.4) showed iron isomaltoside 1000 to be noninferior to iron sucrose as the lower end of 95% CI was greater than –12.5% points. The results in the FAS dataset were consistent with the PP dataset.[11]

The primary analysis of the PROPOSE and PROVIDE trials tested for superiority; however, only PROVIDE found iron isomaltoside 1000 to be better than iron sucrose in raising Hb levels as a statistically significantly greater proportion of iron isomaltoside 1000 participants achieved an increase in Hb of 2 g/dL or more from baseline to any time within one week to five weeks compared with iron sucrose (FAS: $P < 0.0001$; PP: $P = 0.0002$).[9,11] The superiority finding in PROVIDE was most likely related to maximum cumulative iron dose

permitted during the trial. PROVIDE participants were permitted to receive up to 2,000 mg cumulative iron (the highest cumulative dose administered across the included trials) and iron isomaltoside 1000 participants, compared with iron sucrose participants, received a greater mean cumulative iron dose (1,640.20 mg versus 1,127.9 mg, respectively).[11]

The primary efficacy end points were the same for the FERWON-NEPHRO and FERWON-IDA trials. Both trials found iron isomaltoside 1000 to be noninferior to iron sucrose on the ability to raise Hb levels as measured by the mean change in Hb levels from baseline to week 8.[14,16] Statistical data were unavailable for FERWON-NEPHRO.[14] In FERWON-IDA, the estimated treatment difference was 0.00 g/dL (95% CI, –0.13 to 0.13) in the ITT dataset and noninferiority was claimed, as the lower boundary of the 95% CI was greater than –0.5 g/dL. The noninferiority results were consistent across the FAS and PP datasets. FERWON-IDA tested for superiority; however, iron isomaltoside 1000 was not statistically better at raising Hb levels by week 8 as the 95% CI contained 0. Sensitivity analyses using imputation methods to handle missing data were not performed. Thus, the robustness of the noninferiority finding could not be assessed.[16]

Of the secondary end points in PROPOSE, iron isomaltoside 1000 was statistically significantly better at raising s-ferritin levels from baseline to week 2 (treatment difference estimate 123.3600 mcg/L [95% CI, 96.449 to 150.271; P < 0.0001]), which was attributed to the single dose iron isomaltoside 1000 arm. This showed that iron isomaltoside 1000 was better at replenishing iron stores earlier than iron sucrose. However, the difference in s-ferritin was not statistically different for the fractionated iron isomaltoside 1000 treatment group compared with iron sucrose at week 1, week 2, week 4, and week 6. No statistical differences in mean change in Hb levels were seen from baseline to any study time points. This result is unsurprising as the cumulative iron dose administered to PROPOSE participants in the iron isomaltoside 1000 group and iron sucrose group was the lowest of this review's included trials (500 mg) and the baseline Hb levels of participants for both groups was greater compared with the baseline values of participants in this review's other included trials.[9]

Secondary end points in the pivotal trial PROVIDE showed iron isomaltoside 1000 was statistically better at achieving a faster Hb response compared with iron sucrose. The median time to achieving an increase in Hb of 2 g/dL or more was statistically significantly shorter for iron isomaltoside 1000 participants (26 days) compared with iron sucrose participants (37 days) (hazard ratio: 2.488 [95% CI, 1.916 to 3.230]). A statistically significant difference in the mean change in Hb levels from baseline was found at the early time point of two weeks (estimated treatment difference: 0.70 g/dL [95% CI, 0.53 to 0.86]) and was sustained until end of study at week 5 (estimated treatment difference: 0.46 g/dL [95% CI, 0.30 to 0.62]). Further, PROVIDE showed iron isomaltoside was better at raising s-ferritin levels earlier than iron sucrose as the mean change from baseline to week 2 in s-ferritin was statistically significantly greater in iron isomaltoside 1000 participants (estimated treatment difference: 702.9 mcg/L [95% CI, 313.9 to 1,091.9; P < 0.0004]).[11] A statistically significant difference in the mean change s-ferritin from baseline to week 2 was also seen in the pivotal trial PROPOSE: 123.6 mcg/L (95% CI, 96.449 to 150.271; P < 0.0001).[9]

The secondary analyses in FERWON-NEPHRO and FERWON-IDA further supported findings that iron isomaltoside 1000 was better at achieving an earlier and greater Hb response.[14,16] FERWON-NEPHRO found that the mean change in Hb from baseline to week 2 was statistically significantly greater in iron isomaltoside 1000 participants (0.75 g/dL) compared with iron sucrose participants (0.50 g/dL) (P < 0.0001).[14] In FERWON-IDA,

the mean increase in Hb levels from baseline to week 4 was also statistically significantly greater for iron isomaltoside 1000 than iron sucrose (P < 0.0001). A statistically significantly greater proportion of iron isomaltoside 1000 participants (32.6%) compared with iron sucrose participants (20.8%) in FERWON-IDA achieved a better Hb response (i.e., ≥ 2 g/dL) at two weeks (odds ratio: 2.42 [95% CI, 1.80 to 3.26; P < 0.0001]). A statistically significantly greater rise in s-ferritin from baseline to week 2 was achieved in iron isomaltoside 1000 participants compared with iron sucrose participants (P < 0.0001).[16]

The HRQoL outcomes of energy, fatigue, and overall QoL were identified as important to participants and found not to be different for either treatment group across the included trials, with the exception of FERWON-IDA at week 1.[9,11,14,16] In FERWON-IDA, the mean change in FACIT-FS from baseline to week 1 was statistically significant between iron isomaltoside 1000 and iron sucrose, indicating iron isomaltoside 1000 participants experienced a faster improvement in fatigue symptoms compared with iron sucrose. This difference in FACIT-FS was not seen at week 2 or week 8 in FERWON-IDA. The clinical expert on this review suggested a possible reason for the non-significant differences in QoL, fatigue, and RLS was due to the fact that the cumulative doses received by iron isomaltoside 1000 participants and iron sucrose participants was comparable between treatment groups, with the exception of PROVIDE.

The indirect evidence from a published network meta-analysis (NMA) identified no additional evidence for efficacy-related outcomes with the CDR systematic search strategy provided.

Harms Results

The overall incidence of participants reporting at least one treatment-emergent adverse event (TEAE) was similar between the PROPOSE study (iron isomaltoside 1000: 47.8%; iron sucrose: 41.2%)[9] and the PROVIDE study (iron isomaltoside 1000: 43.2%; iron sucrose: 38.7%)[11] and both trials showed the proportion of TEAE reporting to be slightly greater for iron isomaltoside 1000 participants compared with iron sucrose participants. In contrast, FERWON-IDA reported a lower and well-balanced incidence of TEAEs in both treatment groups (iron isomaltoside: 12.5%; iron sucrose: 12.8%).[16]

The frequency of participants reporting at least one serious adverse event (SAE) was also higher in the PROPOSE and PROVIDE trials compared with the FERWON-IDA trial.[9,11,16] The proportion of iron isomaltoside 1000 participants and iron sucrose participants reporting one or more SAEs was similarly balanced between treatment groups for PROVIDE (3.3% and 3.6%, respectively)[11] and FERWON-IDA (0.5% and 0.4%, respectively).[16] However, the proportion of participants reporting one or more SAEs in PROPOSE was higher for iron isomaltoside 1000 participants (9.6%) compared with iron sucrose participants (5.3%) in PROPOSE.[9]

The incidence of participants withdrawing from a trial due to an adverse event (AE) was also higher in the PROPOSE and PROVIDE trials than in the FERWON-IDA trial.[9,11,16] The proportion of participants withdrawing from the study due to an AE was similarly balanced for iron isomaltoside 1000 participants and iron sucrose participants in PROVIDE (3.0% and 3.6%, respectively) and FERWON-IDA (0.7% and 0.6%, respectively). In contrast, more iron isomaltoside 1000 participants than iron sucrose participants withdrew from the PROPOSE trial (3.9% and 0%, respectively) and it is unclear why this imbalance occurred. However, the clinical expert suggested that the imbalance may have been attributed to iron isomaltoside 1000 participants receiving the IV iron over a faster period of time (bolus

injection over approximately two minutes), whereas the majority of iron isomaltoside 1000 participants in FERWON-NEPHRO, PROVIDE, and FERWON-IDA received IV infusions over 15 to 20 minutes.

The incidence of serious or severe hypersensitivity reactions was consistently low across the included trials (PROPOSE: iron isomaltoside 1000 group at 0.4% and iron sucrose group at 0%; FERWON-NEPHRO: iron isomaltoside 1000 group at 0.3% and iron sucrose group at 0%; PROVIDE: iron isomaltoside 1000 group at 1.2% and iron sucrose group at 1.2%; FERWON-IDA: iron isomaltoside 1000 group at 0.3% and iron sucrose group at 0.4%).[9,11,14,16]

The indirect evidence from a published NMA identified no additional evidence for harms-related outcomes with the CDR systematic search strategy provided.

Table 1: Summary of Key Results From Pivotal and Protocol Selected Studies

	CKD studies				IDA studies			
	PROPOSE		FERWON-NEPHRO N = 1,538		PROVIDE		FERWON-IDA	
	IIM N = 226	IS N = 115	IIM	IS	IIM N = 342	IS N = 169	IIM N = 1,009	IS N = 503
Change in Hb (g/dL)								
Week 2								
N contributing to the analysis	219	115	-	-	318	157	1,009	503
Treatment group difference vs. control (95% CI)	0.1138 (–0.031 to 0.259)		-		0.70 (0.53 to 0.86)		-	
P value	0.1239		< 0.0001		< 0.0001		< 0.001	
End of study	**6 weeks**		**8 weeks**		**5 weeks**		**8 weeks**	
N contributing to the analysis	216	113	-	-	322	155	901	437
Treatment group difference vs. control (95% CI)	0.0069 (–0.204 to 0.246)		-		0.46 (0.30 to 0.62)		0.01 (–0.12 to 0.14)[a]	
P value	0.8557		IIM noninferior to IS		< 0.0001		0.871	
Subjects who maintained Hb between 9.5 g/dL and 12.5 g/dL (both values included) at 6 weeks								
PP								
n (%)	167 (83.9)	88 (82.2)	-	-	-	-	-	-
RD (95% CI)	2.2 (–6.4 to 0.9)		-		-		-	
P value	0.0057[b]		-		-		-	
Subjects with Hb increase ≥ 2 g/dL								
Any time from week 1 to week 5								
Event/n (%)	-	-	-	-	218/311 (70.1)	77/143 (53.8)	-	-

	CKD studies				IDA studies			
	PROPOSE		FERWON-NEPHRO N = 1,538		PROVIDE		FERWON-IDA	
	IIM N = 226	IS N = 115	IIM	IS	IIM N = 342	IS N = 169	IIM N = 1,009	IS N = 503
OR or RD (95% CI)	-		-		RD: 15.9 (6.3 to 25.4)		-	
Superiority test, P value	-		-		0.0002		-	
Week 2								
Event/n (%)	-	-	-	-	-	-	297/912 (32.6)	94/452 (20.8)
OR or RD (95% CI)	-		-		-		OR: 2.42 (1.80 to 3.26)	
P value	-		-		-		< 0.0001	
Week 8								
Event/n (%)	-	-	-	-	-	-	606/903 (67.1)	
OR or RD (95% CI)	-		-		-		OR: 1.05 (0.80 to 1.38)	
P value	-		-		-		0.703	
Time to increase Hb ≥ 2 g/dL (days)								
N contributing to the analysis	-	-	-	-	330	161	1,009	503
Median time (range)	-	-	-	-	26 (21.0 to 28.0)	37 (32.0 to 42.0)	28	28
HR (95% CI) [b]	-		-		2.488 (1.916 to 3.230)		-	
P value	-				< 0.0001		0.088	
Change in s-ferritin (mcg/L)								
Week 2								
N contributing to the analysis	220	115	-	-	322	159	1,009	503
Treatment group difference vs. control (95% CI)	123.3600 (96.449 to 150.271)		-		702.9 (313.9 to 1,091.9)		-	
P value	< 0.0001		-		0.0004		0.0001	
End of study	**6 weeks**		**8 weeks**		**5 weeks**		**8 weeks**	
N contributing to the analysis	216	114	-	-	323	155	1,009	503
Treatment group difference vs. control (95% CI)	–15.0585 (–54.196 to 24.079)		-		58.5 (–333.7 to 450.6)		-	
P value	0.4489		-		0.7700		NS	
QoL measures								
	LASA — Energy level				**SF-36 (8 health domains)**			
N contributing to the analysis	204	113	-	-	-	-		

	CKD studies				IDA studies			
	PROPOSE		FERWON-NEPHRO N = 1,538		PROVIDE		FERWON-IDA	
	IIM N = 226	IS N = 115	IIM	IS	IIM N = 342	IS N = 169	IIM N = 1,009	IS N = 503
Treatment group difference vs. control (95% CI)	0.1111 (–3.667 to 3.889)		-		-	-		
P value	0.9539		-		NS			
	LASA — Ability to do daily activities				**SF-36 (2 composite scores)**			
N contributing to the analysis	204	113	-	-	-	-		
Treatment group difference vs. control (95% CI)	–0.8519 (–4.829 to 3.125)		-		-	-		
P value	0.6734		-		NS			
	LASA — Overall QoL				**Change in FACIT-FS score at 5 weeks**		**Change in FACIT-FS score at 8 weeks**	
N contributing to the analysis	204	113	-	-	-	-	-	-
Treatment group difference vs. control (95% CI)	0.4718 (–3.125 to 4.069)		-		-	-	-	-
P value	0.7964		-		NS		NS	
SAE								
n (%)	22 (9.6)	6 (5.3)	-	-	11 (3.3)	6 (3.6)	5 (0.5)	2 (0.4)
WDAEs								
n (%)	9 (3.9)	-	(0.3)	(0)	10 (0.3)	6 (3.6)	7 (0.7)	3 (0.6)
Notable harms								
Serious or severe hypersensitivity AE, n (%)	1 (0.4)	-	(0.3)	(0)	4 (1.2)	2 (1.2)	3 (0.3)	2 (0.4)

AE = adverse event; CI = confidence interval; CKD = chronic kidney disease; FACIT-FS = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; Hb = hemoglobin; HR = hazard ratio; IDA = iron deficiency anemia; IIM = iron isomaltoside 1000; IS = iron sucrose; LASA = Linear Analog Scale Assessment; NS = non-significant; OR = odds ratio; PP = per-protocol; QoL = quality of life; RD = risk difference; s-ferritin = serum ferritin; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; vs. = versus; WDAE = withdrawal due to adverse event.

[a] FERWON-IDA: Noninferiority was achieved if lower boundary of the 95% CI was greater than –0.5 g/dL.

[b] PROPOSE: Noninferiority was achieved if lower boundary of the 95% CI was greater than –10% points.

Source: Clinical Study Reports for PROPOSE[9] and PROVIDE,[11] and publications for FERWON-NEPHRO[14] and FERWON-IDA.[16]

Critical Appraisal

The PROVIDE, FERWON-NEPHRO, and FERWON-IDA trials did not use data imputation methods to handle missing data for the primary analyses nor were sensitivity analyses performed using different methods of handling missing data to assess the robustness of the primary analysis.[11,14,16] This created uncertainty with respect to whether missing data were a potential source of bias in these trials.

The primary outcome measure in the PROPOSE trial was the proportion of participants who maintained an Hb level between 9.5 g/dL and 12.5 g/dL (both values included) at six weeks while in PROVIDE, the primary end point evaluated efficacy by comparing the proportion of

participants who achieved an increase in Hb of 2 g/dL or more from baseline to any time between week 1 and week 5. In FERWON-IDA, noninferiority was claimed if the lower boundary of the 95% CI was greater than –0.5 g/dL. Statistical analysis data were unavailable for FERWON-NEPHRO. In PROPOSE, the noninferiority of results was consistent across different imputation methods except for where missing values were imputed as failures, signalling a potential source of bias as more participants receiving iron isomaltoside 1000 had missing data (9.0%) compared with iron sucrose (3.4%).[9]

Nearly half of screened participants in the PROVIDE and FERWON-IDA trials were excluded, creating concern as to whether the findings are generalizable to those participants not studied, particularly in the pivotal trial of PROVIDE.[11,16] Finally, multiple testing at different time points for superiority and various outcomes is a considerable concern, even though the P values for the claims are relatively small, which may relieve a bit of such concern for increased type I error.[9,11,14,16]

Indirect Comparisons

Description of Studies

The sponsor did not include indirect comparison evidence in its submission. CADTH conducted a supplemental literature search for potential relevant indirect comparisons evidence. From this additional CADTH search, a potentially relevant systematic review and NMA were identified.[18] The NMA was conducted by Aksan el al. in 2016[18] and updated in 2019 (reported in abstracts).[19,20] The objective of the NMA was to compare the efficacy and tolerability of different IV iron formulations and oral iron agents used to treat IDA in participants with IBD. Five RCTs (n = 1,143 participants) were included in the NMA. However, the NMA did not include any of the four studies (two pivotal and two non-pivotal studies)[10,13,14,16] selected for this CADTH review. IV iron agents included in the NMA were iron isomaltoside 1000, iron sucrose, ferric gluconate, and ferric carboxymaltose. The primary outcome was the therapy response (defined as Hb normalization or increase ≥ 2 g/dL), which was not aligned with the key outcomes listed in the protocol for this CADTH review.

Efficacy Results

The NMA reported that there was no statistically significant difference between iron isomaltoside 1000 and iron sucrose in terms of response rate, defined as Hb normalization or increase of 2 g/dL or more (odds ratio: 0.98 [95% credible interval, 0.49 to 2.0]) in the treatment of IDA in participants with IBD. The probability of being the most effective treatment (by the Markov Chain Monte Carlo method) was 39.7% and 49.9% for iron isomaltoside 1000 and iron sucrose, respectively. The NMA also found that the AE rates were 17.0% and 15.3% for iron isomaltose 1000 and iron sucrose, respectively.

No evidence for comparing iron isomaltoside 1000 with ferric gluconate was reported in this NMA.[18]

Critical Appraisal

A regular full scale of summary and critical appraisal of the NMA is not provided in this CADTH report for two reasons. First, the NMA[18] was outdated (i.e., neither of the pivotal studies or two other studies included for this CADTH review were selected in the NMA). Second, the primary outcome (therapy response rate, defined as Hb normalization or

increase ≥ 2 g/dL) was not aligned with the key outcomes listed in the protocol of this CADTH review.

Other Relevant Evidence

Description of Studies

One potentially relevant extension study (P-Monofer-IDA/CKD-EXT-01 [FerWoNExt, NCT02962648]) was mentioned in the sponsor's submission. However, no detailed information was provided upon request by CADTH.[21]

Conclusions

Four phase III, multi-centre, open-label, parallel group, active-controlled, noninferiority RCTs comparing iron isomaltoside 1000 to iron sucrose were identified and included in this systematic review (PROPOSE, FERWON-NEPHRO, PROVIDE, and FERWON-IDA).

In all trials, noninferiority (assessed using different Hb measures from baseline to end of study time points) was demonstrated for maintenance and treatment with iron isomaltoside 1000 compared with iron sucrose. Overall, it also appeared iron isomaltoside 1000 was better than iron sucrose at producing a faster and greater rise in Hb.[9-17] However, considerable threats to internal validity were identified, and lowered the overall confidence in the findings. For example, three trials lacked data imputation methods to compensate for missing data,[11,14,16] three trials lacked sensitivity analyses to test the robustness of the noninferiority results,[11,14,16] one trial had a potential source of bias due to withdrawals,[9] and all trials had a risk of type I error due to multiple testing.[9,11,14,16] Lastly, there was concern about whether the findings were generalizable to the study populations due to a significant proportion of screened participants being excluded from the trials.[11,16]

The HRQoL outcomes of energy, fatigue, and overall QoL were identified as important to participants and found not to be different for either treatment group across three of the included trials. One trial found a statistically significant difference fatigue, favouring iron isomaltoside 1000 at week 1; however, the effect was not sustained. [9,11,14,16]

Overall, the safety profiles of iron isomaltoside 1000 and iron sucrose were similar for three of the four included trials; however, iron isomaltoside 1000 participants in the PROPOSE trial had a slightly higher frequency of TEAEs, SAEs, and withdrawals due to adverse events (WDAEs) compared with iron sucrose. The review did not identify any new safety concerns and the overall incidence of serious or severe hypersensitivity reactions was low for both iron isomaltoside 1000 and iron sucrose.[9,11,14,16]

Introduction

Disease Background

IDA is the most prevalent and treatable form of anemia worldwide.[1,4] WHO estimates that approximately 50% of global anemia cases are the result of iron deficiency (ID).[2] In 2010, the global anemia prevalence was 32.9%, indicating that more than 2.2 billion people worldwide were affected by anemia.[1] WHO reported that between 1993 and 2005, anemia in the general population was approximately 24.8%. Men were the least affected with a prevalence of 12.7% and children up to five years of age were the most affected with a prevalence of 47.4%. Women and the elderly were also significantly affected. Anemia prevalence in non-pregnant women was 30.2% and in pregnant women was 41.8%. The elderly (over 60 years of age) had an anemia prevalence of 23.9%.[22]

In comparison to other countries, the US and Canada are associated with the lowest anemia burden (2.9% envelope), as per McLean (2009). Data from the Canadian Health Measures Survey (2009 to 2011) estimated the overall prevalence of anemia to be approximately 3%, as 97% of Canadians were found to have sufficient Hb levels. Hb sufficiency was significantly greater for men than women. Depleted iron stores, defined as insufficient s-ferritin, were found in 13% of women aged 12 years to 19 years and 9% of women aged 20 years to 49 years. In contrast, almost 100% of males between 12 years and 49 years of age had sufficient s-ferritin levels.[23]

ID is characterized by a decrease in the total iron body content, and IDA manifests when ID is severe enough to reduce erythropoiesis.[24] As there is no natural pathway for the body to excrete iron, blood loss is the primary mechanism for developing ID and is most often the result of either menstruation or gastrointestinal bleeding. Underlying disorders resulting in poor iron absorption (i.e., celiac disease, autoimmune gastritis, Helicobacter pylori, and bariatric surgery) and low dietary intake of iron are also common reasons for developing ID, particularly in non-resource rich countries.[4,5] Patients with chronic underlying diseases such as CKD, IBD, malignancies, and rheumatoid arthritis are also at increased risk of IDA due to anemia associated with chronic disease.[2]

Anemia, in general, is characterized by a decrease in the quantity of red blood cells and reduced Hb levels with concomitant impaired capacity to transport oxygen and/or altered red blood cell morphology.[1,22] Its etiology varies significantly by geography, age, sex, pregnancy, altitude, and smoking habits.[1,2] WHO has defined anemia as an Hb level of less than 13 g/dL in men over 15 years of age, less than 12 g/dL in non-pregnant women over 15 years of age, and less than 11 g/dL in pregnant women.[3] The diagnosis of ID is comparatively more complex,[2] owing to the variety of iron status indicators that may be used to determine iron sufficiency. A systematic review found that guidelines on the diagnosis and treatment of ID vary worldwide and across indications.[25] However, all published guidelines included in the systematic review recommended using the measurement of s-ferritin concentrations to define ID.[25] In the absence of inflammation, s-ferritin is the most specific test that correlates with total body iron stores[2] and is the most efficient and cost-effective test for the diagnosis of ID.[4]

The thresholds used to define ID differ across published guidelines and the patient population. For the majority of published guidelines concerned with defining ID in the general population, s-ferritin cut-off values fall between 12 mcg/L and 50 mcg/L. S-ferritin levels greater than 100 mcg/L are primarily recommended in CKD populations. For patients

with IBD, the threshold for s-ferritin ranged from 25 mcg/L to 100 mcg/L. The 800 mcg/L threshold for s-ferritin was recommended for chemotherapy-induced anemia (two guidelines) and CKD (with or without hemodialysis). In summary, the systematic review of published guidelines showed s-ferritin thresholds for ID ranged from 12 mcg/L to 200 mcg/L for absolute ID and from 100 mcg/L to 800 mcg/L for functional ID. Overall, the systematic review recommended that an s-ferritin threshold less than 100 mcg/L may be used to define ID in most clinical scenarios.[25]

The clinical presentation of IDA varies, as the associated symptoms depend on the speed of anemia onset, its severity, and characteristics of the patient, such as age and presence of comorbidities.[2,24] Patients with IDA or ID may be diagnosed with screening, alone or in combination with symptoms.[24] Symptoms of ID may be related to both depletion of iron and the resultant anemia.[4] The most frequently reported symptoms of IDA included paleness (45% to 50%), fatigue (44%), dyspnea, and headache (63%).[2] In more severe cases of IDA, patients may report dyspnea at rest, angina pectoris, and hemodynamic instability. Symptoms such as fatigue, dyspnea, vertigo, syncope, headache, and tachycardia are the result of hypoxemia. Other commonly reported symptoms include diffuse and moderate alopecia, atrophic glossitis, RLS, dry and rough skin, dry and damaged hair, cardiac murmur, neurocognitive dysfunction.[2] IDA has a large negative effect on a patient's QoL and work productivity, owing largely to the profound symptom of fatigue, which is present with even moderately low iron stores.[2,4,24,25] A strong correlation between iron status and depression and cognitive functioning has been found, and ID is a strong predictor of mortality in congestive heart failure and CKD.[25]

Standards of Therapy

The first step in management of IDA is to determine the underlying cause and to prevent further iron loss. Therapy with iron supplementation is then used to correct the anemia by restoring Hb levels and red cell indices to normal and to replenish body iron stores.[3] The correction of anemia and replenishing of iron stores leads to improved symptoms and QoL, and the prognosis of several chronic conditions.[2]

Treatment guidelines consistently recommend oral iron supplementation as the first line of therapy for ID.[25] A variety of oral iron products are available and no one product is better than another.[2,4] A response, as measured by reticulocyte count, may improve as early as four days after oral treatment is initiated, up to a maximum of seven to 10 days.[2] Hb increases should be seen by the second week of oral therapy. Oral iron supplementation should be given for approximately three months to replenish iron stores.[2,3] The advantages of oral iron supplements include their availability, low cost, and safety.[25]

IV iron supplementation is typically reserved and recommended as the alternative route when blood loss exceeds the absorptive capacity of iron, when oral is ineffective, or when a patient is unable to tolerate or absorb the iron orally. CKD and IBD patients frequently fall into this category and patients often require IV iron supplementation.[25] In patients who are unresponsive to oral therapy, it is also important to reconfirm the diagnosis of IDA and to assess compliance with oral iron supplementation.[2] Additional advantages of IV therapy include good tolerability with respect to gastrointestinal symptoms, improved adherence, and the ability to administer larger amount of iron faster. Disadvantages of IV iron include the risk of anaphylactic reactions.[25]

Target values for Hb following iron supplementation ranged between 10 g/dL to 12 g/dL in eight published guidelines and two guidelines recommended an increase of 1 g/dL to 2 g/dL

in Hb levels monthly as a therapeutic target (nephrology and pediatric populations). For ferritin, 11 guidelines recommended a target greater than 100 mcg/L (CKD, heart disease, chemotherapy, and pregnancy guidelines).[25]

Drug

Iron isomaltoside 1000 for injection (Monoferric) is an IV iron product that has been available in Canada since October 2018 and is indicated for treatment of IDA in adult patients (≥ 18 years of age) with an intolerance or unresponsiveness to oral iron.[6] The diagnosis of IDA must be based on laboratory tests.[6]

The iron isomaltoside 1000 particle consists of iron and a carbohydrate moiety in which iron is tightly bound within a matrix structure, consisting of iron (III) atoms and isomaltoside pentamers.[6-8] This stable structure permits a gradual release of iron to available iron-binding proteins to primarily form ferritin, the storage form of iron, or to a lesser extent, the transport molecule transferrin. The released iron replenishes Hb and iron stores, both of which are significantly diminished with IDA.[6]

Within a few days of the administration of iron isomaltoside 1000, an increase in the reticulocyte count can be seen and is indicative of a therapeutic response. S-ferritin was found to peak between seven and nine days after administration and gradually return to baseline after approximately three weeks.[6]

The iron need and IV administration schedule is individually established prior to initiation of therapy with iron isomaltoside 1000. The goal of iron therapy in patients with IDA is to replenish Hb and iron stores. A patient's cumulative iron need may be calculated using the Ganzoni formula or a simplified table.[6]

Iron isomaltoside 1000 may be administered as an IV bolus injection or an IV drip infusion, or as an injection into a dialyzer:[6]

- IV bolus injections of iron isomaltoside 1000 may be administered up to 500 mg up to once a week at a rate of up to 250 mg iron/minutes. The drug may be administered undiluted or diluted in a maximum of 20 mL sterile 0.9% sodium chloride.
- IV drip infusions may be administered as a single iron isomaltoside 1000 dose up to 20 mg iron/kg body weight or as weekly infusions until the cumulative iron dose is reached. Cumulative iron doses greater than 20 mg iron/kg body weight must be divided into two administrations spaced apart by at least one week. Doses up to 1,000 mg must be administered over 20 minutes or more. Doses greater than 1,000 mg must be administered over 30 minutes or more. Single doses exceeding 1,500 mg are not recommended. Iron isomaltoside 1000 must only be diluted in sterile 0.9% sodium chloride solution (minimum diluted concentration of 1 mg iron/mL, not including the volume of the drug solution, and may be added to a maximum of 500 mL sterile 0.9% sodium chloride).
- Iron isomaltoside 1000 may be directly injected into the venous limb of a dialyzer following the same procedures of an IV bolus injection.

The sponsor is requesting iron isomaltoside 1000 be recommended for reimbursement for the treatment of IDA in adult patients who have intolerance or unresponsiveness to oral iron therapy. The diagnosis of IDA must be based on laboratory tests.[26]

Table 2: Key Characteristics of Iron Isomaltoside 1000, Iron Sucrose, and Sodium Ferric Gluconate Complex in Sucrose

	Iron isomaltoside 1000 (Monoferric)	Iron sucrose (Venofer)	Sodium ferric gluconate complex in sucrose (Ferrlecit)
Mechanism of action	• An iron isomaltoside particle consists of iron and a carbohydrate moiety where iron is tightly bound in a matrix structure (iron [III] atoms and isomaltoside pentamers). • The particle is metabolized by the RES in the liver and spleen and is divided into iron and isomaltoside. • The released iron is bound and stored as ferritin and, to a lesser extent, to transferrin. This iron replenishes hemoglobin and depleted iron stores.	• Iron sucrose is dissociated by the RES into iron and sucrose. • The released iron replenishes body iron stores.	• Sodium ferric gluconate replenishes and maintains total body iron stores. • Approximately 80% of the drug bound iron was delivered to transferrin within 24 hours of administration.
Indication[a]	For treatment of IDA in adult patients (≥ 18 years of age) with an intolerance or unresponsiveness to oral iron. The diagnosis of IDA must be based on laboratory tests.	For treatment of IDA in NDD-CKD patients with or without erythropoietin, HDD-CKD patients with erythropoietin, and PPD-CKD patients with erythropoietin.	For treatment of IDA in chronic HDD-CKD patients who are receiving erythropoietin.
Route of administration	IV	IV	IV
Recommended dosage	• Individual cumulative iron need is determined by the Ganzoni formula or a simplified table. • IV bolus injection: Doses up to 500 mg up to once weekly at a rate of 250 mg iron/minute. • IV infusion: 20 mg iron/kg body weight may be given as a single infusion or as weekly infusions until cumulative iron dose is reached. Cumulative iron doses > 20 mg iron/kg body weight must be divided into 2 administrations spaced apart by a minimum interval of 1 week. Doses up to 1,000 mg must be administered over 20 minutes or more. Doses > 1,000 mg must be administered over 30 minutes of more. Single doses > 1,500 mg are not recommended.	• CKD patients need a minimum cumulative dose of 1,000 mg elemental iron. • NDD-CKD: 1,000 mg total cumulative dose given as a 200 mg slow IV injection over 2 to 5 minutes over 5 sessions within 14 days. • HDD-CKD: 1,000 mg total cumulative dose given undiluted as a 100 mg slow IV injection over 2 to 5 minutes or as an infusion of 100 mg over 15 minutes per hemodialysis session. • PDD-CKD: 1,000 mg total cumulative dose is divided over 3 infusion sessions, each separated by 14 days, over a period of 28 days — the first 2 infusions of 300 mg are administered over 1.5 hours followed by a 400 mg infusion over 2.5 hours.	• HDD-CKD patients will need a minimum cumulative dose of 1,000 mg elemental iron given over 8 sessions during dialysis. • IV infusion: 125 mg (10 mL) diluted in 100 mg of 0.9% normal saline over 1 hour. • IV injection: Undiluted at a rate of up to 12.5 mg/minute • Each vial of sodium ferric gluconate complex in sucrose contains 62.5 mg of elemental iron (12.5 mg/mL).
Serious adverse effects or safety issues	**Serious warnings** • Serious hypersensitivity reactions, including life-threatening and fatal anaphylactic and anaphylactoid reactions, have been reported. • Serious hypotension cases have been reported. **Precautions**	**Serious warnings** • Serious hypersensitivity reactions, including life-threatening and fatal anaphylactic and anaphylactoid reactions, have been reported. **Precautions**	**Serious warnings** • Serious hypersensitivity reactions, including life-threatening and fatal anaphylaxis and anaphylactoid reactions, have been reported. **Precautions** • Only administer when personnel and resuscitative interventions are

	Iron isomaltoside 1000 (Monoferric)	Iron sucrose (Venofer)	Sodium ferric gluconate complex in sucrose (Ferrlecit)
	• Should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. • Patients should be carefully monitored for signs and symptoms of hypersensitivity reactions, including blood pressure and pulse, for a minimum of 30 minutes after administration. • Geriatrics (> 65 years of age): Compared with younger adults, a higher percentage of patients experience SAEs and AEs leading to fatal outcome. • Pregnant women and pediatric patients (< 18 years of age) should not use iron isomaltoside 1000. **Contraindications** • Patients who are hypersensitive to the drug or excipients • Patients with known serious hypersensitivity to other parenteral iron products • Patients with history of multiple allergies • Patients with non-IDA (i.e., hemolytic anemia) • Patients with iron overload or disturbances in utilization of iron (i.e., hemochromatosis) • Patients with decompensated liver cirrhosis or active hepatitis	• Should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. • Geriatrics (> 65 years of age): Use caution when selecting doses, including initiating therapy at the low end of the dosing range. • Pregnancy: Should only be used during pregnancy if the potential benefits outweigh the risks. • Pediatrics: Safety and efficacy in pediatrics has not been established. **Contraindications** • Patients with iron overload • Patients with known hypersensitivity to iron sucrose • Patients with anemia not caused by ID	immediately available for the treatment of serious hypersensitivity reactions. • Seizures: Drug should be discontinued in patients who experience seizures suspected to be related to treatment. • Geriatrics (> 65 years of age): Use caution when selecting dose; usually start at the low end of the dosing range. • Pregnancy: Only give when the potential benefits outweigh the risks. • Pediatrics: Safety and efficacy has not been established. **Contraindications** • All anemias not associated with ID and where there is evidence of iron overload • Patients with known or suspected hypersensitivity to any of the drug's components • Preterm or term newborn infants because the drug contains benzyl alcohol
Other	• Risk of hypophosphatemia (< 2 mg/dL) in 5% to 20% of patients • Risk of serious hypotensive events if IV injection is administered too rapidly • Most common TEAEs: Headache, nasopharyngitis, nausea, vomiting, and constipation	• Risk of clinically significant hypotension (possibly related to rate of administration) • Most common TEAEs: Dysgeusia, hypotension, nausea, and dizziness	• Risk of generalized seizure • Risk of hypotension • Most common AEs: Cardiovascular system AEs (hypotension, hypertension, and vasodilation) and digestive system AEs (diarrhea and nausea)

AE = adverse event; CKD = chronic kidney disease; HDD-CKD = hemodialysis-dependent chronic kidney disease; ID = iron deficiency; IDA = iron deficiency anemia; NDD-CKD = non–dialysis-dependent chronic kidney disease; PDD-CKD = peritoneal dialysis-dependent chronic kidney disease; RES = reticuloendothelial system; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Health Canada–approved indication.

Source: Product monographs: Monoferric,[6] Venofer,[27] and Ferrlecit.[28]

Stakeholder Engagement

Patient Group Input

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

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

Two patient groups — CCC and KFOC — provided input for this review.

CCC is a national, volunteer-based charity focused on finding the cures for Crohn disease and ulcerative colitis (also called IBD) and improving the lives of children and adults affected by IBD. CCC helps to improve the quality of lives by sharing accurate and reliable information on treatments, research, and issues related to life with Crohn disease and colitis through such means as its website, print materials, webinars, and live events. CCC comprises approximately 65,000 supporters, including volunteers, donors, or individuals interested in engaging with the organization across the country.

KFOC is the national volunteer organization committed to eliminating the burden of kidney disease through funding and stimulating innovative research for better treatments and a cure, providing education and support to prevent kidney disease in those at risk and to empower those with kidney disease to optimize their health status, advocating for improved access to high-quality health care, and increasing public awareness and commitment to advancing kidney health and organ donation.

CCC did not receive any direct help in writing this submission. However, a medical science liaison officer from Pfizer (Monoferric's distributor) did provide a briefing to explain the mechanism of action, the reasons why patients with IBD may have ID, how the product is different from oral iron tablets and other iron infusion treatments, and details covered in Monoferric's product monograph. CCC also solicited the help of Canadian gastroenterologists who had prescribed Monoferric to patients with IBD to ask for anonymous patient testimonials regarding their experience with the treatment.

KFOC had no outside assistance to complete this submission. There was no external assistance with data collection or analysis used for this submission.

CCC declared having received funding from multiple companies in amounts ranging from $5,001.00 to more than $50,000.00 over the past two years. KFOC received funding from multiple companies in amounts ranging from $5,000.00 or less to more than $50,000.00 over the past two years.

2. Condition-Related Information

CCC gathered Monoferric patient testimonial data (through gastroenterologists) in Canada from June to July of 2019.

At KFOC, patient information was collected in June 2019. A self-administered questionnaire to people across Canada was open for two weeks and available in both English and French. The survey was directed toward patients with CKD and their caregivers and inquired about respondents' lived experience with CKD and medications, and expectations for new drug therapies in Canada. The survey posed a few questions specifically about Monoferric (iron [III] isomaltoside 1000). At KFOC, a total of 47 people responded to the survey. Of those who answered the question (n = 28), 24 respondents (85.7%) were identified as patients with CKD and four respondents (14.3%) were caregivers for patients

with CKD. Of the 15 people who responded to questions about age and time since diagnosis, their ages ranged from 25 to 70 years old. The duration of diagnosis with CKD ranged from three years to more than 20 years.

The patient input from CCC indicated that IBD is a disabling, life-long gastrointestinal condition that primarily affects working-age Canadians. IBD symptoms include bloody diarrhea, bloating, abdominal pain, and fatigue. Most patients experience isolation, anxiety, and debilitating frequent and urgent bowel movements. Patients with IBD could have bowel movements up to 20 times or more a day. Patients with IBD, particularly during a flare-up, can experience frequent and constant bloody diarrhea and malabsorption of nutrients, vitamins, and minerals due to intestinal malfunction. Blood loss due to gastrointestinal bleeding and malabsorption of iron from nutritional sources can cause anemia. Therefore, ID or IDA is quite common in patients with IBD. Patients with IBD are often prescribed oral iron supplements or, in serious cases, iron IV infusion. As the common symptoms of ID (weakness, fatigue, shortness of breath, and poor concentration) compound with other common IBD symptoms, a patient's QoL can be highly compromised. CKD input indicated that most people with moderate-to-severe kidney disease (stage 4 to stage 5) develop anemia. As anemia becomes more severe, it may lead to low energy, tiredness, shortness of breath, and, sometimes, increased sensitivity to cold, negatively impacting QoL for patients with CKD. Examples of quotes about their conditions (IBD and CKD) are listed as follows:

"When the disease takes control of your body, you feel very tired…".

"Very tired at times, but can't sleep well either, itchy skin, tiredness…" and "energy level low…".

"Symptoms have blended into each other; the anemia compounds the issues that are presenting from end stage renal disease. I am taking iron and injections to attempt to compensate for the deficiencies but still encounter the symptoms to varying degrees…".

"Basically, no social life...either no energy or social life like I had before…".

3. Current Therapy-Related Information

When considering iron supplement treatments, particularly in the context of IBD patients and the chronic and debilitating nature of their disease, evaluating their impact on helping a patient resume a normal QoL is paramount. QoL could be greatly improved in iron-deficient IBD patients if their iron levels were stabilized. The expediency of reducing symptoms is particularly important for patients who face significant consequences from missing school or work. Iron infusions add high value to the lives of patients who require immediate ID symptom relief. Monoferric's rapid impact compared to other spaced-out iron infusion treatments or oral tablets would be highly preferable for this cohort of patient. It was described that patients, families, and caregivers, when choosing iron supplementation therapies, face trade-offs between slower response (oral tablets) but with the convenience of taking the treatment at home compared to iron infusions in a clinical setting, which require an appointment and potentially missing school or work. This trade-off may be preferable to patients who prioritize immediate results over the inconvenience of travelling to a clinic for an infusion.

At KFOC, the majority of respondents (73%) have taken a medication for anemia. The medications that had been taken or are currently being taken at the time of survey completion included vitamin or mineral supplements such as B12, folic acid, and

multivitamins formulated for kidney disease (70%), iron tablets (44%), IV iron (65%), intramuscular iron (9%), erythropoietin (70%), blood transfusions (26%), and other (4.3%). Twenty-five respondents answered how satisfied they were with the medication or combination of medications currently being taken for anemia; 13 were “very satisfied” (n = 2) or “satisfied” (n = 11), four were neither satisfied nor satisfied and two responded that they were “very unsatisfied.” Five indicated that the question was not applicable to them as they were not currently taking medication(s) for anemia. The following are some direct quotes that describe what patients like and dislike about their current therapy:

“It takes such a long time to get my hemoglobin up.”

“Iron supplements make me feel very sick/nauseated.”

“Not sure I notice much of a difference in symptoms, as I have gone on and off the pills a few times and I don’t feel any different.”

“The costs are astronomical. I don’t know how patients without a job make ends meet.”

4. Experience and Expectations About the Drug Being Reviewed

Two patients with IBD who had received Monoferric infusions provided testimonials. KFOC was unable to respond to this question. Examples of direct quotes from two patients from CCC are as follows:

“I found the Monoferric amazing - my body responded to the treatment very well, could not believe how quickly my energy levels returned and held with only one infusion.”

“I liked that it was a one-time treatment instead of the previous every 6 to 8 weeks infusion.”

“Benefit is that it is quick and easy, and the effects were noticed within a few days.”

“It is expensive for anyone who does not have coverage. There are not that many clinics that provide it, and if they do it is during work hours, therefore I had to miss work for it.”

“It has allowed me to get back to my daily activity much quicker than in the past and I don't have to worry about going back every 3 weeks to be infused.”

“No side effects, I have not experienced any side effects with any treatment.”

“Yes, I seemed to have some sort of reaction to it when the infusion first started. My body began to feel like it was burning, my face and ears turned red and I had heart palpitations. The nurse quickly stopped the treatment, gave me benadryl and started the infusion again at a lower speed.”

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, and interpreting the clinical relevance of the results and providing guidance on their potential place in therapy). The following input was provided by one clinical specialist with expertise in the diagnosis and management of adults with IDA (≥ 18 years of age) who have an intolerance or unresponsiveness to oral iron.

Description of the Current Treatment Paradigm for the Disease

IDA is a common clinical problem due typically to chronic blood loss (i.e., menses, gastrointestinal bleeding from hemorrhoids or polyps, or tumours). Treatment of IDA focuses on replenishing iron as well as addressing the underlying cause of blood loss. Symptoms of IDA include fatigue, decreased exercise tolerance, decreased mental concentration, and shortness of breath, particularly upon exertion.

Iron supplementation, with either oral or IV products, is used to treat IDA by correcting anemia and replenishing iron stores. Oral iron therapies are easier to administer and less expensive compared with IV products. However, the time required to correct anemia and to replete iron stores is longer with oral therapy. As well, oral iron is associated with gastrointestinal side effects. There are a variety of oral iron supplements available in Canada, with variable side effect profiles. Not all oral iron supplements are covered by private drug insurance. IV iron is reserved for patients who have a poor response or do not tolerate oral iron therapy. IV iron may also be used when rapid iron repletion and correction of anemia is desired (i.e., patients with severe anemia or preoperative patients). However, iron sucrose, the commonly used IV iron product, requires two hours per infusion (300 mg/dose) and thus imposes practical limitations associated with the availability of chair time in infusion clinics.

Clinical symptoms associated with ID (i.e., fatigue and mental fogginess) will improve rapidly with any iron supplementation (either oral or IV therapy) even before any improvement in anemia is observed, but symptoms due to assaociated anemia will take longer to resolve with oral therapy (i.e., decreased exercise tolerance and shortness of breath upon exertion). Patients without anemia but with ID may still experience symptoms of fatigue; these will improve with either oral or IV therapy. It is important to note that decreased exercise tolerance and shortness of breath upon exertion are also related to ID; it is not possible to completely dissociate the ID from the anemia.

Treatment Goals

The goal of iron supplementation is to correct anemia and replenish iron stores. This will improve clinical symptoms associated with IDA and a patient's QoL.

Unmet Needs

Iron sucrose is currently used by most practitioners when IV iron is indicated within a dosing range of 100 mg to 300 mg per treatment session. A minimum of two hours is required to administer a 300 mg dose of iron sucrose. An IV iron formulation that delivers a higher iron dose over a shorter infusion time would improve delivery convenience and use of resources (i.e., decreased chair time in a medical day unit and lower frequency of dosing). Furthermore, the ability to deliver a larger amount of iron in a single dose would benefit patients with significant ongoing blood loss (i.e., severe menorrhagia) that are difficult to offset with iron sucrose due to practical limitations on frequency of dosing and administration.

Place in Therapy

Iron isomaltoside 1000 would likely replace iron sucrose as the IV iron formulation of choice as it provides approximately three times the amount of iron in a single infusion (1,000 mg versus 300 mg iron for iron isomaltoside 1000 compared with iron sucrose, respectively) in

a fraction of the time (30-minute infusion versus three individual two-hour infusions for iron isomaltoside 1000 and iron sucrose, respectively) compared with iron sucrose.

Iron isomaltoside 1000 would be used for the same clinical indications as iron sucrose (i.e., treatment of IDA in patients who cannot tolerate or do not well respond to oral iron supplements). The same recommendations that apply to iron sucrose would apply to iron isomaltoside 1000. As well, iron isomaltoside 1000 may sometimes be used when faster iron repletion and anemia correction is desired (i.e., for patients with very severe anemia or preoperatively). Iron sucrose is also used clinically in this clinical setting; however, iron isomaltoside 1000 would provide larger doses of iron more rapidly and this would be more advantageous when time is at a premium.

Patient Population

All patients with uncomplicated IDA are expected to respond well to IV iron therapy and benefit more from iron isomaltoside 1000 than from iron sucrose, due to the reduced infusion time and number of treatment visits required for the administration of iron isomaltoside 1000. In addition, patients with significant blood loss and high iron requirements will benefit more from iron isomaltoside 1000 than they would from iron sucrose due to the practical limitations associated with iron sucrose infusions (i.e., lower dose per infusion). In some cases, patients with IDA may have comorbidities that will blunt the response to IV iron treatment (i.e., chronic inflammatory conditions and malignancy). However, generally even such patients may be given a trial of IV iron to assess response if clinically indicated, as response cannot be predicted.

Patients with IDA are easily diagnosed with complete blood counts and s-ferritin. Further, patients with IDA being considered for IV therapy will have been given a trial of oral iron supplementation and either not tolerated it or had a poor response.

Assessing Response to Treatment

Hb and s-ferritin are the two key laboratory parameters used to assess whether a patient is responding to IV iron therapy. A good response would entail a rise in Hb level and once Hb is normalized, a rise in ferritin level reflecting improved iron stores. Both Hb and s-ferritin should be regularly monitored. Outside of a clinical trial setting, four weeks to six weeks is a reasonable time frame for monitoring key laboratory parameters such as Hb and ferritin. Compared with iron sucrose, clinicians may check key monitoring parameters after each dose owing to the larger amount of iron dose given in a single session. For patients on maintenance IV therapy (i.e., Crohn disease), assessing key laboratory parameters every three weeks is reasonable in a clinical practice. Patients with IDA may require more than one dose of IV iron to correct Hb, depending on a patient's initial Hb and whether there is ongoing blood loss.

Clinically meaningful responses to IV iron include improvement of Hb and improvement in IDA symptoms. Each 1,000 mg dose of iron isomaltoside 1000 should give a rise in Hb of approximately 3 g/dL. The response in Hb will vary between patients and assumes there is no ongoing blood loss. Further, normalization may not be possible in all patients, depending on comorbidities and ongoing bleeding.

Discontinuing Treatment

Overall, IV iron therapy should lead to normalization of Hb and restoration of iron stores (s-ferritin). Some patients with ongoing blood loss and/or who are unable to tolerate oral iron supplementation may need maintenance treatment with IV iron in order to prevent IDA disease (i.e., hemodialysis for CKD and IBD patients).

In the absence of concurrent inflammatory conditions or bleeding, the Hb response is usually fairly predictable. Hb response may vary due to inflammation. This may blunt the utilization of iron supplements and degree of ongoing bleeding, which will offset new red blood cell production by the bone marrow.

Prescribing Conditions

In practice, IV iron for treatment of IDA is usually given by a specialist (an internist or hematologist), as community family doctors do not have access to hospital infusion clinics. However, any physician or nurse practitioner can diagnose, treat, and monitor patients with uncomplicated IDA.

The most common patient population for iron isomaltoside 1000 will be outpatients. Iron isomaltoside 1000 can be administered in an infusion clinic or a hospital day unit. Occasionally, patients with severe IDA may be seen in emergency departments. As well, preoperative patients may be considered for iron isomaltoside 1000 if rapid correction of anemia is desired.

Clinical Evidence

The clinical evidence included in the review of iron isomaltoside 1000 is presented in three sections. Section 1, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. Section 3 includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of iron isomaltoside 1000 injection (100 mg elemental iron/mL) for the treatment of IDA in adults (≥ 18 years of age) who have an intolerance or unresponsiveness to oral iron.

Methods

Studies selected for inclusion in the systematic review will include pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient population	**Specify population(s)** Adults (≥ 18 years of age) with IDA who have an intolerance or unresponsiveness to oral iron; the diagnosis must be based on laboratory tests **Subgroups** • Comorbidities (i.e., inflammatory bowel disease, malignancy, and chronic kidney disease) • Severity of IDA (mild, moderate, severe) • Body weight
Intervention	Iron isomaltoside 1000 up to 500 mg administered by IV bolus injection or up to 1,500 mg administered by a single IV infusion or as weekly infusions until the cumulative iron dose per participant has been administered
Comparators	**IV iron preparations available in Canada** • Iron sucrose injection • Sodium ferric gluconate complex in sucrose injection

Outcomes	**Efficacy outcomes**
	• Hb:
	  ○ Proportion of participants with normal Hb level at study completion
	  ○ Proportion of participants with an increase in Hb of ≥ 2 g/dL compared with baseline Hb value
	  ○ Change in Hb level from baseline to study completion
	  ○ Hb level at study completion, and/or
	  ○ Time to increase Hb ≥ 2 g/dL
	• Iron parameters (change in and/or value at end of study):
	  ○ Serum ferritin
	  ○ Serum transferrin saturation
	  ○ Total iron-binding capacity, and/or
	  ○ Serum iron
	• Red blood cell indices
	• Blood transfusions given during study

	• Anemia symptoms (i.e., weakness, fatigue, shortness of breath, and poor concentration)[a] • Quality of life[a] **Harms outcomes** AEs, serious adverse events, withdrawal due to AEs, mortality, and notable harms/harms of special interest (i.e., hypersensitivity, allergic, anaphylactic, and anaphylactoid AEs)
Study design	Published and unpublished phase III and phase IV randomized controlled trials.

AE = adverse event; Hb = hemoglobin; IDA = iron deficiency anemia.

[a] These outcomes were identified as being of importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the checklist for the Peer Review of Electronic Search Strategies.[29]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Monoferric (iron isomaltoside). Clinical trial registries searched were the US National Institutes of Health's ClinicalTrials.gov and WHO's International Clinical Trials Registry Platform search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on July 25, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on November 20, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist:[30] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and Table 5. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

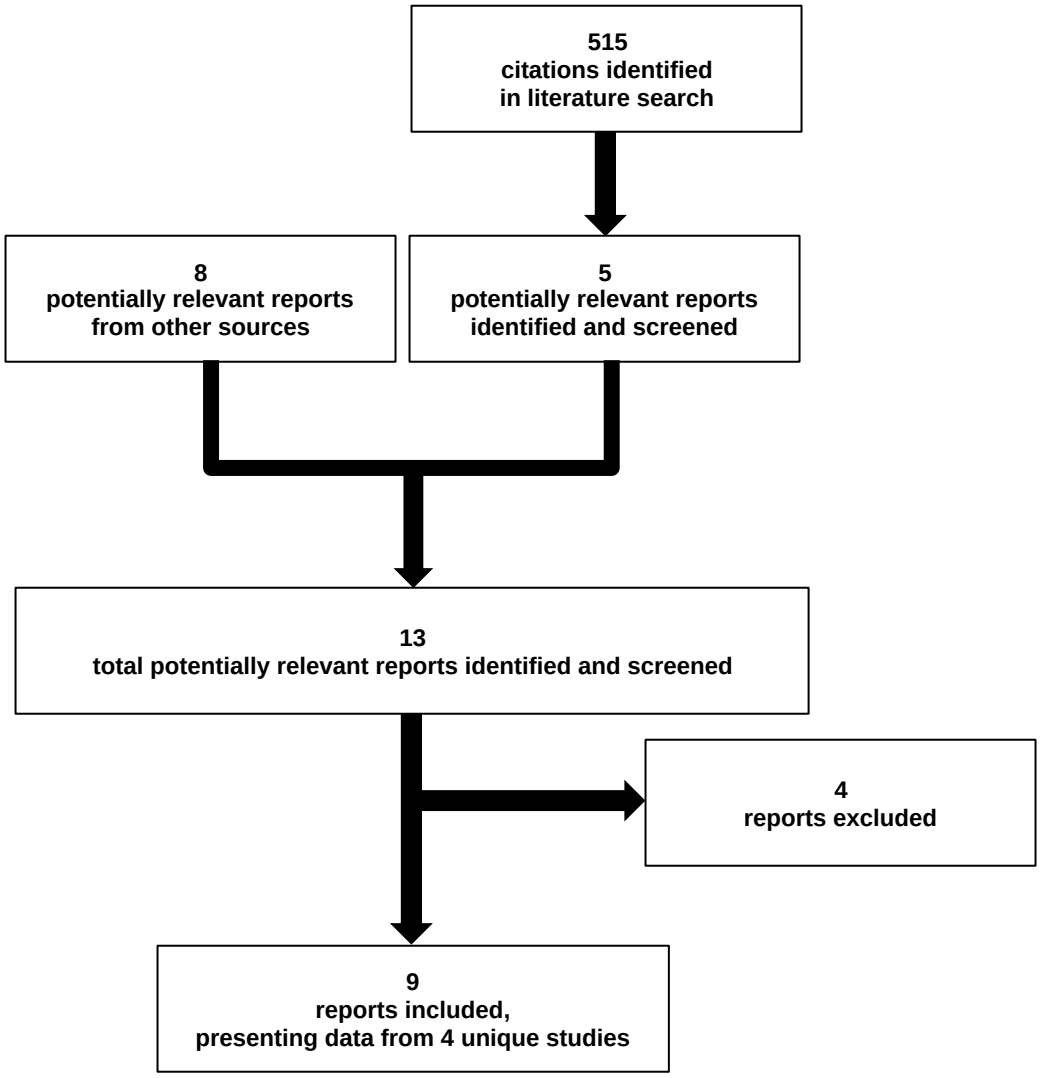

Table 4: Details of Included Studies: CKD Study Populations

		PROPOSE	FERWON-NEPHRO
DESIGNS AND POPULATIONS	**Study design**	OL, parallel group, active-controlled, NI RCT	OL, parallel group, active-controlled, NI RCT
	Locations	48 enrolling centres of 50 initiated centres in India, the UK, Russia, Poland, Sweden, Switzerland, Romania, Denmark, and the US	US
	Randomized (N)	351	1,538

	Inclusion criteria	• Women and men aged ≥ 18 years
		• CKD-5D and in hemodialysis therapy for at least 90 days
		• Hb concentrations between 9.5 g/dL and 12.5 g/dL (both values included)
		• S-ferritin < 800 ng/mL
		• TSAT < 35%
		• Receiving ESA with stable dose for previous 4 weeks prior to screening (only 1 missed dose allowed)
		• Receiving no IV iron or an average of no more than 100 mg/week for the previous 4 weeks
			• Women or men ≥ 18 years of age
			• Hb ≤ 11 g/dL
			• Chronic renal impairment, defined as either:
			  ○ eGFR < 60 mL/minute/1.73m^2 at screening or
			  ○ eGFR < 90 mL /minute/1.73m^2 at screening and kidney damage as indicated by abnormalities in urine composition per medical history and/or intermediate or high risk of cardiovascular disease based on the Framingham model
			• Screening s-ferritin ≤ 100 ng/mL or ≤ 300 ng/mL if TSAT ≤ 30%
			• Either no ESAs or ESAs as a stable dose 4 weeks before randomization

	Exclusion criteria	• Anemia caused primarily by factors other than renal-related anemia • Iron overload or disturbances in utilization of iron • Subjects concurrently undergoing treatment with immunosuppressives (≤ 10 mg prednisolone/day was permitted) • Difference of Hb ≥ 1.0 g/dL between screening visits 1a and 1b • History of multiple allergies • Decompensated liver cirrhosis or active hepatitis (ALT 3 times normal) or history of hepatitis B or hepatitis C • Active or chronic infections • Rheumatoid arthritis with symptoms or signs of active joint inflammation • Pregnant or nursing • Blood transfusions within the previous 12 weeks • Planned elective surgery in the next 8 weeks • Untreated vitamin B12 or folate deficiency	• Anemia primarily caused by factors other than IDA • Hemochromatosis or other iron storage disorders • Previous serious hypersensitivity reactions to IV iron compounds • Prior to screening or during the trial period, has or will be treated with red blood cell transfusion, radiotherapy, and/or chemotherapy • Undergoing dialysis for treatment of CKD • Planned surgical procedure within the trial period • Decompensated liver cirrhosis or active hepatitis • Alcohol or drug abuse within past 6 months • Pregnant or nursing

DRUGS	**Intervention**	**IIM**
		• Subgroup A1: IIM 500 mg IV bolus injection
		  ○ IIM was administered during dialysis undiluted as a single IV bolus of 500 mg over approximately 2 minutes at baseline.
		• Subgroup A2: IIM 500 mg fractionated (100 mg + 200 mg + 200 mg) IV bolus injection
		  ○ IIM was administered during dialysis undiluted in fractionated doses of 100 mg at baseline and 200 mg each at week 2 and week 4. Doses were administered as IV bolus injections over approximately 2 minutes.
			IIM
			• IV infusion of 1,000 mg over 20 minutes

	Comparator(s)	**Iron sucrose** • Group B: Iron sucrose 500 mg fractionated (100 mg + 200 mg + 200 mg) IV bolus injection	**Iron sucrose** • IV injection of 200 mg according to label and repeated up to 5 times

		PROPOSE	FERWON-NEPHRO
		○ Iron sucrose was administered undiluted in fractionated doses of 100 mg at baseline and 200 mg during week 2 and week 4. Doses were administered as per local SmPC and/or local hospital guidelines or package insert. Test dose was administered if recommended or compulsory, according to local SmPC and/or hospital guidelines.	
DURATION	**Phase**		
	Run-in	-	-
	Screening	1 to 16 days Screening was split into 2 visits: • 1a: Within 16 days prior to baseline • 1b: Minimum 7 days from visit 1a Re-screening was included in a protocol amendment and was permitted up to 3 times. If the participant failed visit 1a or 1b, then re-screening was permitted after 2 weeks.	Duration not specified
	Baseline	Duration not specified	Duration not specified
	Treatment	4 weeks ± 2 days	8 weeks
	Follow-up	2 weeks ± 2 days	Duration not specified
OUTCOMES	**Primary end point**	Proportion of participants who were able to maintain Hb between 9.5 g/dL and 12.5 g/dL (both values included) at 6 weeks	**Co-primary end point** • Serious or severe hypersensitivity reactions • Change in Hb from baseline to week 8
	Secondary and exploratory end points	**Secondary** • Change in Hb from baseline to week 2, week 4, and week 6 • Change in concentration of s-iron, TSAT, s-ferritin, and reticulocyte count from baseline to week 1, week 2, week 4, and week 6 • Number of participants in each randomization group who discontinued study because of lack of response or intolerance of investigational drugs • Change in total QoL score (LASA) from baseline to week 4 and week 6 • Change in RLS symptoms (CH-RLSq questionnaire) from baseline to week 6 in participants with RLS symptoms at baseline	**Secondary** • Composite end point of cardiovascular adverse events and hypophosphatemia (time frame: 8 weeks) • Change in Hb from baseline to week 1, week 2, and week 4 • Changes in s-ferritin (ng/mL) and TSAT (%) (time frame: 8 weeks)
	Publications	Bhandari 2015	Bhandari 2019

ALT = alanine aminotransferase; CH-RLSq = Cambridge–Hopkins Restless Legs Syndrome Questionnaire; CKD = chronic kidney disease; CKD-5D = chronic kidney disease stage 5; eGFR = estimated glomerular filtration rate; ESA = erythropoiesis-stimulating agent; Hb = hemoglobin; IDA = iron deficiency anemia; IIM = iron isomaltoside 1000; LASA = Linear Analog Scale Assessment; NI = noninferiority; OL = open-label; QoL = quality of life; RCT = randomized controlled trial; RLS = restless legs syndrome; s-ferritin = serum ferritin; s-iron = serum iron; SmPC: summary of product characteristics; TSAT = transferrin saturation.

Source: Clinical Study Report for PROPOSE[9] and publication for FERWON-NEPHRO.[14,15]

Table 5: Details of Included Studies: IDA Study Populations

		PROVIDE	FERWON-IDA
DESIGNS AND POPULATIONS	**Study design**	OL, parallel group, active-controlled, NI/superiority, RCT	OL, parallel group, active-controlled, NI RCT
	Locations	48 enrolling centres of 52 initiated centres in the US	114 centres in the US
	Randomized (N)	511	1,512

	Inclusion criteria	• Women and men aged ≥ 18 years
		• IDA caused by different etiologies (documented in the medical history and verified in the source document) and other conditions leading to significant blood loss and with a documented history of intolerance or unresponsiveness to oral therapy (should be documented with a sign or symptom in the medical history and verified in the source document) for at least 1 month (should be documented as per the investigator's judgment within the last 2 years and they would not be candidates for oral iron again) prior to trial enrolment or where, at the investigator's judgment, there was a clinical need to deliver iron rapidly
		• Hb < 11 g/dL
		• TSAT < 20%
		• *S*-ferritin < 100 ng/mL
			• Women or men ≥ 18 years
			• IDA caused by different etiologies (documented in the medical history and verified in the source document) and conditions leading to significant blood loss
			• Subjects with:
			  ○ up to 1 month run-in phase indicating intolerance or lack of response to oral iron or
			  ○ a documented history of intolerance to oral iron therapy of at least 1 month of oral iron within 9 months prior to enrolment or
			  ○ screening Hb, in investigator's opinion, was sufficiently low as to require rapid repletion of iron stores to minimize the risk of eventual blood transfusion.
			• Hb ≤ 11 g/dL
			• TSAT < 20%
			• S-ferritin < 100 ng/mL
			
			After the run-in period, inclusion criteria included:
			• Hb ≤ 11 g/dL
			• S-ferritin ≤ 800 ng/mL
			• Lack of efficacy: Hb increase < 1 g/dL and compliance to oral iron (pill counts) ≥ 67%
			
			or
			
			• Hb ≤ 11 g/dL
			• S-ferritin ≤ 800 ng/mL
			• Inability to tolerate oral iron, as per discretion of the investigator

	Exclusion criteria	• Anemia caused primarily by factors other than IDA • Iron overload or disturbances in utilization of iron • Decompensated liver cirrhosis or active hepatitis (ALT > 3 times upper limit of normal) • Active or chronic infections • Body weight < 50 kg • Rheumatoid arthritis with symptoms or signs of active inflammation • Pregnant or nursing • Known hypersensitivity to parenteral iron or any excipients in the investigational drug products • Erythropoietin treatment within 8 weeks prior to the screening visit • Other IV iron treatment or blood transfusion within 4 weeks prior to the screening visit • Planned elective surgery during the trial • Participation in any other interventional trial within 3 months prior to screening • Any other medical condition that may have caused the participant to be unsuitable for the completion	• Anemia caused primarily by factors other than IDA • Hemochromatosis or other iron storage disorders • Known hypersensitivity reaction to any component of IIM or iron sucrose • Previous serious hypersensitivity reactions to any IV iron compounds • Previously randomized in a clinical trial with IIM • Received an investigational drug within 30 days of screening • Was treated with IV iron during the 10-day period prior to screening • Erythropoiesis-stimulating treatment (within 30 days prior to screening) • Prior to screening (within 30 days) or during the trial period, was or will be treated with a red blood cell transfusion, radiotherapy, and/or chemotherapy • Prior to screening (within 30 days) or during the trial period, was or will require a surgical procedure that necessitated(es) general anesthesia • ALT and/or AST > 3 times upper limit of normal

		PROVIDE	FERWON-IDA
		of the trial or placed the participant at potential risk from being in the trial	• Any non-viral infection • Required dialysis for treatment of CKD • Alcohol or drug abuse within the past 6 months • Pregnant or nursing • Any other laboratory abnormality, medical condition or psychiatric disorders which, in the opinion of the investigator, will put the participant's disease management at risk or may result in the participant being unable to comply with the trial requirements
DRUGS	**Intervention**	**IIM** • Cumulative dose was individually determined and was dependent on a participant's Hb and weight[a] • Cumulative dose of 1,000 mg: 1,000 mg IV infusion administered at baseline • Cumulative dose of 1,500 mg: 1,000 mg IV infusion administered at baseline and 500 mg bolus IV injection at visit 3 (1 week apart) • Cumulative dose of 2,000 mg: 1,000 mg IV infusion administered at baseline and at visit 3 (1 week apart) • 1,000 mg infusions were diluted in 100 mg 0.9% sodium chloride and given over approximately 15 minutes (range: 12 to 18) • 500 mg bolus injections were given over approximately 2 minutes (range: 1 to 3)	**IIM** • Single baseline IV infusion dose of 1,000 mg administered over 20 minutes
	Comparator(s)	**Iron sucrose** • Cumulative dose was individually determined using the Ganzoni formula[b] • IV infusions of 200 mg were given over approximately 30 minutes at baseline and up to twice weekly • Maximum cumulative dose was set at 2,000 mg	**Iron sucrose** • Baseline IV injection of 200 mg according to label and repeated up to 5 times • Cumulative dose of 1,000 mg was recommended
DURATION	**Phase**		
	Run-in	-	Up to 1 month • To document intolerance or lack of response to oral iron if participant had no documentation of oral iron intolerance
	Screening	2 weeks maximum	Duration not specified
	Baseline	0 weeks	Duration not specified
	Treatment	4 weeks ± 2 days	8 weeks
	Follow-up	1 week ± 3 days	Duration not specified
OUTCOMES	**Primary end point**	Proportion of participants with an Hb increase ≥ 2 g/dL from baseline to any time between week 1 and week 5	**Co-primary end point** • Number of participants with adjudicated serious or severe hypersensitivity reaction, starting on the first dose of treatment • Change in Hb from baseline to week 8
	Secondary and exploratory end points	**Secondary** • Time to Hb increase ≥ 2 g/dL • Number of participants who achieve Hb levels of > 12 g/dL; or achieve increase in Hb concentration > 3 g/dL; or serum (s-) ferritin increase of at least 160 ng/mL; or achieve a TSAT of 20-50 % at week	**Secondary** • Hb increase of ≥ 2 g/dL • S-ferritin increase of ≥ 100 ng/mL • TSAT of 20% to 50% • Changes in Hb (baseline to week 1, week 2, and week 4), s-ferritin (baseline to week 1, week 2, week 4, and week 8), TSAT (baseline to week 1,

		PROVIDE	FERWON-IDA
		2, 4, or 5Change in Hb from baseline to week 2, week 4, and week 5 • Change in s-ferritin, TSAT, and s-iron from baseline to week 1, week 2, week 4, and week 5 • Change in fatigue symptoms from baseline to week 2 and week 5 (FACIT-FS) • Change in QoL from baseline to week 2 and week 5 (SF-36 questionnaire)	week 2, and week 8), and FACIT-FS (baseline to week 1, week 2, and week 8) • Time to Hb response ≥ 2 g/dL was measured but was not a pre-specified secondary end point
	Publications	Derman (2017), Derman (2018)	Auerbach (2019)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CKD = chronic kidney disease; FACIT-FS = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; Hb = hemoglobin; IDA = iron deficiency anemia; IIM = iron isomaltoside 1000; NI = noninferiority; OL = open-label; RCT = randomized controlled trial; s-ferritin = serum ferritin; s-iron = serum iron; SF-36 = Short Form (36) Health Survey; TSAT = transferrin saturation.

[a] Cumulative dose determination for IIM: (1) Hb of 10 g/dL or more and body weight less than 70 kg = 1,000 mg total IIM; (2) Hb of 10 g/dL or more and body weight of 70 kg or more = 1,500 mg total IIM; (3) Hb less than 10 g/dL and body weight less than 70 kg = 1,500 mg total IIM; (4) Hb less than 10 g/dL and body weight of 70 kg or more = 2,000 mg total IIM.

[b] Ganzoni formula for iron sucrose cumulative dose determination: Total iron dose = (body weight × [target Hb – actual Hb]) × 2.4 + iron storage depot. Depot iron was 500 mg and target Hb was 13.0 g/dL.

Source: Clinical Study Reports, publications for PROVIDE,[11] and publications for FERWON-IDA.[16,17]

Description of Studies

Four phase III RCTs were identified and included in this systematic review (PROPOSE, FERWON-NEPHRO, PROVIDE, and FERWON-IDA).[9-17] PROPOSE[9] and PROVIDE[11] were the pivotal studies identified by the sponsor and FERWON-NEPHRO[14] and FERWON-IDA[16] were identified through the systematic search per the CDR review protocol.

Of the four included studies, two enrolled participants with CKD and anemia (PROPOSE and FERWON-NEPHRO).[9,14] PROPOSE enrolled participants with CKD-5D on hemodialysis who had anemia due to renal-related causes while FERWON-NEPHRO enrolled participants with IDA with NDD-CKD participants.[9,14] The remaining two included studies, PROVIDE and FERWON-IDA, enrolled participants with IDA caused by a variety of etiologies.[11,16] Given the two distinct study populations — CKD (± hemodialysis) with anemia or IDA and IDA caused by different factors — the findings are presented and grouped according to the study populations.

PROPOSE and FERWON-NEPHRO

PROPOSE and FERWON-NEPHRO were multi-centre, open-label, parallel group, active-controlled, noninferiority RCTs. The studies differed in overall objective and in primary end points measured.[9,14] PROPOSE was designed to determine whether iron isomaltoside 1000 was noninferior to iron sucrose for maintenance therapy of anemia in participants with CKD-5D on dialysis, and its primary outcome measure was the proportion of participants who maintained an Hb level between 9.5 g/dL and 12.5 g/dL (both values included) at week 6.[9] In contrast, FERWON-NEPHRO was a noninferiority trial designed to evaluate the safety and efficacy of iron isomaltoside 1000 compared to iron sucrose in participants with IDA and NDD-CKD, and had a co-primary end point that measured, first, the proportion of participants with serious or severe hypersensitivity reactions and, second, the change in Hb from baseline to week 8 (i.e., the ability to increase Hb and correct anemia).[14]

PROPOSE enrolled participants from 48 centres (15 in India, 14 in the UK, four in Poland, three each in Russia, Sweden, and Switzerland, two each in the US and Romania, and one in Denmark), whereas FERWON-NEPHRO enrolled participants from multiple centres in the US. Information on the number of US enrolment centres was not available for

FERWON-NEPHRO. Neither trial included Canadian enrolment centres. Trial initiation and completion occurred between June 2011 and December 2013 for PROPOSE and between October 2016 and May 29, 2018, for FERWON-NEPHRO (see ClinicalTrials.gov for details).[9,14]

The screening phases of both the PROPOSE and FERWON-NEPHRO trials were to include or exclude participants based on study inclusion criteria. For the PROPOSE trial, 660 participants with CKD-5D diagnoses were screened (143 of the 660 were re-screened). Eligible participants for PROPOSE (N = 351) and FERWON-NEPHRO (N = 1,538) were randomized 2:1 into iron isomaltoside 1000 and iron sucrose groups. PROPOSE evaluated two iron isomaltoside 1000 administration subgroup groups (single IV bolus injection and fractionated IV bolus injection). Allocation to the iron isomaltoside subgroups was equal (1:1 randomization schedule). The randomization schedule was created using a computer-generated list (via the statistical software SAS) and an interactive web response system to randomize eligible PROPOSE participants to study groups. The method of randomization was not available for FERWON-NEPHRO. Treatment and follow-up periods were six weeks and eight weeks for the PROPOSE and FERWON-NEPHRO trials, respectively.[9,14]

PROVIDE and FERWON-IDA

PROVIDE and FERWON-IDA were also multi-centre, open-label, parallel group, active-controlled, noninferiority RCTs.[11,16] In addition, PROVIDE planned to test for superiority on the primary efficacy end point if noninferiority was shown.[11] The objectives of PROVIDE and FERWON-IDA were to evaluate the efficacy and safety of iron isomaltoside 1000 compared with iron sucrose in participants with IDA caused by various etiologies and who were intolerant or unresponsive to oral iron therapy or who needed iron rapidly. However, the primary efficacy end points differed between the trials.[11,16] The primary efficacy measure in PROVIDE was the proportion of participants with an increase in Hb of 2 g/dL or more from baseline to any time between week 1 and week 5.[11] In contrast, FERWON-IDA had a co-primary end point that evaluated both efficacy and safety.[16] The safety component compared the number of participants with serious or severe hypersensitivity reactions and the efficacy component compared the change in Hb concentration from baseline to week 8.[16]

PROVIDE and FERWON-IDA enrolled participants from 48 and 114 centres across the US. Neither study included Canadian enrolment centres. PROVIDE was initiated May 15, 2014, and completed on August 18, 2015. FERWON-IDA was initiated on November 21, 2018, and finished March 28, 2019 (see ClinicalTrials.gov for details).[11,16]

The screening phases of PROVIDE and FERWON-IDA were to apply inclusion and exclusion study criteria and to ensure participants had a documented intolerance to oral iron for at least one month within the nine months before enrolment.[11,16] However, a run-in period was initiated (up to one month) if a potential FERWON-IDA participant did not have documented oral intolerance. Subjects received oral iron during the run-in-period and one to four additional visits (one telephone visit to initiate the run-in period and three visits to assess compliance and tolerance).[16]

Eligible participants for PROVIDE (N = 511)[11] and FERWON-IDA (N = 1,512)[16] were randomized 2:1 to iron isomaltoside 1000 and iron sucrose. Randomization lists for the PROVIDE trial were computer-generated (via the electronic case report form system eClinicalOS) and study sites used an interactive web response system for the randomization of participants (see the trial's Clinical Study Report, page 38).

Randomization to PROVIDE study groups was stratified by screening Hb (< 10.0 g/dL and ≥ 10.0 g/dL) and type of underlying disease (gastroenterology, gynecology, oncology, and other).[11] Treatment and follow-up periods were five weeks and eight weeks for PROVIDE and FERWON-IDA, respectively. The method of randomization was not available for FERWON-IDA.[11,16]

Populations

Inclusion and Exclusion Criteria

PROPOSE and FERWON-NEPHRO

The study populations for PROPOSE and FERWON-NEPHRO consisted of women and men aged 18 years or older.[9,14] In PROPOSE, participants were required to have CKD-5D, receiving hemodialysis and maintenance iron therapy for renal-related anemia with baseline Hb, and have s-ferritin and transferrin saturation (TSAT) of 9.5 g/dL and 12.5 g/dL (both values included), less than 800 mcg/L, and less than 35%, respectively.[9] In contrast, FERWON-NEPHRO participants included participants with NDD-CKD and IDA with baseline Hb of 11 g/dL or less and a s-ferritin level of 100 mcg/L or less or 300 g/dL or less if TSAT was 30% or less.[14] Both PROPOSE and FERWON-NEPHRO excluded participants with iron overload or other iron storage disorders, decompensated liver cirrhosis or active hepatitis, blood transfusions (prior to screening), or who had planned elective surgery during the trial, or who were pregnant or nursing.[9,14] FERWON-NEPHRO also excluded participants undergoing radiotherapy and/or chemotherapy and participants with a history of alcohol or drug abuse (within six months).[14] PROPOSE excluded participants receiving concomitant immunosuppressive therapy, active or chronic infections, rheumatoid arthritis (symptomatic or with active joint inflammation), and untreated vitamin B12 or folate deficiency.[9]

PROVIDE and FERWON-IDA

The PROVIDE and FERWON-IDA study populations consisted of women and men aged 18 years or older. Inclusion criteria were similar for PROVIDE and FERWON-IDA in that both trials enrolled participants with IDA caused by various etiologies who had a documented intolerance or unresponsiveness to oral iron therapy or a need for rapid iron repletion identified by the investigators.[11,16] Potential participants for the FERWON-IDA trial without a documented history of oral iron intolerance were enrolled in a run-in period (up to one month) where they were administered oral iron to document intolerance (as per the investigator) or lack of response (Hb increase < 1 g/dL). Hb of 11 g/dL or less, s-ferritin of less than 100 mcg/L and TSAT of less than 20% were the thresholds for inclusion for participants in both trials, provided they did not require participation in the run-in phase of FERWON-IDA. The inclusion cut-off value for Hb remained 11 g/dL or less and s-ferritin was increased to 800 mcg/L or less for run-in participants.[16] Many of the exclusion criteria were similar between the PROVIDE and FERWON-IDA trials. Both excluded participants with anemia primarily caused by factors other than IDA, with iron overload or disturbances, with decompensated liver cirrhosis, who were pregnant or nursing, and had known hypersensitivity to IV iron products, and participants who had received IV iron, red blood cell transfusion, or erythropoiesis-stimulating agents (ESAs) before screening were excluded.[11,16] PROVIDE excluded participants with any type of infection (active and chronic) and FERWON-IDA only excluded participants with non-viral infections. PROVIDE also excluded participants with rheumatoid arthritis (symptomatic or signs of inflammation).[11] Subjects receiving radiotherapy or chemotherapy or who required dialysis for CKD were only excluded from FERWON-IDA.[16]

Baseline Characteristics

PROPOSE and FERWON-NEPHRO

The baseline characteristics were balanced between study groups for PROPOSE with the exception of ischemic heart disease.[9]

A greater number of iron isomaltoside 1000 participants had ischemic heart disease compared with iron sucrose participants (13.7% and 6.8%, respectively).[9] Baseline weight and Hb levels were well balanced in the FERWON-NEPHRO trial. No other baseline characteristics were available for FERWON-NEPHRO.[14] Study participants in the FERWON-NEPHRO trial were on average 10 years older than PROPOSE participants (mean age of 69 years versus 59.97 years, respectively). The mean baseline Hb was higher for participants in the PROPOSE study (11.20 g/dL and 11.08 g/dL for iron isomaltoside and iron sucrose, respectively) compared to those in the FERWON-NEPHRO study (9.66 g/dL and 9.71 g/dL for iron isomaltoside and iron sucrose, respectively).[9,14] The majority of PROPOSE participants were male (66.1%) and Caucasian (65.0%) or Asian (28.8%), with hypertension arterial (70.4%), diabetes mellitus (33.9%), and a mean of 3.5 years (standard deviation [SD] 3.98 years) of dialysis prior to study enrolment.[9]

Table 6 summarizes baseline characteristics for PROPOSE and FERWON-NEPHRO.

PROVIDE and FERWON-IDA

The baseline characteristics were balanced between iron isomaltoside 1000 and iron sucrose for the PROVIDE and FERWON-IDA trials. The mean age of study participants was similar for the PROVIDE trial (49.2 years and 46.8 years for iron isomaltoside 1000 and iron sucrose, respectively) and the FERWON-IDA trial (44.1 years and 43.8 years for iron isomaltoside 1000 and iron sucrose, respectively). The majority of participants in both treatment groups were female (> 88%) and of Caucasian (> 50%) or African-American descent (> 33%) in the PROVIDE and FERWON-IDA trials.[11,16] In the PROVIDE trial, gastroenterology (> 32%) and gynecology (> 47%) were the most common types of diseases causing IDA for both treatment groups. Mean baseline Hb concentrations were similar for iron isomaltoside 1000 and iron sucrose participants in the PROVIDE trial (9.39 g/dL for both groups) and the FERWON-IDA trial (9.25 g/dL and 9.17 g/dL, respectively).[11] Mean baseline *s*-ferritin was similar in the PROVIDE trial (both arms) and the iron isomaltoside 1000 arm of the FERWON-IDA trial (range: 14.3 mcg/L to 15.6 mcg/L).[11,16] Iron sucrose participants in FERWON-IDA had a slightly lower mean baseline s-ferritin (11.9 mcg/L).[16] Baseline TSAT across the trials ranged from 5.8% to 7.43%.[11,16]

Table 6: Summary of Baseline Characteristics — CKD Study Populations

Characteristics	PROPOSE		FERWON-NEPHRO	
	IIM (N = 234)	IS (N = 117)	IIM	IS
Age (years)				
Mean (SD)	60.20 (16.21)	59.50 (15.39)	69	
Range	18 to 89	26 to 84	25 to 97	
Gender, n (%)				
Men	158 (67.5)	74 (63.2)	-	-
Women	76 (32.5)	43 (36.8)	-	-
Ethnic origin, n (%)				
Caucasian	154 (65.8)	74 (63.2)	-	-

Characteristics	PROPOSE		FERWON-NEPHRO	
	IIM (N = 234)	IS (N = 117)	IIM	IS
Black or African-American	14 (6.0)	5 (4.3)	-	-
Asian	64 (27.4)	37 (31.6)	-	-
American Indian or Alaska Native	-	-	-	-
Native Hawaiian or other Pacific Islander	-	-	-	-
Others	1 (0.4)	1 (0.9)	-	-
Current smoker, n (%)				
Yes	30 (12.8)	8 (6.8)	-	-
No	203 (86.8)	109 (93.2)	-	-
Weight (kg)				
N	233	117	-	-
Mean (SD)	77.58 (19.64)	75.83 (19.15)	86.3 (23.4)	82.6 (20.3)
Range	43.5 to 147.0	41.0 to 126.9		
Height (cm)				
N	232	117	-	-
Mean (SD)	167.42 (9.29)	166.21 (10.61)	-	-
Range	145.0 to 188.0	140.8 to 193.0	-	-
BMI (kg/m^2)				
N	232	117	-	-
Mean (SD)	27.65 (6.77)	27.41 (6.34)	-	-
Range	15.3 to 55.8	17.1 to 44.3	-	-
Mean dialysis time before entering the study (years)				
N	233	117	-	-
Mean (SD)	3.46 (3.95)	3.59 (4.08)	-	-
Range	0.25 to 26.82	0.27 to 22.25	-	-
Common concomitant illnesses, n (%)				
Diabetes mellitus	83 (35.5)	36 (30.8)	-	-
Hypertension, arterial	160 (68.4)	87 (74.4)	-	-
Ischemic heart disease	32 (13.7)	8 (6.8)	-	-
Medical history, n (%)				
Baseline Hb (g/dL)				
N	225	114	-	-
Mean (SD)	11.20 (0.83)	11.08 (0.93)	9.66 (1.14)	9.71 (1.12)
Range	9.1 to 15.6	8.4 to 14.6	-	-
Baseline s-ferritin (ng/mL)				
N	225	114	-	-
Mean (SD)	350.88 (186.17)	357.74 (192.98)	-	-
Range	9.5 to 997.6	12.4 to 986.7	-	-
Baseline TSAT (%)				
N	225	113	-	-
Mean (SD)	22.20 (17.90)	22.57 (8.49)	-	-
Range	2.0 to 265.0	5.5 to 48.2	-	-
Baseline s-iron (µmol/L)				
N	225	113	-	-
Mean (SD)	10.36 (4.02)	10.78 (4.01)	-	-

Characteristics	PROPOSE		FERWON-NEPHRO	
	IIM (N = 234)	IS (N = 117)	IIM	IS
Range	0.9 to 30.8	2.5 to 21.8	-	-

BMI = body mass index; CKD = chronic kidney disease; Hb = hemoglobin; IIM = iron isomaltoside 1000; IS = iron sucrose; s-ferritin = serum ferritin; s-iron = serum iron; SD = standard deviation; TSAT = transferrin saturation.

Source: Clinical Study Report for PROPOSE[9] and publication for FERWON-NEPHRO.[14]

Table 7 summarizes baseline characteristics for PROVIDE and FERWON-IDA.

Table 7: Summary of Baseline Characteristics — IDA Study Populations

Characteristics	PROVIDE		FERWON-IDA	
	IIM (n = 330)	IS (n = 161)	IIM (n = 1,009)	IS (n = 503)
Age (years)				
Mean (SD)	49.2 (15.7)	46.8 (15.1)	44.1 (14.8)	43.8 (14.4)
Range	19 to 95	19 to 87	18 to 91	18 to 91
Gender, n (%)				
Men	33 (10.0)	15 (9.3)	117 (11.6)	47 (9.3)
Women	297 (90.0)	146 (90.7)	892 (88.4)	456 (90.7)
Ethnic origin, n (%)				
Caucasian	208 (63.0)	99 (61.5)	504 (50.0)	264 (52.5)
Black or African-American	111 (33.6)	54 (33.5)	484 (48.0)	223 (44.3)
Asian	2 (0.6)	1 (0.6)	8 (0.8)	4 (0.9)
American Indian or Alaska Native	1 (0.3)	0 (0.0)	4 (0.4)	1 (0.2)
Native Hawaiian or other Pacific Islander	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Others	7 (2.1)	7 (4.3)	8 (0.8)	9 (1.8)
Current smoker, n (%)				
Yes	54 (16.4)	21 (13.0)	-	-
No	276 (83.6)	140 (87.0)	-	-
Weight (kg)				
n	330	161	-	-
Mean (SD)	85.6 (23.3)	82.2 (20.8)	-	-
Range	50 to 209	50 to 152	-	-
Height (cm)				
n	330	161	-	-
Mean (SD)	163.1 (8.3)	163.6 (8.5)	-	-
Range	125 to 191	141 to 195	-	-
Medical history, n (%)				
Surgical and medical procedures	200 (60.6)	103 (64.0)	-	-
Gastrointestinal disorders	153 (46.4)	72 (44.7)	-	-
Musculoskeletal and connective tissue disorders	107 (32.4)	44 (27.3)	-	-
Metabolism and nutrition disorders	111 (33.6)	53 (32.9)	-	-
Psychiatric disorders	99 (30.0)	47 (29.2)	-	-
Nervous system disorders	111 (33.6)	55 (34.2)	-	-

Characteristics	PROVIDE		FERWON-IDA	
	IIM (n = 330)	IS (n = 161)	IIM (n = 1,009)	IS (n = 503)
Reproductive system and breast disorders	107 (32.4)	61 (37.9)	-	-
Vascular disorders	121 (36.7)	52 (32.3)	-	-
Respiratory disorders	86 (26.1)	40 (24.8)	-	-
General disorders and administration site conditions	64 (19.4)	28 (17.4)	-	-
Infections and infestations	58 (17.6)	29 (18.0)	-	-
Neoplasms — benign, malignant, and unspecified	78 (23.6)	28 (17.4)	-	-
Immune system disorders	64 (19.4)	38 (23.6)	-	-
Renal and urinary disorders	50 (15.2)	19 (11.8)	-	-
Skin and subcutaneous tissue disorders	49 (14.8)	18 (11.2)	-	-
Cardiac disorders	45 (13.6)	18 (11.2)	-	-
Eye disorders	47 (14.2)	22 (13.7)	-	-
Blood and lymphatic system disorders	47 (14.2)	20 (12.4)	-	-
Endocrine disorders	49 (14.8)	17 (10.6)	-	-
Type of disease causing IDA, n (%)				
Gastroenterology	111 (33.6)	53 (32.9)	-	-
Gynecology	158 (47.9)	79 (49.1)	-	-
Oncology	6 (1.8)	3 (1.9)	-	-
Others	55 (16.7)	26 (16.1)	-	-
Baseline Hb level (g/dL)				
N	330	161	-	-
< 10	199 (60.3)	97 (60.2)	-	-
> 10	131 (39.7)	64 (39.8)	-	-
Baseline Hb (g/dL)				
N	330	161	1,009	503
Mean (SD)	9.39 (1.15)	9.39 (1.31)	9.25 (1.28)	9.17 (1.27)
Range	4.4 to 12.1	6.1 to 12.2	4.0 to 13.5	5.2 to 13.8
Baseline s-ferritin (ng/mL)				
N	330	161	1,009	503
Mean (SD)	14.3 (32.8)	15.6 (47.2)	14.4 (42.6)	11.9 (37.6)
Range	2 to 543	2 to 581	1 to 729	1 to 715
Baseline TSAT (%)				
N	330	161	1,009	503
Mean (SD)	5.8 (5.0)	6.4 (5.9)	7.43 (10.93)	6.69 (7.44)
Range	1 to 43	1 to 40	1 to 176	1 to 84

Hb = hemoglobin; IDA = iron deficiency anemia; IIM = iron isomaltoside 1000; IS = iron sucrose; s-ferritin = serum ferritin; SD = standard deviation; TSAT = transferrin saturation.

Sources: Clinical Study Report for PROVIDE[11] and publication for FERWON-IDA.[16]

Interventions

PROPOSE and FERWON-NEPHRO

The dose, method, and rate of administration of iron isomaltoside 1000 differed between the PROPOSE and FERWON-NEPHRO trials.[9,14] The cumulative iron dose was greater and was given over a longer infusion period for participants enrolled in the FERWON-NEPHRO trial (single 1,000 mg IV infusion given over 20 minutes) compared with PROPOSE, where participants received either iron isomaltoside 1,000 as a single 500 mg IV bolus or 500 mg fractionated IV bolus (100 mg at baseline + 200 mg at week 2 + 200 mg at week 4) over approximately two minutes during hemodialysis. The cumulative dose of iron sucrose was also greater for participants in the FERWON-NEPHRO trial compared with the PROPOSE trial (up to 1,000 mg and 500 mg, respectively). However, the dose of iron sucrose given per injection was similar between the trials (dosing range: 100 mg to 200 mg). No blinding of investigational products was performed for either trial.[9,14] All included PROPOSE participants received concomitant ESA therapy.[9] FERWON-NEPHRO participants may or may not have received concomitant ESA therapy during the trial.[14,15] The ESA dose had to be stable four weeks prior to study enrolment for both trials.[9,15]

PROVIDE and FERWON-IDA

The maximum cumulative iron dose of iron isomaltoside 1000 and iron sucrose permitted was higher in PROVIDE than in FERWON-IDA (2,000 mg versus 1,000 mg, respectively). The administration rate of IV iron isomaltoside 1000 infusions of 1,000 mg were similar for the PROVIDE trial (approximately 15 minutes) and FERWON-IDA trial (20 minutes).[11,16] PROVIDE iron isomaltoside 1000 participants could receive a single baseline dose of 1,000 mg or a 1,000 mg baseline dose followed in one week by either a 500 mg IV bolus (given over approximately two minutes) or a second IV infusion of 1,000 mg.[11] In contrast, FERWON-IDA participants received a single baseline dose of iron isomaltoside 1000 (1,000 mg).[16] PROVIDE and FERWON-IDA participants received 200 mg of iron sucrose at baseline and subsequent visits. PROVIDE participants received iron sucrose as an infusion over 30 minutes up to twice weekly until cumulative dose was reached and FERWON-IDA participants received IV injections of iron sucrose repeated up to five times. No blinding of investigational products was performed for either trial.[11,16] Laboratory parameters were assessed at a central laboratory in the FERWON-IDA trial.[16] Other iron supplements, blood transfusions, and ESAs were prohibited in both PROVIDE and FERWON-IDA.[11,16]

Outcomes

PROPOSE and FERWON-NEPHRO

The primary efficacy end points for the PROPOSE and FERWON-NEPHRO trials used Hb measures to evaluate response to treatments. PROPOSE analyzed the proportion of study participants who were able to maintain an Hb level between 9.5 g/dL and 12.5 g/dL at six weeks. FERWON-NEPHRO used a co-primary end point of, first, the proportion of participants with serious or severe hypersensitivity reactions and, second, the mean change in Hb level from baseline to week 8.[9,14,15]

Secondary end points measured in both PROPOSE and FERWON-NEPHRO included change in Hb and change in s-ferritin and TSAT at different study time points. PROPOSE and FERWON-NEPHRO analyzed the change in Hb at week 2, week 4, and week 6 and at week 1, week 2, week 4, and week 8, respectively. Change in s-ferritin and TSAT were

analyzed at week 1, week 2, week 4, and week 6 for PROPOSE and over an eight-week time frame for FERWON-NEPHRO.[9,14,15]

Other secondary end points measured by PROPOSE included change in serum iron (s-iron) (week 1, week 2, week 4, and week 6), change in reticulocyte count (week 1, week 2, week 4, and week 6), change in QoL as measured by linear analogue scale (LASA at week 4 and week 6) and change in RLS symptoms as measured by the CH-RLSq at week 6). Safety end points included were the number of participants who experienced any adverse drug reaction (ADR). Post hoc, PROPOSE evaluated the proportion of participants who were able to maintain an Hb level of 9.5 g/dL or more at week 6.[9]

PROPOSE used LASA, a self-administered questionnaire, for assessing QoL.[9,31] LASA consists of three domains assessed with visual analogue scales (VASs): energy level, activities of daily living, and overall QoL. Each VAS has a seven-day recall period and consists of a 100 mm line with a left anchor representing the worst possible score (0) and the right anchor representing the best possible score (100). Higher scores indicate better functioning and HRQoL (HRQoL). The VAS scale has been established as a valid and reliable patient-reported outcome tool.[31] However, the validity and minimal clinically important difference (MCID) of information from LASA in participants with IDA is currently lacking (see Appendix 4).

The CH-RLSq is a self-completed 22-item questionnaire, with seven of the items being used to make the diagnosis and the remaining to further characterize the condition.[9,32] The CH-RLSq includes items covering the basic diagnostic and differential diagnostic features of RLS.[32] A number of questionnaires are available for assessing the severity of RLS and, generally, a higher number is associated with greater RLS severity.[33] However, the validity of CH-RLSq information in participants with IDA population was not identified. The information on the CH-RLSq severity scale (i.e., the validity, MCID) was not provided in the sponsor's submission and not identified from the CADTH search, either.

Safety outcomes measures reported by PROPOSE included the type and incidence of ADRs, the number of AEs of special interest (i.e., hypersensitivity symptoms), and change in hematology parameters (i.e., serum sodium, serum potassium, and serum calcium).[9]

Composite cardiovascular AEs and hypophosphatemia were captured as key secondary end points in FERWON-NEPHRO (over the eight-week time frame). Cardiovascular AEs and hypophosphatemia were adjudicated and confirmed by an independent and blinded adjudication committee.[14]

PROVIDE and FERWON-IDA

The primary efficacy end points for the PROVIDE and FERWON-IDA trials used Hb measures to assess response to treatment.[11,16] PROVIDE defined its primary efficacy variable as the proportion of participants with an increase in Hb of 2 g/dL or more from baseline to any time between week 1 and week 5 and FERWON-IDA evaluated the ability to increase Hb measured as the change in Hb concentration from baseline to week 8.[11,16] FERWON-IDA utilized a co-primary end point that also measured the number of participants with adjudicated serious or severe hypersensitivity reactions (starting on or after the first treatment dose). The proportion of participants with an increase in Hb of 2 g/dL or more was measured as a secondary efficacy outcome in FERWON-IDA.[16]

Secondary efficacy end points measured by the PROVIDE and FERWON-IDA trials included changes from baseline in Hb (PROVIDE: week 2, week 4, and week 5;

FERWON-IDA: week, 1, week 2, and week 4), and s-ferritin and TSAT (PROVIDE: week 1, week 2, week 4, and week 5; FERWON-IDA: week 1, week 2, week 4, and week 8). PROVIDE and FERWON-IDA also both measured the time to achieve an Hb response of 2 g/dL or more; however, this end point was not listed a priori by FERWON-IDA.[11,16] Additional secondary efficacy end points in FERWON-IDA included the number of participants with an increase in s-ferritin of 100 mcg/L or more and TSAT of 20% to 50% at any time between baseline and week 8.[16]

The PROVIDE and FERWON-IDA trials measured a participant's change in fatigue, using the FACIT-FS. The change in FACIT-FS scores were evaluated as change in baseline to week 2 and week 5 for PROVIDE and week 1, week 2, and week 5 for FERWON-IDA.[11,16] FACIT-FS is a subscale of the Functional Assessment of Chronic Illness Therapy (FACIT), used to assess fatigue symptoms related to QoL.[34,35] It is a self-administered questionnaire that was completed by participants at baseline, at various time points throughout the trial, and at the end of the trial. The FACIT- FS[36,37] is a 13-item instrument designed to assess fatigue and tiredness and their impact on daily activities and functioning (HRQoL) in many chronic diseases. In the US, the validity, reliability, and responsiveness of FACIT-FS have been assessed in participants with IDA due to various underlying diseases. Higher scores for FACIT-FS's scales and subscales indicate better QoL.[38] A score of less than 30 indicates severe fatigue.[11]

The PROVIDE trial assessed QoL by measuring the change from baseline to week 2 and week 5, using the SF-36 questionnaire.[11] The SF-36 consists of eight health domains — physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[39] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a SD of 10 in the general US population. Therefore, all scores above or below 50 are considered above or below average for the general US population. The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 points and 5 points.[40-42] No MCID of SF-36 was identified in the IDA population.

Key safety outcomes measured by PROVIDE included ADRs (type and incidence), serious AEs (SAEs), AEs of special interest (including hypersensitivity symptoms), and change in hematology parameters (i.e., change in serum sodium, serum potassium, and serum calcium).[11]

In the FERWON-IDA trial, the co-primary end point adjudicated serious or severe hypersensitivity reactions (starting on or after the first treatment dose). The adjudicators of serious or severe hypersensitivity reactions were blinded to treatments, which were performed by an independent clinical end point adjudication committee. Hypersensitivity terms defined by a standardized set of the *Medical Dictionary for Regulatory Activities* were used in FERWON-IDA. Secondary safety end points evaluated by FERWON-IDA included the number of adjudicated composite cardiovascular AEs (starting on or after the first randomized treatment) and the incidence of hypophosphatemia defined as serum phosphate of 2.0 mg/dL or less.[16]

Statistical Analysis

PROPOSE and FERWON-NEPHRO

Details on the FERWON-NEPHRO statistical analysis plan were not available.[14] Statistical analysis for PROPOSE is provided as follows.

Primary Outcome(s) of the Studies

Power Calculation: The PROPOSE trial referenced a previous trial (P-Monofer-CKD-01) and justified the selection of the NIM on clinical results from the previous trial. PROPOSE assumed that approximately 90% of participants receiving 500 mg of iron isomaltoside 1000 would be able to maintain an Hb level between 9.5 g/dL and 12.5 g/dL at week 6. Thus, 10% points were used to define the NIM. Using a stratified blocked 2:1 randomization, a two-sided significance level of 0.05, and a NIM of 10% points, there was approximately 80% power to demonstrate noninferiority with 214 participants and 107 participants in iron isomaltoside 1000 and iron sucrose, respectively. The PP power calculation assumed approximately 10% of participants would have a major protocol violation, and determined 234 participants and 117 participants needed to be randomized to iron isomaltoside 1000 and iron sucrose, respectively, to demonstrate noninferiority.[9]

The power calculation for the FERWON-NEPHRO trial was not available. The NIM for the co-primary safety end point in FERWON-NEPHRO of serious or severe hypersensitivity reactions was set at less than 3% for the upper boundary of the 95% CI. FERWON-NEPHRO referenced a previous trial (IDA-301) and justified the selection of the NIM on the clinical results from a previous trial. Noninferiority on the primary efficacy end point between iron isomaltoside 1000 and iron sucrose could be declared if the lower boundary of the 95% CI was above –0.5 g/dL.[14]

Statistical Model: The primary analysis of PROPOSE was designed to evaluate noninferiority between iron isomaltoside 1000 and iron sucrose for the primary end point. A generalized linear model using the identity link function was used to compare the proportion of participants with Hb concentration between 9.5 g/dL and 12.5 g/dL (both values included) at week 6 using the last observation carried forward (LOCF) method for both FAS and PP study populations. The primary analysis was also conducted using the unadjusted and adjusted risk difference method with missing values accounted by LOCF, missing values (early dropouts) imputed as failures (i.e., participants who did not complete six weeks of treatment were categorized as nonresponders and, for observed cases only, listed in the FAS and PP datasets). Treatment and stratum (s-ferritin < 100 versus ≥ 100) were used as factors and baseline values as covariate. No adjustments for multiplicity were performed. No interim analyses were planned; however, serum phosphate was analyzed after 25 participants, 50 participants, and 100 participants were exposed to iron isomaltoside 1000 as a planned safety assessment. All statistical tests were two-tailed and the significance level was 0.05.[9]

Post-Hoc Efficacy Analysis: PROPOSE conducted a post-hoc efficacy analysis to assess the proportion of participants who were able to maintain an Hb level of 9.5 g/dL or more at week 6. The post-hoc analysis followed the primary analysis plan; however, due to non-convergence of the adjusted model, only the unadjusted model in observed cases was used.[9]

Secondary Outcomes of the Studies

The PROPOSE trial used a mixed-effects model for repeated measures (MMRM) analysis to compare the average change in Hb concentration from baseline to week 2, week 4, and week 6, change in s-ferritin, change in TSAT, change in s-iron and reticulocyte count from baseline to week 1, week 2, week 4, and week 6, and the change in QoL score (LASA) at week 4 and week 6. Treatment, visit, treatment x visit interactions, country, and stratum (s-ferritin < 100 mcg/L versus ≥ 100 mcg/L) were used as factors and baseline values as covariates. Visit x treatment estimate for the applicable week was used as the estimate model.[9]

In PROPOSE, an analysis of covariance model was used to compare the change in RLS (CH-RLSq) from baseline to week 6 in participants with RLS. Treatment and stratum (s-ferritin < 100 versus ≥ 100) were used as factors and baseline RLS score values as covariates.[9]

All statistical tests on secondary outcome variables were two-tailed and the significance level was 0.05.[9]

No subgroup analyses were planned or conducted for the PROPOSE trial.[9]

PROVIDE and FERWON-IDA

Primary Outcome(s) of the Studies

Power Calculation: PROVIDE referenced a previous trial (P-Monofer-IBD-01) and justified the selection of the NIM on clinical results from the previous trial. PROVIDE assumed that 80% of participants receiving iron isomaltoside 1000 and iron sucrose would achieve an increase in Hb of at least 2 g/dL. The NIM was set at 12.5% points. Using a stratified blocked 2:1 randomization and a two-sided significance level of 5%, there would be 90% power to demonstrate noninferiority with an absolute NIM of 12.5% points with 300 participants and 150 participants (N = 450) in the iron isomaltoside 1000 and iron sucrose groups, respectively. The PP power calculation assumed that approximately 10% of participants would have major protocol violations and determined that a total of 500 participants had to be randomized to demonstrate noninferiority in both the FAS and PP datasets.[11]

In FERWON-IDA, the significance level was set at 0.05 for both co-primary end points (safety and efficacy). With 1,000 participants in the iron isomaltoside 1000 group, the power calculation was 88% to show that the upper boundary of the 95% CI of treatment-emergent serious or severe hypersensitivity reactions was less than 3%. With 500 participants in the iron sucrose group, power calculations for FERWON-IDA for the co-primary efficacy end point of change in Hb from baseline to week 8 assumed no difference between treatment groups and a common SD of 1.5 g/dL. The power calculation was 100% for demonstrating noninferiority using a NIM of –0.5 g/dL. FERWON-IDA referenced a previous trial (IDA-301) and justified the selection of the NIM on the clinical results from a previous trial. The total power calculation for demonstrating both primary end points was 88%. Noninferiority of the primary efficacy end point between iron isomaltoside 1000 and iron sucrose could be declared if the lower boundary of the 95% CI was above –0.5 g/dL.[16]

Statistical Model: In the PROVIDE trial, the risk difference was used to compare the primary end point (i.e., the number of participants with increase in Hb of 2 g/dL or more from baseline to any time between week 1 and week 5). Risk difference and corresponding two-

sided 95% CI of the difference in percentage of participants were calculated and adjusted for strata (screening Hb [< 10 g/dL and ≥ 10 g/dL] and type of disease [gastroenterology, gynecology, oncology, and others]) using the Cochran–Mantel–Haenszel method. The primary analysis was performed on FAS and PP datasets to ensure the robustness of the noninferiority analyses. The primary analysis did not use baseline Hb (i.e., Hb) as a covariate because it was not suitable to adjust for continuous covariates using the Cochran–Mantel–Haenszel method. Noninferiority could be declared if both the FAS and PP analyses were similar and the lower bound of the 95% CI was greater than –12.5% points. Superiority was declared if the lower bound of the 95% CI was greater than 0.

P values were calculated if superiority was determined. Sensitivity analyses were conducted to calculate the unadjusted risk differences in the FAS and PP datasets. Statistical analyses for all end points in the PROVIDE trial (with the exception of the FACIT scale and the SF-36 questionnaire) were conducted with observed cases and no imputation of missing data. No statistical adjustments for multiplicity were made for the primary analyses. Subgroup analyses on the primary end point were planned a priori and conducted by strata (screening Hb [< 10.0 g/dL and ≥ 10.0 g/dL]) and type of disease [gastroenterology, gynecology, oncology, and others]). Exploratory subgroup analysis based on the underlying cause of IDA was also conducted for the primary end point. An interim analysis, performed by an independent sponsor statistician, was performed April 8, 2015, to re-estimate the PROVIDE trial sample size. The risk difference of the response rate without adjustment and the SD of the overall primary response were used to perform the interim sample size calculation.[11]

FERWON-IDA analyzed the co-primary efficacy end point of change in Hb from baseline to week 8 using an MMRM with a restricted maximum likelihood-based method to test for noninferiority between treatment groups. The statistical model included the fixed, categorical effects of treatment, week, treatment x week interaction, strata and the continuous covariates of baseline Hb and Hb x week interaction. Strata used were underlying disease (gastroenterology, gynecology, oncology, and others) and baseline cardiovascular risk (history of myocardial infarction, stroke, or congestive heart failure). Noninferiority between treatments could be declared if the lower boundary of the 95% CI was greater than –0.5 g/dL. The co-primary efficacy end point was performed in ITT, FAS, and PP datasets. The co-primary safety end point was analyzed using the ITT dataset and the safety objective was reached if the upper boundary of the 95% CI was less than 3%. The risk difference for the co-primary safety end point between treatment groups was calculated with associated 95% CI.[16]

Secondary Outcomes of the Studies

Secondary end points for the PROVIDE and FERWON-IDA trials were two-tailed and the significance level was 0.05.[11,16]

The PROVIDE trial analyzed the secondary end point of time to an increase in Hb of 2 g/dL or more using the Kaplan–Meier method and tested the null hypothesis of no treatment difference between study groups with a log-rank test. A Cox proportional hazards model, using treatment and strata as factors and baseline Hb as a covariate, was also used to analyze time to an Hb increase of 2 g/dL or more. The Efron method was used to manage ties. Estimated hazard ratios with corresponding 95% Wald CIs and P value for iron isomaltoside 1000 compared with iron sucrose were provided. Missing events of time to an Hb increase of 2 g/dL or more were managed using censoring.[11]

PROVIDE used MMRM to compare the other secondary end points of change in Hb, s-ferritin, TSAT, s-iron, fatigue symptoms (FACIT-FS scores), and QoL measures (i.e., the eight health domain scores and the PCS and MCS scores of the SF-36) from baseline to the specified follow-up week. The MMRM used treatment, visit, treatment x visit interactions, and strata as factors, and baseline values as covariates. Secondary end points were analyzed with observed cases (i.e., no imputation of missing data) with the exception of the FACIT scale and SF-36 questionnaire. Items missing from the FACIT scale were handled by imputing the average of the non-missing items for the participant and visit where less than 50% of the FACIT items (6 out of 13) were missing. The half-scale rule was employed for missing values on the SF-36 questionnaire. The score was calculated if a minimum of 50% of the items were answered for a participant at the relevant visit. The missing items were imputed by averaging the non-missing items. Sensitivity analyses were conducted using only observed cases (i.e., without imputation of missing items) for change in FACIT scores and for the eight health domain scores and the PCS and MCS scores of the SF-36. No adjustments for multiplicity were made for the secondary analyses in PROVIDE.[11]

FERWON-IDA secondary efficacy end points were tested for superiority. A repeated measures logistic regression model with treatment, visit, strata, and treatment x visit interaction as fixed effects and baseline values as covariate was used to analyze the incidence of participants with an increase in Hb of 2 g/dL or more from baseline to week 1, week 2, week 4, and week 8. The Kaplan–Meier method was used to analyze time to an Hb increase of 2 g/dL or more and a two-sided log-rank test was used to test for treatment differences. The average change in Hb, s-ferritin, TSAT, and fatigue symptoms were analyzed using the MMRM, with treatment, week, treatment x week interaction, and strata as factors and baseline value x week interactions as covariates. A logistic regression model with treatment and strata as fixed effects was used to evaluate and compare the incidence of participants who reached an s-ferritin level of 100 mcg/L or more and TSAT of 20% to 50%. Secondary safety end points in FERWON-IDA used the Fisher's exact test to analyze the difference between treatments for the secondary safety end points (i.e., incidence of composite AEs and frequency of participants with ADRs).[16]

Analysis Populations

Details on the FERWON-NEPHRO analysis populations were not available.[14]

The study populations of the PROPOSE and FERWON-IDA trials were separated into four distinct datasets: randomized population or intention-to-treat (ITT), FAS, PP, and safety population.[9,16] PROVIDE utilized three distinct datasets: FAS, PP, and safety population.[11] Definitions of each dataset were similar across the three trials and were as follows:

- Randomized: Included all participants in the PROPOSE and FERWON-IDA trials who were randomized in the studies as per study protocol criteria.[11,16]
- FAS: Included all participants in the PROPOSE, PROVIDE, and FERWON-IDA trials who were randomized in the studies, received at least one dose of the study drug, and had at least one post-baseline Hb assessment. Subjects were included as randomized, regardless of the treatment they actually received.[9,11,16]
- PP: Included all participants in the PROPOSE and FERWON-IDA FAS trials who did not have any major protocol deviation of clinical or statistical relevance. Subjects (data) with a major protocol deviation deemed to have substantial impact on efficacy measurements were excluded from the PP dataset.[9,16] The PP analysis for PROVIDE included all participants in the FAS who did not have a major protocol deviation.[11]

- Safety population: All PROPOSE, PROVIDE, and FERWON-IDA participants who were randomized and received at least one dose of iron isomaltoside 1000 or iron sucrose.[9,11,16]

Results

Patient Disposition

PROPOSE and FERWON-NEPHRO

Details on participant disposition in the FERWON-NEPHRO trial were not available.[14]

Overall, a total of 351 PROPOSE participants were randomized (234 iron isomaltoside 1000 and 117 iron sucrose); 323 (92%) completed the study and 28 (8%) discontinued the study. The proportion of participants who discontinued the PROPOSE trial was greater for those receiving iron isomaltoside 1000 compared with iron sucrose (10.1% versus 3.4%, respectively). AEs were the most common reason given for iron isomaltoside 1000 participants discontinuing the PROPOSE trial (4.70%) and the least common for iron sucrose participants (0.85%). Discontinuation of the trial due to death occurred in three iron isomaltoside 1000 participants (1.3%) and none of the iron sucrose participants. Withdrawal of consent by participant and screen failure occurred slightly more frequently in the iron isomaltoside 1000 group (2.56% and 1.38%, respectively) compared with the iron sucrose group (1.70% and 0.0%, respectively).[9]

PROVIDE and FERWON-IDA

The proportion of participants who discontinued the trial was similar for the PROVIDE trial (7.3% for iron isomaltoside 1000 and 10.1% for iron sucrose)[11] and the FERWON-IDA trial (10.1% for iron isomaltoside 1000 and 10.7% for iron sucrose).[16] The most common reason for discontinuing the trial early was lost to follow-up for the iron sucrose arm of PROVIDE (3.0%)[11] and both treatment groups of FERWON-IDA (4.9% iron isomaltoside 1000 and 4.2% iron sucrose).[16] In contrast, fewer iron isomaltoside 1000 PROVIDE participants were lost to follow-up (1.5%).[11] Withdrawal of consent by participant was the second most common reason for discontinuing the trial early for the iron sucrose arm of PROVIDE (3.6%)[11] and both treatment groups of FERWON-IDA (2.8% for iron isomaltoside 1000 and 4.0% for iron sucrose).[16] Iron isomaltoside 1000 participants in PROVIDE gave withdrawal of consent by participant (1.8%) less frequently as the reason for discontinuing the trial.[11] Study discontinuation due to death occurred once for the iron isomaltoside 1000 treatment groups in both PROVIDE and FERWON-IDA.[11,16]

Table 8 presents the patient disposition data for the PROPOSE, FERWON-NEPHRO, PROVIDE, and FERWON-IDA trials.

Table 8: Patient Disposition

	CKD studies				IDA studies			
	PROPOSE		FERWON-NEPHRO		PROVIDE		FERWON-IDA	
	IIM	IS	IIM	IS	IIM	IS	IIM	IS
Screened, N	660		-		1,112		3,108	
Randomized, N	234	117	1,538		342	169	1,009	503
Subjects completed study, N (%)	210 (89.7)	113 (96.6)	-	-	317 (92.7)	152 (89.9)	907 (89.9)	449 (89.3)
Discontinued, N (%)	24 (10.1)	4 (3.4)	-	-	25 (7.3)	17 (10.1)	102 (10.1)	54 (10.7)
Reason for discontinuation, N (%)								
Lost to follow-up	-	-	-	-	5 (1.5)	5 (3.0)	49 (4.9)	21 (4.2)
Adverse events	11 (4.70)	1 (0.85)	-	-	5 (1.5)	5 (3.0)	7 (0.7)	3 (0.6)
Death	3 (1.3)	-	-	-	1 (0.3)	-	1 (0.1)	-
Withdrawal of consent by participant	6 (2.56)	2 (1.70)	-	-	6 (1.8)	6 (3.6)	28 (2.8)	20 (4.0)
Investigator decision	1 (0.43)	-	-	-	1 (0.3)	-	9 (0.9)	4 (0.8)
Protocol violation	-	-	-	-	2 (0.6)	1 (0.6)	1 (0.1)	2 (0.4)
Sponsor request	-	-	-	-	1 (0.3)	-	-	1 (0.2)
Lack of efficacy	-	-	-	-	-	-	1 (0.1)	-
Other reasons	3 (1.28)	1 (0.85)	-	-	2 (0.6)	-	7 (0.7)	3 (0.6)
Other (randomized but screen failure)	3 (1.28)	-	-	-	-	-	-	-
ITT, N	234	117	-	-	342	169	1,009	503
FAS, N	226	115	-	-	330	161	972	485
PP, N	199	107	-	-	454	311	901	437
Safety, N	230	114	-	-	333	168	989	494

CKD = chronic kidney disease; FAS = full analysis set; IDA = iron deficiency anemia; IIM = iron isomaltoside 1000; IS = iron sucrose; ITT = intention-to-treat; PP = per-protocol.

Source: Clinical Study Reports for PROPOSE[9] and PROVIDE,[11] and publications for FERWON-NEPHRO[14] and FERWON-IDA.[16]

Exposure to Study Treatments

PROPOSE and FERWON-NEPHRO

Details on exposure to study treatments for the FERWON-NEPHRO trial were not available.[14]

A cumulative dose of 500 mg of IV iron was administered to all participants in the PROPOSE trial. Iron isomaltoside 1000 was given as either a single IV bolus injection of 500 mg at baseline or over three fractionated doses of 100 mg at baseline and 200 mg at week 2 and at week 4. Iron sucrose was administered in fractionated doses of 100 mg at baseline and 200 mg at week 2 and at week 4.[9]

The mean rate of IV iron administration was shorter for participants receiving iron isomaltoside 1000 compared to iron sucrose. Iron isomaltoside 1000 participants received a mean IV bolus injection rate of 2.32 minutes, 2.72 minutes, and 2.37 minutes for baseline, week 2, and week 4, respectively. The mean duration of iron sucrose administration was 5.01 minutes, 8.64 minutes, and 8.74 minutes for baseline, week 2, and week 4, respectively.[9]

PROVIDE and FERWON-IDA

Of the PROVIDE trial's 342 participants and 169 participants randomized to iron isomaltoside 1000 and iron sucrose, respectively, 333 participants were exposed to iron isomaltoside 1000 and 168 participants were exposed to iron sucrose. The majority of iron isomaltoside 1000 participants (49%) received 1,500 mg, 39% received 2,000 mg, and 9.6% received 1,000 mg. Approximately 96% of iron isomaltoside 1000 participants given 1,000 mg received one dose and the majority of iron isomaltoside 1000 participants given between 1,500 mg and 2,000 mg (96%) received two doses. In the iron sucrose arm of PROVIDE, 23.2% of participants received five doses (1,000 mg), 30.4% received six doses (1,200 mg), 17.3% received seven doses (1,400 mg), 8.9% received eight doses (1,600 mg), and 7.7% received nine doses (1,800 mg). Fewer than 4% of iron sucrose participants received 10 doses (2,000 mg).[11]

Of the FERWON-IDA trial's 1,009 participants and 503 participants randomized to iron isomaltoside 1000 and iron sucrose, respectively, 989 participants received iron isomaltoside 1000 and 494 participants received iron sucrose. All iron isomaltoside 1000 participants in FERWON-IDA received a single IV infusion. The majority of iron sucrose participants (80%) received 4.5 administrations.[16]

The mean cumulative iron dose received by participants was greater in PROVIDE (1,640.20 mg [SD 357.6] iron isomaltoside 1000 and 1,127.9 mg [SD 343.3] iron sucrose)[11] than in FERWON-IDA (975 mg [SD 145] and 905 mg [SD 217] iron sucrose).[16] Iron isomaltoside 1000 participants received a higher cumulative iron dose in both trials compared with iron sucrose participants.[11,16]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported as follows. See Appendix 3 for detailed efficacy data.

PROPOSE and FERWON-NEPHRO

Change in Mean Hb

In the PROPOSE trial, the mean change in Hb was not statistically different between the iron isomaltoside 1000 group and the iron sucrose group from baseline to week 2, week 4, and week 6. The treatment difference for change in Hb levels between iron isomaltoside 1000 and iron sucrose from baseline to week 2 and week 6 was 0.1138 (95% CI, –0.031 to 0.259) and –0.0069 (95% CI ,–0.204 to 0.246), respectively. The absolute mean Hb levels at baseline for iron isomaltoside 1000 and iron sucrose were similar at baseline (11.20 g/dL and 11.08 g/dL, respectively), at week 2 (11.24 g/dL and 11.03 g/dL, respectively), at week 4 (11.22 g/dL and 11.05 g/dL, respectively), and at week 6 (11.13 g/dL and 11.01g/dL, respectively) (see Table 9 and Appendix 3).[9]

The mean change in Hb from baseline to week 8 was the co-primary efficacy end point in the FERWON-NEPHRO trial. Iron isomaltoside 1000 was found to be noninferior to iron sucrose for the mean change in Hb from baseline to week 8. The mean change in Hb levels for iron isomaltoside 1000 from baseline to week 1, week 2, and week 4 were 0.43 g/dL, 0.75 g/dL, and 1.06 g/dL respectively. The mean change in Hb levels for iron sucrose from baseline to week 1, week 2, and week 4 were 0.21 g/dL, 0.50 g/dL, and 0.91 g/dL, respectively. The treatment differences in change in mean Hb levels between iron isomaltoside 1000 and iron sucrose were statistically significant from baseline to week 1

(P < 0.0001) and week 2 (P < 0.0001), but not for week 4 (P = 0.021) (see Table 9 and Appendix 3).[14]

Proportion of Subjects Who Were Able to Maintain Hb Between 9.5 g/dL and 12.5 g/dL (Both Values Included) at Week 6

The primary efficacy end point for the PROPOSE trial was the proportion of participants who were able to maintain Hb levels between 9.5 g/dL and 12.5 g/dL at week 6. The findings of the PROPOSE adjusted analyses with the LOCF method were consistent between FAS and PP datasets and showed iron isomaltoside 1000 was noninferior to iron sucrose in the proportion of participants who were able to maintain Hb between 9.5 g/dL and 12.5 g/dL at six weeks. The FAS adjusted analysis, with LOCF method, found that 187 participants (82.7%) and 95 participants (82.6%) treated with iron isomaltoside 1000 and iron sucrose, respectively, were able to maintain an Hb level between 9.5 g/dL and 12.5 g/dL from baseline to week 6. The PP analysis was similar: 167 participants (83.9%) and 88 participants (82.2%) treated with iron isomaltoside 1000 and iron sucrose, respectively, maintained Hb between 9.5 g/dL to 12.5 g/dL at week 6. The adjusted risk difference comparing iron isomaltoside 1000 to iron sucrose for the FAS and PP primary analyses was comparable (1% point [95% CI, –7.4 to 9.4] and 2.2% points [95% CI, –6.4 to 10.9], respectively) and noninferiority was declared between iron isomaltoside1000 and iron sucrose by the test of noninferiority for both datasets (FAS: P = 0.0106; PP: P = 0.0057). Superiority (i.e., statistical differences) could not be claimed as both 95% CIs for FAS and PP datasets included the value 0 (Table 9).[9]

Using the primary efficacy end point of proportion of participants who were able to maintain Hb between 9.5 g/dL and 12.5 g/dL, the PROPOSE trial conducted adjusted and unadjusted sensitivity analyses (with the LOCF method, missing values as failures, and observed cases) in both the FAS and PP datasets. Noninferiority of iron isomaltoside 1000 compared with iron sucrose held for all sensitivity analyses and datasets, with the exception of the FAS unadjusted analysis with missing values imputed as failures (P = 0.0840), as the 95% CI for the risk difference between iron isomaltoside 1000 and iron sucrose was outside of –10% points (–2.1% [95% CI, –11.1 to 6.8]).[9]

Proportion of Subjects Who Maintained Hb 9.5 g/dL or More at Week 6

In the PROPOSE trial, post-hoc analyses of the proportion of participants who maintained an Hb of 9.5 g/dL or more at six weeks found that this proportion was comparable between iron isomaltoside 1000 and iron sucrose in the FAS dataset for the unadjusted analysis (iron isomaltoside 1000: 92.6%; iron sucrose: 92.0%), for the unadjusted analysis with the LOCF method (iron isomaltoside 1000: 92.5%; iron sucrose: 92.2%), and for the unadjusted analysis with imputed missing value as failure approach (iron isomaltoside 1000: 88.5%; iron sucrose: 90.4%). Iron isomaltoside 1000 was declared noninferior to iron sucrose for each of the aforementioned unadjusted analyses using the PROC FREQ noninferiority test (unadjusted P = 0.0006; unadjusted with LOCF P = 0.0008; unadjusted with imputed missing value as failure method P = 0.0202). Adjusted analyses were not performed due to the non-convergence of the adjusted model (see Appendix 3).[9]

Change in Mean S-Ferritin

In the PROPOSE trial, the treatment difference for the mean change in s-ferritin levels in the FAS dataset between iron isomaltoside 1000 and iron sucrose from baseline to week 2 and week 4 were 123.36 mcg/L (95% CI, 96.449 to 150.271) and 49.3393 mcg/L (95% CI, 18.174 to 80.505), respectively, in favour of iron isomaltoside 1000 (P < 0.0001 and P =

0.0020). At the end of the study (week 6), the mean change in s-ferritin level treatment difference was small and no statistical differences were found between iron isomaltoside 1000 and iron sucrose (treatment difference: –15.0585 mcg/L [95% CI, –54.196 to 24.079; P = 0.4489]) (see Table 9 and Appendix 3).[9]

The secondary end point of mean change in s-ferritin was not reported in FERWON-NEPHRO.[14]

Change in Mean TSAT, S-Iron, and Reticulocyte Count

In the PROPOSE trial, TSAT and s-iron concentrations increased from baseline to week 2, week 4, and week 6 for both iron isomaltoside 1000 and iron sucrose treatment groups. However, the treatment differences (change from baseline to the relevant weeks) were small and statistically non-significant. The treatment difference for TSAT in the FAS dataset between iron isomaltoside 1000 and iron sucrose from baseline to week 2 was 1.1992% (95% CI, –1.350 to 3.748; P = 0.355) and –0.0207 (95% CI, –2.118 to 2.077) from baseline to week 6. For s-iron, the treatment difference between iron isomaltoside 1000 and iron sucrose from baseline to week 2 and week 6 was 0.3761 (95%CI, –0.797 to 1.549; P = 0.5277) and 0.0066 (95% CI, –0.965 to 0.978; P = 0.9894), respectively.[9]

In the PROPOSE trial, the treatment difference in reticulocyte count between iron isomaltoside 1000 and iron sucrose from baseline to week 1 was 0.1540 (95% CI, 0.066 to 0.242) and favoured iron isomaltoside 1000 (P = 0.0006). However, the change in reticulocyte count from baseline to week 2, week 4, and week 6 was small and non-significant between the iron isomaltoside 1000 and iron sucrose groups (see Appendix 3).[9]

The secondary end point of mean change in TSAT was not reported in FERWON-NEPHRO.[14]

Change in QoL

In the PROPOSE trial, small increases were found in the absolute mean LASA energy level scores for iron isomaltoside 1000 and iron sucrose from baseline (57.98 [SD 21.31]) and 62.14 [SD 20.30], respectively) and to week 6 (62.20 [SD 22.21] and 64.46 [SD 19.96], respectively). The treatment difference at week 6 between study arms was 0.1111 (95% CI, –3.667 to 3.889) and did not favour either treatment group (P = 0.9539). Similar results were attained for the LASA QoL measure of ability to do daily activities and overall QoL. The mean LASA ability to do daily activities score for iron isomaltoside 1000 was increased from 61.34 (SD 23.57) at baseline to 64.94 (SD 23.16) at week 6 and iron sucrose increased from 65.43 (SD 22.51) at baseline to 68.26 (SD 23.02) at week 6. The treatment difference in LASA ability to do daily activities score at week 6 was –0.8519 (95% CI, –4.829 to 3.125) and did not favour either treatment group (P = 0.6734). Minimal increases in the LASA overall QoL were observed over the study period for iron isomaltoside 1000 (baseline: 64.46 [SD 20.99]; week 6: 66.40 [SD 21.13]) and iron sucrose (baseline: 68.31 [SD 20.24]; week 6: 68.34 [SD 20.99]). The treatment difference was 0.4718 (95% CI, –3.125 to 4.069) and not statistically significant (P = 0.7964) (see Table 9).[9]

Change in RLS Symptoms

The decrease in the PROPOSE trials' CH-RLSq for the FAS dataset was non-significant between the iron isomaltoside 1000 group and iron sucrose group from baseline to week 6 (treatment difference: 0.4033 [95% CI, –1.880 to 2.686; P = 0.7267]) (see Table 9).[9]

PROVIDE and FERWON-IDA

Change in Mean Hb

Hb levels in the PROVIDE and FERWON-IDA trials increased from baseline to end of study for both iron isomaltoside 1000 and iron sucrose.[11,16]

In the PROVIDE trial, the mean change in Hb from baseline to week 2 and week 4 was statistically significantly greater for iron isomaltoside 1000 compared with iron sucrose. The estimated difference in mean Hb levels between iron isomaltoside 1000 from baseline to week 2 was 0.70 g/dL (95% CI, 0.53 to 0.86; P < 0.0001) and 0.60 g/dL (95% CI, 0.44 to 0.77; P < 0.0001) from baseline to week 4. At the study end point, PROVIDE found that the mean change in Hb from baseline to week 5 remained statistically greater for iron isomaltoside 1000 compared with iron sucrose (treatment difference: 0.46 g/dL (95% CI, 0.30 to 0.62); P < 0.0001).[11]

In the FERWON-IDA trial, the co-primary efficacy end point of change in Hb level from baseline to study end point of week 8 showed that iron isomaltoside 1000 was noninferior to iron sucrose as the lower boundary of the 95% CI for the treatment difference was greater than –0.5 g/dL in the ITT dataset (treatment difference estimate: 0.00 [95% CI, –0.13 to 0.13]), the FAS dataset (treatment difference estimate: 0.01 [95% CI, –0.12 to 0.14]) and the PP dataset (treatment difference estimate: 0.01 [95% CI, –0.12 to 0.14]). FERWON-IDA tested iron isomaltoside 1000 for superiority against iron sucrose for the co-primary efficacy end point and found iron isomaltoside 1000 was not superior to iron sucrose for the change in Hb level from baseline to week 8 in the ITT dataset (P = 0.977), FAS dataset (P = 0.834), and PP dataset (P = 0.871). Although FERWON-IDA did not provide the detailed results for the mean change in Hb at week 2, it did report that the mean change was statistically significantly larger in iron isomaltoside 1000 compared with iron sucrose (P < 0.0001).[16]

Proportion of Subjects With Hb Increase of 2 g/dL or More

The PROVIDE and FERWON-IDA trials defined responders as the proportion of participants with an Hb increase of 2 g/dL or more from baseline to the relevant study time point.[11,16]

The primary efficacy analysis of PROVIDE demonstrated that there were more responders from baseline to any time between week 1 and week 5 in the iron isomaltoside 1000 group (FAS dataset: 68.5%; PP dataset: 70.1%) compared with iron sucrose (FAS dataset: 51.5%; PP dataset: 53.8%). The risk difference in the FAS dataset (16.7% [95% CI, 7.5 to 25.7]) and the PP dataset (15.9% [95% CI, 6.3 to 25.4]) both showed iron isomaltoside 1000 was noninferior to iron sucrose as the lower end of the 95% CI for the risk difference was greater than –12.5% in both FAS and PP analyses. Since noninferiority was declared, the test for superiority was performed and found iron isomaltoside 1000 to be superior to iron sucrose for the proportion of responders at any time from week 1 to week 5 (FAS dataset: P < 0.0001; PP dataset: P = 0.0002).[11]

The FERWON-IDA trial found the proportion of responders at week 2 to be statistically greater in iron isomaltoside 1000 (32.6%) compared with iron sucrose (20.8%) in the ITT dataset (odds ratio: 2.42 [95% CI, 1.80 to 3.26]; P < 0.0001). However, the proportion of responders at week 8 was 67.1% and 68.1% for iron isomaltoside 1000 and iron sucrose, respectively, and was not statistically different (odds ratio: 1.05 [95% CI, 0.80 to 1.38]; P = 0.703) (see Table 10).[16]

Time to Increase Hb by 2 g/dL or More

The median time to increase Hb by 2 g/dL or more was found to be shorter for iron isomaltoside 1000 (26 days) compared to iron sucrose (28 days) in the PROVIDE trial (hazard ratio: 2.488 [95% CI, 1.916 to 3.230]; P < 0.0001).[11] In contrast, the median time to increase Hb by 2 g/dL or more was identical for both treatment groups in the FERWON-IDA trial (28 days) (see Table 10).[16]

Change in Mean S-Ferritin

S-ferritin concentration levels increased in both the iron isomaltoside 1000 group and the iron sucrose group from baseline to the relevant study time points in the PROVIDE trial (week 2 and week 5)[11] and in the FERWON-IDA trial (week 2 and week 8).[16] In PROVIDE, the difference in the mean increase in s-ferritin level from baseline to week 2 was greater for iron isomaltoside 1000 (825.4 mcg/L [SD: 5,548.1]) than for iron sucrose (126.2 mcg/L [SD 87.2]) and favoured iron isomaltoside 1000 (treatment difference: 702.9 mcg/L [95% CI, 313.9 to 1,091.9; P = 0.0004]).[11] Comparable results were found for FERWON-IDA. The mean increase in s-ferritin at week 2 was again greater in iron isomaltoside 1000 compared with iron sucrose and the difference favoured iron isomaltoside 1000 (P < 0.0001).[16] For PROVIDE and FERWON-IDA, the difference in the mean increase of s-ferritin from baseline to end of study (week 5 and week 8, respectively) was non-significant between iron isomaltoside 1000 and iron sucrose for PROVIDE (treatment difference: 58.5 mcg/L [95% CI, – 333.7 to 450.6]; P = 0.770)[11] and FERWON-IDA (no mean difference and 95% CI reported) (see Table 10).[16]

Change in TSAT and S-Iron

In the PROVIDE trial, the mean TSAT change from baseline was significantly greater for iron isomaltoside 1000 (17.9% [SD 9.8]) than for iron sucrose (5.7% [SD 6.8]) at week 2 and favoured iron sucrose 1000 (treatment difference: 11.98% [95% CI, 10.37 to 13.59]; P < 0.0001).[11] The results in the FERWON-IDA trial for the mean TSAT change at week 2 were comparable and also favoured iron isomaltoside 1000 over iron sucrose (P = 0.0001).[16] At the end of the study, PROVIDE found iron isomaltoside 1000 had a significantly greater mean TSAT change from baseline to week 5 compared with iron sucrose (treatment difference: 3.50 [95% CI, 1.89 to 5.10]; P < 0.0001).[11] In contrast, the treatment difference between study groups was not significant in FERWON-IDA at week 8 for mean change in TSAT (P = 0.016) (see Appendix 3).[16]

Only the PROVIDE trial evaluated the mean change in s-iron from baseline to relevant study time points. The mean change from baseline to week 2 in s-iron was markedly greater in iron isomaltoside 1000 (10.94 µmol/L [SD: 7.41]) compared with iron sucrose (3.71 µmol/L [SD 5.64]) and the treatment difference favoured iron isomaltoside 1000 (treatment difference: 6.94 µmol/L [95% CI, 5.84 to 8.04]; P < 0.0001). At the end of the study (week 5), the mean change in s-iron from baseline was similar for the iron isomaltoside 1000 group (7.75 µmol/L [SD: 5.84]) and the iron sucrose group (6.71 µmol/L [SD: 7.37]), and the treatment difference was not statistically significant between the study groups (0.76 µmol/L [95% CI, 0.34 to 1.85]; P = 0.1777) (see Appendix 3).[11]

Change in QoL

In the PROVIDE trial, QoL was evaluated using the SF-36. The mean change in the eight health domains and for the two composite scores (MCS and PCS) increased from baseline to week 2 and week 5, indicating improved health status. However, no statistically

significant differences between iron isomaltoside 1000 and iron sucrose were found for any of the SF-36 measures at either study end point.[11]

Change in FACIT-FS Scores

The median and mean FACIT-FS scores at baseline in the PROVIDE and FERWON-IDA trials, respectively, were less than 30 for the iron isomaltoside 1000 group and the iron sucrose group, indicating that the majority of participants in both trials, regardless of treatment group, had severe fatigue at the beginning of the trials. Improvements in FACIT-FS scores from baseline to week 5 and week 8 for PROVIDE and FERWON-IDA, respectively, showed that iron isomaltoside 1000 participants and iron sucrose participants no longer had severe fatigue at the end of the study periods.[11,16] In PROVIDE, the median FACIT-FS scores at baseline and week 5 were 22.0 and 42.0, respectively, for iron isomaltoside 1000, and 23.0 and 43.0, respectively, for iron sucrose.[11] In FERWON-IDA, the mean FACIT-FS score increased from baseline to week 8 in iron isomaltoside 1000 participants from 25.72 to 39.98 and from 24.63 to 39.93 in iron sucrose participants.[16] A statistically significant difference for the increase in FACIT-FS between IV iron groups from baseline to week 1 was found in PROVIDE and favoured iron isomaltoside 1000 over iron sucrose. However, increases from baseline in FACIT-FS scores were not statistically significant between treatment groups at week 2 (PROVIDE and FERWON-IDA), at week 5 (PROVIDE), and at week 8 (FERWON-IDA).[11,16] Figure 3 and Figure 4 display the mean change in FACIT-FS scores from baseline to end of the study for PROVIDE and FERWON-IDA, respectively.

Subgroups

A subgroup analysis of the primary efficacy end point (i.e., proportion of responders) in the PROVIDE trial was performed across eight strata (see Table 15 and Table 16). The largest subgroups were for screening Hb less than 10 g/dL and gynecology (N = 160) and gastroenterology (N = 87). Across the four strata with screening Hb less than 10 g/dL, iron isomaltoside 1000 was found to be noninferior to iron sucrose in the proportion of responders from baseline to any time between week 1 and week 5, as the lower end of the 95% CI was not greater than –12.5% points. The risk difference between treatments groups in the four strata with Hb less than 10 g/dL was largest for the oncology subgroup (risk difference: 66.7 [95% CI, 13.3 to 100.00]) and similar for the gastroenterology subgroup (15.5 [95% CI, –3.7 to 34.8]), gynecology subgroup (15.0 [95% CI, 1.0 to 28.9]), and other subgroups (risk difference: 15.2 [95% CI –11.4, 41.8]). The screening Hb less than 10 g/dL and gynecology subgroup also demonstrated iron isomaltoside to be superior to iron sucrose (P = 0.0236). The largest subgroups of the four strata with screening Hb of 10 g/dL or more were also in the gynecology and gastroenterology subgroups (N = 77 for both groups). Unlike the strata with screening Hb less than 10 g/dL, noninferiority of iron isomaltoside 1000 compared with iron sucrose was not demonstrated for participants with screening Hb of 10 g/dL or more in the gynecology or gastroenterology subgroups. The magnitude of risk differences was also lower for both gynecology and gastroenterology subgroups with screening Hb of 10 g/dL or more (risk difference: 8.4 [95% CI, –13.5 to 30.2] and risk difference: 10.1 [95% CI, –13.0 to 33.2], respectively). For the two smaller subgroups of participants with screening Hb of 10 g/dL or more, noninferiority between treatments was declared for the oncology subgroup (risk difference: 66.7 [95% CI,13.3 to 100.0]) and superiority of iron isomaltoside 1000 compared with iron sucrose was found for the “other” subgroup (risk difference: 48.0 [95% CI, 28.4 to 67.6]; P = 0.0040).[11]

The PROVIDE trial also conducted an exploratory subgroup analysis of the primary efficacy end point (i.e., proportion of participants with increase in Hb of 2 g/dL or more from baseline to any time between week 1 and week 5) by underlying cause of IDA (Appendix 3). Iron isomaltoside 1000 was found to be noninferior to iron sucrose for each underlying cause of IDA (i.e., gastroenterology, gynecology, oncology, and other). The risk differences between treatment groups was lowest for the gastroenterology cause of IDA subgroup (12.0% points [95% CI, –4.1 to 28.1]) and the gynecology cause of IDA subgroup (13.9% points [95% CI, 0.9 to 26.9]). Oncology and other causes of IDA subgroups were associated with larger risk differences between treatment groups for the proportion of responders (risk difference: 66.7% points [95% CI, 28.9 to 100.0]) and risk difference: 30.6% points [95% CI, 8.3 to 53.0], respectively). Iron isomaltoside 1000 was found to be superior to iron sucrose for the gynecology cause of IDA subgroup (P = 0.0330) and the "other" cause of IDA subgroup (P = 0.0736) (see Appendix 3).

In the PROVIDE trial, analysis of the gynecology subgroup with IDA showed the time required to increase Hb by 2 g/dL or more was significantly less for iron isomaltoside 1000 compared with iron sucrose (hazard ratio: 1.71 [95% CI, 0.19 to 0.89]; P = 0.0026).[11]

Table 9: Key Efficacy Outcomes — CKD Study Populations

	PROPOSE		FERWON-NEPHRO N = 1,538	
	IIM N = 226	IS N = 115	IIM	IS
Hb (g/dL)				
Change in Hb				
Week 2				
FAS				
Number of patients contributing to the analysis	219	115	-	-
Baseline, mean (SD)	11.20 (0.83)	11.08 (0.93)	-	-
End of treatment time point (**2 weeks**), mean (SD)	11.24 (0.88)	11.03 (0.89)	-	-
Change from baseline, mean (SD)	0.04 (0.71)	–0.05 (0.69)	0.75	0.50
LS mean estimate	0.1072	–0.0066	-	-
Treatment group difference vs. control (95% CI)	0.1138 (–0.031 to 0.259)		-	-
SE	0.0737		-	-
P value	0.1239		< 0.0001	
End of study — Week 6				
FAS				
Number of patients contributing to the analysis	216	113	-	-
Baseline, mean (SD)	11.20 (0.83)	11.08 (0.93)	-	-
End of treatment time point (**6 weeks**), mean (SD)	11.13 (1.22)	11.01 (1.12)	-	-
Change from baseline, mean (SD)	–0.07 (1.11)	–0.06 (0.99)	-	-
LS mean estimate	–0.0069	–0.0277	-	
Treatment group difference vs. control (95% CI)	–0.0069 (–0.204 to 0.246)		-	
SE	0.1143		-	
P value	0.8557		-	
End of study — Week 8				

	PROPOSE		FERWON-NEPHRO N = 1,538	
	IIM N = 226	IS N = 115	IIM	IS
FAS				
P value	-	-	IIM noninferior to IS	
Subjects who maintained Hb between 9.5 g/dL and 12.5 g/dL (both values) at 6 weeks				
FAS				
n (%)	187 (82.7)	95 (82.6)	-	-
RD (95% CI) [a]	1.0 (–7.4 to 9.4)		-	-
P value	0.0106		-	-
PP				
n (%)	167 (83.9)	88 (82.2)	-	-
RD (95% CI) [a]	2.2 (–6.4 to 10.9)		-	
P value	0.0057		-	
S-ferritin (mcg/L)				
Change in s-ferritin			-	-
Week 2				
FAS				
Number of patients contributing to the analysis	220	115	-	-
Baseline, mean (SD)	350.88 (186.17)	357.74 (192.98)	-	-
End of treatment time point (**2 weeks**), mean (SD)	492.25 (278.53)	379.18 (198.68)	-	-
Change from baseline, mean (SD)	142.58 (187.82)	20.85 (94.84)	-	-
LS mean estimate	134.6967	11.3367	-	-
Treatment group difference vs. control (95% CI)	123.3600 (96.449 to 150.271)		-	
SE	13.6719		-	
P value	< 0.0001		-	
End of study				
FAS				
Number of patients contributing to the analysis	216	114	-	-
Baseline, mean (SD)	350.88 (186.17)	357.74 (192.98)	-	-
End of treatment time point (**6 weeks**), mean (SD)	487.80 (256.11)	511.77 (267.66)	-	-
Change from baseline, mean (SD)	136.20 (154.59)	156.30 (183.63)	-	-
LS mean estimate	129.8617		-	-
Treatment group difference vs. control (95% CI)	–15.0585 (–54.196 to 24.079)		-	
SE	19.8434		-	
P value	0.4489		-	
QoL measures				
LASA — Energy level				
End of study				
FAS				
Number of patients contributing to the analysis	204	113	-	-

	PROPOSE		FERWON-NEPHRO N = 1,538	
	IIM N = 226	IS N = 115	IIM	IS
Baseline, mean (SD)	57.98 (21.31)	62.14 (20.30)	-	-
End of treatment time point (**6 weeks**), mean (SD)	62.20 (22.21)	64.46 (19.96)	-	-
Change from baseline, mean (SD)	3.9 (18.91)	2.3 (17.54)	-	-
LS mean estimate	4.0874	3.8895	-	-
Treatment group difference versus control (95% CI)	0.1111 (–3.667 to 3.889)		-	
SE	1.9182		-	
P value	0.9539		-	
LASA — Ability to do daily activities				
End of study				
FAS				
Number of patients contributing to the analysis	204	113	-	-
Baseline, mean (SD)	61.34 (23.57)	65.43 (22.51)	-	-
End of treatment time point (**6 weeks**), mean (SD)	64.94 (23.16)	68.26 (23.02)	-	-
Change from baseline, mean (SD)	3.3 (19.60)	2.8 (17.91)	-	-
LS mean estimate	4.9889	4.8968	-	-
Treatment group difference versus control (95% CI)	–0.8519 (–4.829 to 3.125)		-	
SE	2.0186		-	
P value	0.6734		-	
LASA — Overall QoL				
End of study				
FAS				
Number of patients contributing to the analysis	204	113	-	-
Baseline, mean (SD)	64.46 (20.99)	68.31 (20.24)	-	-
End of treatment time point (**6 weeks**), mean (SD)	66.40 (21.13)	68.34 (20.99)	-	-
Change from baseline, mean (SD)	2.0 (18.56)	0.1 (15.65)	-	-
LS mean estimate	0.6786	0.1254	-	-
Treatment group difference vs. control (95% CI)	0.4718 (–3.125 to 4.069)		-	
SE	1.8264		-	
P value	0.7964		-	

CI = confidence interval; CKD = chronic kidney disease; FAS = full analysis set; Hb = hemoglobin; IIM = iron isomaltoside 1000; IS = iron sucrose; LASA = Linear Analog Scale Assessment; LS = least squares; PP = per-protocol; QoL = quality of life; RD = risk difference; s-ferritin = serum ferritin; SD = standard deviation; SE = standard error; vs. = versus.

[a] PROPOSE: Noninferiority was achieved if lower boundary of the 95% CI was greater than –10% points.

Source: Clinical Study Report for PROPOSE[9] and publication for FERWON-NEPHRO.[14]

Table 10: Key Efficacy Outcomes — IDA Study Populations

	PROVIDE		FERWON-IDA	
	IIM N = 342	IS N = 169	IIM N = 1,009	IS N = 503
Hb (g/dL)				
Change in Hb				
Week 2				
FAS (PROVIDE), ITT (FERWON-IDA)				
Number of patients contributing to the analysis	318	157	1,009	503
Baseline, mean (SD)	9.39 (1.15)	9.39 (1.31)	9.25 (1.28)	9.17 (1.27)
Change from baseline, mean (SD)	1.56 (1.03)	0.87 (0.90)	-	-
Treatment group difference vs. control (95% CI)	0.70 (0.53 to 0.86)		-	
P value	< 0.0001		< 0.001	
Week 4				
FAS				
Number of patients contributing to the analysis	317	148		
Baseline, mean (SD)	9.39 (1.15)	9.39 (1.31)		
Change from baseline, mean (SD)	2.35 (1.32)	1.74 (1.17)		
Treatment group difference vs. control (95% CI)	0.60 (0.44 to 0.77)			
P value	< 0.0001			
End of study — Week 5				
FAS				
Number of patients contributing to the analysis	322	155	-	-
Baseline, mean (SD)	9.39 (1.15)	9.39 (1.31)	-	-
Change from baseline, mean (SD)	2.52 (1.41)	2.05 (1.27)	-	-
Treatment group difference vs. control (95% CI)	0.46 (0.30 to 0.62)		-	
P value	< 0.0001		-	
End of study — Week 8				
PP				
Number of patients contributing to the analysis	-	-	901	437
Baseline, mean (SD)	-	-	9.25 (1.28)	9.17 (1.27)
LS mean (95% CI)	-	-	2.58 (2.50 to 2.65)	2.57 (2.46 to 2.68)
Treatment group difference vs. control (95% CI)	-		0.01 (–0.12 to 0.14)[a]	
P value	-		0.871	
Subjects with Hb increase ≥ 2 g/dL				
PP				
Any time from week 1 to week 5				
Responders/n (%)	218/311 (70.1)	77/143 (53.8)	-	-
RD (95% CI)	15.9 (6.3 to 25.4)[b]		-	
Superiority test, P value	0.0002		-	
Subjects with Hb increase ≥ 2 g/dL				
ITT				
Week 2				

	PROVIDE		FERWON-IDA	
	IIM N = 342	IS N = 169	IIM N = 1,009	IS N = 503
Responders/n (%)	-	-	297/912 (32.6)	94/452 (20.8)
OR (95% CI)	-		2.42 (1.80 to 3.26)	
P value	-		< 0.0001	
Week 8				
Responders/n (%)	-	-	606/903 (67.1)	
OR (95% CI)	-		1.05 (0.80 to 1.38)	
P value	-		0.703	
Time to increase Hb ≥ 2 g/dL (days)				
Number of patients contributing to the analysis	330	161	1,009	503
Median time (range)	26 (21.0 to 28.0)	37 (32.0 to 42.0)	28	28
HR (95% CI)	2.488 (1.916 to 3.230)		-	
P value	< 0.0001		0.088	
S-ferritin (mcg/L)				
Change in s-ferritin				
Week 2				
FAS				
Number of patients contributing to the analysis	322	159	1,009	503
Baseline, mean (SD)	14.3 (32.8)	15.6 (47.2)	14.4 (42.6)	11.9 (37.6)
Change from baseline, mean (SD)	825.4 (5,548.1)	126.2 (87.2)	-	-
Treatment group difference vs. control (95% CI)	702.9 (313.9 to 1,091.9)		-	
P value	0.0004		< 0.0001	
End of study (week 5)				
FAS				
Number of patients contributing to the analysis	323	155	-	-
Baseline, mean (SD)	14.3 (32.8)	15.6 (47.2)	-	-
Change from baseline, mean (SD)	241.2 (209.3)	185.7 (166.8)	-	-
Treatment group difference vs. control (95% CI)	58.5 (–333.7 to 450.6)		-	
P value	0.7700		-	
End of study (week 8)				
ITT				
Number of patients contributing to the analysis	-	-	1,009	503
Baseline, mean (SD)	-	-	14.4 (42.6)	11.9 (37.6)
Change from baseline, mean (SD)	-	-	-	-
Treatment group difference vs. control (95% CI)	-		-	
P value	-		NS	
QoL				
Change in overall QoL (SF-36, 8 health domains) at week 2 and week 5			-	-

	PROVIDE		FERWON-IDA	
	IIM N = 342	IS N = 169	IIM N = 1,009	IS N = 503
P value	NS		-	
Change in overall QoL (SF-36, 2 composite scores) at week 2 and week 5			-	-
P value	NS		-	
Fatigue symptoms				
Change in FACIT-FS at week 5				
Baseline median FACIT-FS (25th quartile, 75th quartile)	22.0 (15.0 to 32.0)	23.0 (15.0 to 36.0)	-	-
End of study (week 5) median FACIT-FS (25th quartile, 75th quartile)	42.0 (35.0 to 49.0)	43.0 (34.0 to 48.0)	-	-
P value	NS		-	
Change in FACIT-FS at week 8				
Baseline mean FACIT-FS	-	-	25.72	24.63
End of study (week 8) mean FACIT-FS	-	-	39.98	39.93
P value	-		NS	

CI = confidence interval; FACIT-FS = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; FAS = full analysis set; Hb = hemoglobin; HR = hazard ratio; IDA = iron deficiency anemia; IIM = iron isomaltoside 1000; IS = iron sucrose; ITT = intention-to-treat; LS = least squares; NS = non-significant; OR = odds ratio; PP = per-protocol; QoL = quality of life; RD = risk difference; s-ferritin = serum ferritin; SD = standard deviation; SF-36 = Short Form (36) Health Survey; vs. = versus.

[a] FERWON-IDA: Noninferiority was achieved if lower boundary of the 95% CI was greater than –0.5 g/dL.

[b] PROVIDE: Noninferiority was achieved if lower boundary of the 95% CI was 12.5% points or more.

Source: Clinical Study Report PROVIDE[11] and publication for FERWON-IDA.[16]

Harms

Only those harms identified in the review protocol are reported as follows.

Adverse Events

The incidence of participants reporting at least one TEAE was greater in the PROPOSE trial (iron isomaltoside 1000: 47.8%; iron sucrose: 41.2%)[9] and the PROVIDE trial (iron isomaltoside 1000: 43.2%; iron sucrose: 38.7%)[11] compared with the FERWON-IDA trial (iron isomaltoside 1000: 12.5%; iron sucrose: 12.8%).[16]

The most commonly reported TEAEs in iron isomaltoside 1000 participants in PROPOSE were headache (3.0%), nasopharyngitis (2.6%), and diarrhea.[9] In PROVIDE, the most commonly reported TEAEs for iron isomaltoside 1000 participants were nausea (5.1%), rash (4.2%), headache (2.7%), and diarrhea (2.7%).[11] In the FERWON-IDA trial, the incidence of TEAE patient-reported nausea was less for iron isomaltoside 1000 participants (2.0%).[16]

In iron sucrose participants, the most commonly reported TEAEs in PROPOSE were headache (3.5%) and lower respiratory tract infection (2.6%).[9] In PROVIDE, the most commonly reported TEAEs were headache (6.5%), nausea (4.2%), and upper respiratory tract infections (3.6%).[11] In FERWON-IDA, the incidence of TEAE patient-reported nausea was less for iron isomaltoside 1000 participants (1.6%).[16]

Serious Adverse Events

The proportion of iron isomaltoside 1000 participants and iron sucrose participants reporting one or more SAEs was similar between treatment groups for the PROVIDE trial (3.3% and 3.6%, respectively)[11] and the FERWON-IDA trial (0.5% and 0.4%, respectively).[16] However, the proportion of participants reporting one or more SAEs in PROPOSE was higher for iron isomaltoside 1000 participants (9.6%) compared with iron sucrose participants (5.3%).[9]

Withdrawals Due to AEs

The proportion of participants withdrawing from the study due to an AE was similar for iron isomaltoside 1000 participants and iron sucrose participants in the PROVIDE trial (3.0% and 3.6%, respectively)[11] and the FERWON-IDA trial (0.7% and 0.6%, respectively).[16] In contrast, more iron isomaltoside 1000 participants than iron sucrose participants withdrew from the PROPOSE trial (3.6% and 0%, respectively).[9]

Mortality

Deaths were reported in iron isomaltoside 1000 treatment groups for the PROPOSE trial (1.3%),[9] the PROVIDE trial (0.3%),[11] and the FERWON-IDA trial (0.1%). No deaths in iron sucrose treatment groups were reported.[16]

Notable Harms

The incidence of hypersensitivity reactions was 8.4% and 6.0%, respectively, for iron isomaltoside 1000 participants and iron sucrose participants in the PROVIDE trial.[11] In contrast, PROPOSE reported that 0.4% and 0% of iron isomaltoside 1000 participants and iron sucrose participants, respectively, experienced a hypersensitivity reaction.[9]

The proportion of iron isomaltoside 1000 participants and iron sucrose participants reporting serious or severe hypersensitivity reactions was low for the PROPOSE trial (0.4% and 0%, respectively)[9], the FERWON-NEPHRO trial (0.3% and 0%, respectively),[14] the PROVIDE trial (1.2% and 1.2%, respectively),[11] and the FERWON-IDA trial (0.3% and 0.4%, respectively).[16]

The co-primary end points in FERWON-NEPHRO and FERWON-IDA evaluated the safety of iron isomaltoside 1000 compared to iron sucrose for the proportion of serious or severe hypersensitivity reactions. Both trials found that iron isomaltoside 1000 was noninferior to iron sucrose, as the upper boundary of the 95% CI was less than 3% in iron isomaltoside 1000 and iron sucrose for the proportion of serious or severe hypersensitivity reactions.[14,16] FERWON-IDA also examined adjudicated and confirmed treatment-emergent serious or severe hypersensitivity reactions and found no statistical differences between iron isomaltoside 1000 and iron sucrose, as the 95% CI contained the value of 0 (risk difference: –0.10% [95% CI, -0.91 to 0.71]).[16] PROVIDE tested for differences in serious or severe hypersensitivity and allergic reactions and found no statistical differences between iron isomaltoside 1000 and iron sucrose.[11]

Secondary safety end points in FERWON-NEPHRO and FERWON-IDA were the proportion of participants with composite cardiovascular AEs and hypophosphatemia.[14,16] FERWON-NEPHRO found iron isomaltoside 1000 participants had significantly lower incidence of composite cardiovascular AEs compared with iron sucrose participants (4.1% versus 6.9%, P = 0.026).[14] In contrast, no statistical differences were found between iron isomaltoside 1000 participants (0.8%) and iron sucrose participants (1.2%) for the composite end point of

cardiovascular AEs in FERWON-IDA (P > 0.05).[16] In both FERWON-NEPHRO and FERWON-IDA, the incidence of hypophosphatemia was low for both iron isomaltoside 1000 participants and iron sucrose participants and no patient had a serum level less than 1 mg/dL.[14,16]

Table 11: Summary of Harms — CKD and IDA Studies

	CKD studies				IDA studies			
	PROPOSE		FERWON-NEPHRO		PROVIDE		FERWON-IDA	
	IIM N = 230	IS N = 114	IIM	IS	IIM N = 333	IS N = 168	IIM N = 989	IS N = 494
TEAEs								
Total TEAEs reported, Events	202	85	-	-	357	183	230	138
Subjects reporting ≥ 1 TEAE, n (%)	110 (47.8)	47 (41.2)	-	-	144 (43.2)	65 (38.7)	124 (12.5)	63 (12.8)
Most common TEAEs								
Gastrointestinal disorders, n (%)	-	-	-	-	47 (14.1)	19 (11.3)	-	-
Diarrhea	5 (2.2)	2 (1.8)	-	-	4 (1.2)	5 (3.0)	-	-
Vomiting	-	-	-	-	7 (2.1)	5 (3.0)	-	-
Nausea	-	-	-	-	17 (5.1)	7 (4.2)	20 (2.0)	8 (1.6)
Infections and infestations			-	-	24 (7.2)	10 (6.0)	-	-
Nasopharyngitis	6 (2.6)	1 (0.9)	-	-	-	-	-	-
Lower respiratory tract infection	4 (1.7)	3 (2.6)	-	-	-	-	-	-
Upper respiratory tract infection	-	-	-	-	4 (1.2)	6 (3.6)	-	-
Urinary tract infection	-	-	-	-	8 (2.4)	1 (0.6)	-	-
Musculoskeletal and connective tissue disorders	-	-	-	-	27 (8.1)	9 (5.4)	-	-
Pain in extremity	5 (2.2)	-	-	-	-	-	-	-
Back pain	-	-	-	-	8 (2.4)	2 (1.2)	-	-
Arthralgia	-	-	-	-	7 (2.1)	2 (1.2)	-	-
Nervous system disorders								
Headache	7 (3.0)	4 (3.5)	-	-	18 (5.4)	11 (6.5)	-	-
Dizziness	-	-	-	-	9 (2.7)	4 (2.4)	-	-
Dysgeusia	-	-	-	-	2 (0.6)	5 (3.0)	9 (1.8)	1 (0.2)
Skin and subcutaneous tissue disorder					31 (9.3)	7 (4.2)		
Rash			-	-	14 (4.2)	1 (0.6)	15 (1.5)	-
Pruritus	3 (1.3)	2 (1.8)	-	-				
General disorders and administration site conditions			-	-	26 (7.8)	14 (8.3)	-	-
Fatigue	-	-	-	-	4 (1.2)	5 (3.0)	-	-
Other								
Chest discomfort	-	-	-	-	-	-	11 (1.1)	-
Overdose	-	-	-	-	-	-	8 (0.8)	-
Fall	7 (3.0)	-	-	-	-	-	-	-
Procedural hypotension	5 (2.2)	1 (0.9)	-	-	-	-	-	-
C-reactive protein increased	6 (2.6)	1 (0.9)	-	-	-	-	-	-

	CKD studies				IDA studies			
	PROPOSE		FERWON-NEPHRO		PROVIDE		FERWON-IDA	
	IIM N = 230	IS N = 114	IIM	IS	IIM N = 333	IS N = 168	IIM N = 989	IS N = 494
Hyperphosphatemia	5 (2.2)	4 (3.5)	-	-	-	-	-	-
Hypophosphatemia	-	-	-	-	-	-	(3.9)	(2.3)
Composite cardiovascular AEs	-	-	4.1	6.9	-	-	(0.8)	(1.2)
Patients with ≥ 1 SAE								
n (%)	22 (9.6)	6 (5.3)	-	-	11 (3.3)	6 (3.6)	5 (0.5)	2 (0.4)
Most common events								
Gastrointestinal disorders	3 (1.3)	-	-	-	-	-	-	-
Duodenal ulcer hemorrhage	1 (0.4)	-	-	-	-	-	-	-
Gingival bleeding	1 (0.4)	-	-	-	-	-	-	-
Lower gastrointestinal hemorrhage	1 (0.4)	-	-	-	-	-	-	-
Infections and infestations	5 (2.2)	2 (1.8)	-	-	-	-	-	-
WDAEs								
n (%)	9 (3.9)	-	-	-	10 (3.0)	6 (3.6)	7 (0.7)	3 (0.6)
Deaths								
n (%)	3 (1.3)	-	-	-	1 (0.3)	-	1 (0.1)	-
Causes of death								
Worsening of pre-existing cancer	-	-	-	-	-	-	1 (0.1)	-
Cardiorespiratory arrest	-	-	-	-	1 (0.3)	-	-	-
Sudden death	1 (0.4)	-	-	-	-	-	-	-
Vascular graft occlusion	1 (0.4)	-	-	-	-	-	-	-
Brain stem infarction	1 (0.4)	-	-	-	-	-	-	-
Notable harms								
Hypersensitivity, n (%)	1 (0.4)	-			28 (8.4)	10 (6.0)		
Serious or severe hypersensitivity, n (%)	1 (0.4)	-	(0.3)	(0)	4 (1.2)	2 (1.2)	3 (0.3)	2 (0.4)
Treatment-emergent serious or severe hypersensitivity RD (95% CI)							–0.10% (–0.91 to –0.71)	

AE = adverse event; CI = confidence interval; CKD = chronic kidney disease; IDA = iron deficiency anemia; IIM = iron isomaltoside 1000; IS = iron sucrose; RD = risk difference; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

Source: Clinical Study Reports for PROPOSE[9] and PROVIDE,[11] and publications for FERWON-NEPHRO[14] and FERWON-IDA.[16]

Critical Appraisal

Internal Validity

Baseline and demographic characteristics were generally well balanced between the iron isomaltoside 1000 and iron sucrose treatment groups for the PROPOSE, PROVIDE, and FERWON-IDA trials, except where — in the PROPOSE trial — smoking was imbalanced (12.8% versus 6.8%), as was ischemic heart disease (13.7% versus 6.8%).[9,11,16] The

success of randomization in the FERWON-NEPHRO trial could not be evaluated as baseline characteristics for treatment groups were not available.[14]

For each of the included four trials, the risk of bias introduced by using an open-label design was likely small as the primary efficacy variables and the majority of secondary efficacy variables were evaluated using objective laboratory tests (i.e., Hb, s-ferritin, TSAT, and s-iron levels).[9,11,14,16] However, patient recall bias may have been present for participative outcomes (i.e., for self-administered QoL questionnaires consisting of LASA, SF-36, FACIT-FS, and CH-RLSq).[9,11,16]

Power calculations were based on the primary end point for the PROPOSE and PROVIDE trials and it seemed that the selected sample sizes were sufficient enough to support the claim of noninferiority in terms of the primary end point for the trials.[9,11] Power calculations were unavailable for the FERWON-NEPHRO and FERWON-IDA trials.[14,16] However, the secondary end points in the PROPOSE, PROVIDE, and FERWON-IDA trials with power calculations may have been underpowered to demonstrate any potential differences between treatment groups, particularly for the subgroup of interest (i.e., IDA severity) and AEs.[9,11,16] Overall, iron isomaltoside 1000 consistently showed noninferiority to, or similar treatment effect with, iron sucrose in correcting ID by various measures from baseline to study end. It appeared that iron isomaltoside 1000 compared with iron sucrose could more rapidly correct the deficiency back to normal. The increases tended to be higher in the first two to four weeks of the study treatment period but, toward the study end, the differences became similar.[9,11,14,16]

The rationale for the selection of the NIM was provided for all included trials and was based on results of previous trials.[9,11,14,16] Overall, the clinical implication of the NIM was not a concern for the following reasons: first, in the PROPOSE trial, the adjusted risk difference between iron isomaltoside 1000 and iron sucrose was 1%;[10] second, in the PROVIDE trial, iron isomaltoside 1000 was found to be superior to iron sucrose for the primary end point;[12] and third, in the FERWON-IDA trial, the difference in mean change in Hb at week 8 between iron isomaltoside 1000 and iron sucrose was found to be zero in the ITT dataset.[16] However, in the FERWON-NEPHRO trial, although the NIM was known and justification was provided, the absence of statistical analysis created uncertainty around the clinical interpretation of the primary analyses.[14] All four trials based the selection of the NIM on the results of previous trials. However, the clinical implication of the selected differences was not clarified, for example, in terms of –12.5% NIM in patients with an increase in Hb of 2 g/dL or more from baseline to week 5, despite the fact that the study results showed a small difference that satisfied the pre-specified criteria for noninferiority.[9,11] For the FERWON-IDA study, a noninferiority between treatments could be claimed if the lower boundary of the 95% CI in the mean difference of change in Hb from baseline to week 8 was greater than –0.5 g/dL; however, justification for the selection was not provided.[16] In FERWON-NEPHRO, the NIM was not available.[14]

The robustness of the primary efficacy analysis was tested in the PROPOSE and PROVIDE trials by using FAS and PP datasets and in the FERWON-IDA trial by using ITT, FAS, and PP datasets. Our confidence in the noninferiority claims of iron isomaltoside 1000 compared to iron sucrose for the primary efficacy end points in PROPOSE (the proportion of participants who maintained Hb between 9.5 g/dL and 12.5 g/dL [both values included]), PROVIDE (the proportion of participants with an increase in Hb of 2 g/dL or more from baseline to any time between week 1 and week 5), and FERWON-IDA (the change in Hb at week 8) was strengthened as the findings were consistent in different datasets.[9,11,16] In

PROVIDE, superiority of iron isomaltoside 1000 over iron sucrose was also consistent across the FAS and PP datasets for the primary efficacy end point, further strengthening the confidence in the result.[11] In contrast, only one dataset was reported in FERWON-NEPHRO and the dataset was not defined.[14] It is unknown whether the noninferiority claim of change in Hb at week 8 would have remained consistent across different datasets in FERWON-NEPHRO.

The proportion of iron isomaltoside 1000 participants and iron sucrose participants who withdrew from the PROVIDE trial (7.3% and 10.1%, respectively)[11] and the FERWON-IDA trial (10.1% and 10.7%, respectively)[16] was similar and balanced between treatment groups. However, a greater proportion of iron isomaltoside 1000 participants (10.1%) discontinued the PROPOSE trial compared with iron sucrose participants (3.4%).[9] The imbalance in dropouts between treatment groups in PROPOSE was due to an increased number of patients on iron isomaltoside 1000 withdrawing due to AEs compared with patients on iron sucrose (4.7% and 0.85%, respectively). A greater proportion of iron isomaltoside 1000 participants also withdrew their consent (2.56%) compared with iron sucrose participants (1.70%).[9] Subject withdrawal information was not available for FERWON-NEPHRO.[14]

A data imputation method using the LOCF approach was used for missing data in the PROPOSE trial for the primary efficacy end point but not for secondary end points. Sensitivity analyses using different methods of handling missing data were also performed for the primary efficacy end point in PROPOSE. The noninferiority of results was consistent across different imputation methods except for where missing values were imputed as failures, signalling a potential source of bias as more participants receiving iron isomaltoside 1000 had missing data (9.0%) compared with iron sucrose participants (3.4%). In the FERWON-NEPHRO and FERWON-IDA trials, multiple imputations and tipping point analyses were conducted on the primary efficacy end point; however, the types of imputations used or the results of the tipping point analyses were unavailable.[14, 17] The PROVIDE trial conducted sensitivity analyses analyzing the primary end point in all randomized participants with patients without post-baseline Hb values set as nonresponders. The extent to which missing data may or may not have affected the findings' primary analyses in FERWON-NEPHRO, PROVIDE, and FERWON-IDA is unknown.

The PROVIDE trial also performed sensitivity analyses on the secondary end points of change in FACIT-FS and SF-36, using methods to handle missing data.[11] However, no imputation methods for missing data were described in the PROPOSE trial (LASA and CH-RLSq)[9] and the FERWON-IDA trial (FACIT-FS).[16] Thus, the extent of the missing data and distribution of missing data by treatment for the patient-relevant scales in PROPOSE (LASA, CH-RLSq)[9] and FERWON-IDA (FACIT-FS)[16] is unclear.

QoL was measured using the self-administered patient questionnaires LASA (in the PROPOSE trial)[9] and SF-36 (in the PROVIDE trial).[11] Patient symptoms of fatigue were measured by the self-administered patient questionnaire FACIT-FS (in the PROVIDE and FERWON-IDA trials)[11,16] and RLS by the CH-RLSq (in the PROPOSE trial).[9] LASA, SF-36, and CH-RLSq have not been validated in patients with IDA and the MCID is not available for the LASA and CH-RLSq measurement scales. Thus, whether the changes are clinically significant in each treatment group remain unclear. The FACIT-FS has been validated in patients with IDA and the MCID is unknown. Although information on the validity and MCID is lacking for the majority of patient-relevant scales, interpretation of the results is not

compromised as the differences between iron isomaltoside 1000 participants and iron sucrose participants was almost certainly non-significant for LASA (energy level, ability to do daily activities, and overall QoL), CH-RLSq, and SF-36 (eight health domains as well as the PCS and MCS).

No statistical adjustments were made for multiplicity for the primary efficacy end point in the PROPOSE or PROVIDE trials.[9,11] Details on adjustments for multiplicity were not available for the FERWON-NEPHRO and FERWON-IDA trials.[14,16] Nevertheless, the fact that all the outcome measures around ID in the trials could be deemed highly correlated (e.g., Hb, s-ferritin, and QoL) and that all the tests of statistical significance performed at various time points; would render the issue of multiplicity a considerable threat to the validity of some of the statistical significance findings. For example, it is unknown to what extent a conclusion on superiority could be reliably drawn without concern of inflated type I error when iron isomaltoside 1000 was reported to be superior to iron sucrose in the proportion of patients with an increase in Hb of 2 g/dL or more from baseline to week 5 (FAS: $P < 0.0001$; PP: $P = 0.0002$).[11]

Subgroup analyses performed in PROVIDE on the primary efficacy end point were identified a priori and were primarily based on stratifications to maintain randomization. The subgroups were not tested for interactions and no adjustments for multiplicity were made. The width of the 95% CIs for two subgroups (Hb < 10 g/dL and gynecology; Hb ≥ 10 g/dL and gynecology) was similar to the 95% CI for the whole trial population for the primary efficacy end point. The wider 95% CIs seen in the other six subgroups potentially reflect imprecision of the outcome measure.[11]

External Validity

Study participants were recruited from a number of countries in the PROPOSE trial (including the US[9]) and from multiple centres in the US in the FERWON-NEPHRO, PROVIDE, and FERWON-IDA trials.[11,14,16] Although none of the study participants were recruited from Canada, the clinical expert consulted in this review suggested that the study populations were generally representative of the Canadian adult population seen in clinical practice. The study populations for each of the four included trials were 18 years or older and thus are not generalizable to the pediatric population.

The study populations of the pivotal study PROPOSE and of the FERWON-NEPHRO trial consisted of CKD patient populations. PROPOSE enrolled CKD patients with CKD-5D on dialysis therapy with renal-related anemia who were receiving maintenance iron therapy and FERWON-NEPHRO enrolled NDD-CKD patients with IDA. Thus, the included patient population was not completely aligned with Health Canada's approved indication for iron isomaltoside 1000 (i.e., adults with IDA who have an intolerance or unresponsiveness to oral iron). In particular, neither PROPOSE nor FERWON-NEPHRO included participants with an intolerance or unresponsiveness to oral iron.[9,14,15]

The study populations of the PROVIDE and FERWON-IDA trials were generally aligned with Health Canada's approved indication of iron isomaltoside 1000, and both trials also included participants in whom there was a need to deliver iron rapidly. Thus, the results of PROPOSE and FERWON-IDA were likely generalizable to patients with IDA who are intolerant or unresponsive to oral treatment caused by a variety of different etiologies, despite the fact that a considerable proportion of patients (in both trials, about 50% of screened patients) was not eligible for the studies due to relatively stringent criteria for inclusion and exclusion.[6,11,16]

The iron isomaltoside 1000 treatment regimens given in the FERWON-NEPHRO, PROVIDE, and FERWON-IDA trials (1,000 mg IV given over 15 to 20 minutes in a single session) were similar to how the treatment would be administered in clinical practice (1,000 mg IV given over 30 minutes in a single session).[11,14,16] The dosing regimen in the PROPOSE trial of iron isomaltoside 1000 (500 mg IV bolus in a single session over approximately two minutes) was aligned with the Canadian product monograph for iron isomaltoside 1000.[6,9]

The comparator used in the four included trials for review was iron sucrose and, as indicated by the clinical expert on this review, is currently the IV drug of choice for treating IDA in Canada. The doses administered during each IV treatment session in the four included trials were aligned with the Canadian product monograph. The dosing schedule available for iron sucrose in the PROPOSE and PROVIDE trials was aligned with the Canadian product monograph.[6] The rate of administration of iron sucrose was not described in the four included trials.[9,11,14,16] Overall, the dosing schedule for iron sucrose across the four included trials was similar to how the treatment would be administered in clinical practice. The duration of the four included trials ranged from five weeks to eight weeks and was of adequate duration as per the clinical expert on this review. In the absence of significant bleeding or hemolysis, the study time frames of five weeks to eight weeks should be sufficient to evaluate a response to IV iron, assuming the patient is able to respond. In most uncomplicated patients who have IDA due to chronic blood loss, this period is adequate.

Indirect Evidence

The sponsor did not include indirect comparison evidence in its submission. A supplemental literature search was conducted by CADTH for potential relevant indirect comparisons evidence. From the additional CADTH search, a potentially relevant systematic review and NMA was identified.[18] The NMA was conducted by Aksan et al. in 2016[18] and updated in 2019 (reported in abstracts).[19,20] The objective of the NMA was to compare the efficacy and tolerability of different IV iron formulations and oral iron agents used to treat IDA in patients with IBD. Five RCTs (n = 1,143 patients) were included in the NMA. However, the NMA did not include any of the four studies (two pivotal and two non-pivotal studies)[10,13,14,16] selected for this CADTH review. IV iron agents included in the NMA were iron isomaltoside 1000, iron sucrose, ferric gluconate, and ferric carboxymaltose. The primary outcome was the therapy response (defined as Hb normalization or increase ≥ 2 g/dL), which was not aligned with the key outcomes listed in the protocol for this CADTH review.

Key Findings (Iron Isomaltoside 1000 Versus Iron Sucrose)

The NMA reported that there was no statistically significant difference between iron isomaltoside 1000 and iron sucrose in terms of response rate, defined as Hb normalization or increase of 2 g/dL or more (odds ratio: 0.98 [95% credible interval, 0.49 to 2.0]) in the treatment of IDA in patients with IBD. The probability of being the most effective treatment (by the Markov Chain Monte Carlo method) was 39.7% and 49.9% for iron isomaltoside 1000 and iron sucrose, respectively. The NMA also found that the AE rates were 17.0% and 15.3% for iron isomaltose 1000 and iron sucrose, respectively.

No evidence for comparing iron isomaltoside 1000 with ferric gluconate was reported in this NMA.[18]

A regular full scale of summary and critical appraisal of the NMA is not provided in this CADTH report for two reasons. First, the NMA [18] was outdated (i.e., neither of the pivotal studies or two other studies included in this CADTH review were selected in the NMA). Second, the primary outcome (therapy response rate, defined as Hb normalization or increase ≥ 2 g/dL) was not aligned with the key outcomes listed in the protocol of this CADTH review.

Other Relevant Studies

One potentially relevant extension study (P-Monofer-IDA/CKD-EXT-01 [FerWoNExt, NCT02962648]) was included in the sponsor's submission. However, no detailed information was available. No information on the study was provided by the sponsor at CADTH's request.[21]

Discussion

Summary of Available Evidence

Four phase III RCTs were identified and included in this systematic review (PROPOSE, FERWON-NEPHRO, PROVIDE, and FERWON-IDA).[9-17] PROPOSE[9] and PROVIDE[11] were the pivotal studies identified by the sponsor and FERWON-NEPHRO[14] and FERWON-IDA[16] were trials identified with the CDR systematic search strategy.

Each of the four included trials was a multi-centre, open-label, parallel group, active-controlled, noninferiority RCT comparing iron isomaltoside 1000 to iron sucrose. Each trial enrolled adult men and women aged 18 or older.[9,11,14,16] Eligible participants for the PROPOSE trial (N = 351),[9] the FERWON-NEPHRO trial (N = 1,538),[14] the PROVIDE trial (N = 511),[11] and the FERWON-IDA trial (1,512)[16] were randomized 2:1 into iron isomaltoside 1000 and iron sucrose treatment groups. In PROPOSE, participants were required to have CKD-5D, receiving hemodialysis and maintenance iron therapy for renal-related anemia,[9] while FERWON-NEPHRO included patients with NDD-CKD and IDA.[14] In PROVIDE and FERWON-IDA, patients with IDA caused by various etiologies and who had a documented intolerance or unresponsiveness to oral iron therapy or a need for rapid iron repletion identified by the investigators were eligible for enrolment.[11,16] If a potential FERWON-IDA participant did not have documented oral intolerance, a run-in period was initiated (up to one month).[16]

The PROPOSE trial was designed to assess whether iron isomaltoside 1000 was noninferior to iron sucrose for maintenance therapy of renal-related anemia in CKD-5D participants on dialysis and receiving iron maintenance therapy. The primary outcome measure was the proportion of participants who maintained an Hb level between 9.5 g/dL and 12.5 g/dL (both values included) at six weeks.[9]

The FERWON-NEPHRO, PROVIDE, and FERWON-IDA trials were designed to assess the efficacy and safety of iron isomaltoside 1000 compared with iron sucrose for treatment of IDA. As such, primary end points in these studies compared the IV iron products for noninferiority on their ability to raise Hb levels.[11,14,16] FERWON-NEPHRO and FERWON-IDA had the same co-primary end point that measured, first, the proportion of participants with serious or severe hypersensitivity reactions and, second, the change in Hb from baseline to week 8.[14,16] The primary end point of PROVIDE evaluated efficacy by

comparing the proportion of participants who achieved an increase in Hb of 2 g/dL or more from baseline to any time between week 1 and week 5.[11]

Secondary end points in the included studies further compared the IV iron products' abilities to raise Hb (i.e., change in Hb levels at earlier time points and the time to achieve an increase ≥ 2 g/dL) and to replenish iron stores (i.e., change in s-ferritin levels).[9,11,14-16] The QoL of patients was evaluated in the PROVIDE trial (SF-36)[11] and the PROPOSE trial (LASA).[9] Fatigue symptoms were assessed in PROVIDE and the FERWON-IDA trial (FACIT-FS)[11,16] and PROPOSE assessed RLS (CH-RLSq).[9]

Key Critical Appraisal Issues

The key critical appraisal issues identified across the four included trials were as follows:

- The extent to which missing data may or may not have affected the findings' primary analyses in the FERWON-NEPHRO, PROVIDE, and FERWON-IDA trials is unknown as the results from sensitivity analyses using data imputation was unavailable.[12,14,17]
- In the PROPOSE trial, the noninferiority of results was consistent across different imputation methods except for where missing values were imputed as failures, signalling a potential source of bias as more participants receiving iron isomaltoside 1000 had missing data (9.0%) compared with iron sucrose participants (3.4%).[9]
- Nearly half of screened patients in PROVIDE and FERWON-IDA were excluded; this created significant concern as to whether the findings are generalizable to those patients not studied, particularly in the pivotal trial of PROVIDE.[11,16]
- Multiple testing at different time points for superiority and various outcomes is a considerable concern, even though the P values for the claims are relatively small, which may relieve a bit of concern for increased type I error.[9,11,14,16]

Interpretation of Results

Efficacy

The primary purpose of the PROPOSE trial differed from the other three included trials for review as it was designed to maintain Hb levels in CKD-5D participants, rather than treat or correct Hb levels. Subjects were only included for study if baseline Hb levels fell within the range of 9.5 g/dL and 12.5 g/dL. The primary efficacy analysis of PROPOSE evaluated the proportion of participants who were able to maintain Hb between 9.5 g/dL and 12.5 g/dL (both values) at six weeks. For the primary efficacy analysis, PROPOSE found iron isomaltoside 1000 to be noninferior to iron sucrose in both FAS and PP datasets. The robustness of the primary end point was tested using different data imputation methods; testing showed that noninferiority held for all sensitivity analyses except for the FAS unadjusted analysis with missing values imputed as failures. Even though this inconsistent finding was based on a worst-case scenario, it may have signalled a biased estimate due to a disproportional discontinuation due to AEs in the iron isomaltoside 1000 group (10.1%) compared with the iron sucrose group (3.4%). Secondary analyses showed no statistically significant change in Hb levels from baseline to week 2 and week 6. Given that the baseline Hb levels in PROPOSE for iron isomaltoside 1000 and iron sucrose were higher compared with the other three included trials and that the cumulative IV iron doses given were lower (500 mg) compared to the other three included trials (1,000 mg or higher), the non-significant change in Hb level is not surprising. However, the secondary end points of mean change in s-ferritin from baseline to week 2 and week 4 were found to be statistically

significantly greater for iron isomaltoside 1000 patients compared with iron sucrose patients. It is unclear why this statistically significant difference was found for change in s-ferritin and not Hb at earlier evaluation time points.[9]

In the PROVIDE trial, the primary end point analyzed the proportion of participants with Hb increase greater than or equal to 2 g/dL from baseline to any time between week 1 and week 5 (i.e., the proportion of responders) and found iron isomaltoside 1000 to be both noninferior and superior to iron sucrose. Noninferiority and superiority results were consistent for the FAS and PP datasets. However, the extent to which missing data may or may not have affected the primary analysis is unknown as the results of the sensitivity analyses using data imputation were unavailable. Further, as no statistical adjustments were made for multiplicity, it remains unknown to what extent the claim of superiority could be reliably drawn without concern for inflated type I error for this end point. With these internal validity caveats in mind, the primary analysis of PROVIDE showed that iron isomaltoside 1000 produced a statistically greater rise in Hb compared with iron sucrose within one to five weeks. It is likely that the finding of superiority was related to the fact that the mean cumulative iron dose given to iron isomaltoside 1000 patients (1,640.20 mg) was higher compared with iron sucrose patients (1,127.9 mg). As well, the majority of iron isomaltoside 1000 patients receiving between 1,000 mg and 2,000 mg received the total cumulative iron dose in two doses. Iron sucrose patients receiving between 1,000 mg and 2,000 mg required frequent dosing ranging from five doses (23.2%) to 10 doses (< 4%). Further, although PROVIDE demonstrated statistically that a greater number of iron isomaltoside 1000 patients achieved an increase in Hb levels of 2 g/dL or more, it is unclear whether this difference is clinically meaningful.[11]

Statistically significant differences between iron isomaltoside 1000 and iron sucrose was found for the secondary end points in the PROVIDE trial that examined time to achieve an increase in Hb of 2 g/dL or more as well as change in Hb from baseline to week 2 and week 5, and change in s-ferritin from baseline to week 2. Thus, a statistically significant shorter length of time needed for iron isomaltoside 1000 to achieve an increase in Hb level of 2 g/dL or more indicated that iron isomaltoside 1000 produced a faster rise in Hb levels compared with iron sucrose. The statistically greater rise in Hb levels at week 2 and week 5 in iron isomaltoside 1000 patients further supports the finding that iron isomaltoside 1000 corrected anemia faster than iron sucrose. As well, the statistically greater rise in s-ferritin at week 2 in iron isomaltoside 1000 patients indicates that iron isomaltoside 1000 replenishes iron stores earlier than iron sucrose. As with the primary end point, the favourable statistical results were likely related to the higher cumulative iron dose received by iron isomaltoside 1000 patients over a shorter time frame compared with iron sucrose patients.[11]

The co-primary efficacy end point of the FERWON-NEPHRO trial was change in Hb levels from baseline to week 8; iron isomaltoside 1000 was found to be noninferior to iron sucrose in NDD-CKD patients with IDA. The noninferiority result was reported using only one dataset. Whether the reported dataset was an ITT, FAS, or PP dataset was not specified. Thus, the consistency of the noninferiority results could not be evaluated. Results from sensitivity analyses using data imputation methods were not available; thus, the robustness of the noninferiority claim could not be assessed. Background noise such as substantive protocol violation and missing data on study outcomes could all increase the likelihood of noninferiority. Overall confidence in this noninferiority finding is low due to these critical appraisal issues.[14]

The FERWON-NEPHRO trial also evaluated the mean change in Hb from baseline to week 2 as a secondary end point and found a statistically significantly greater rise in Hb for iron isomaltoside 1000 than iron sucrose. Despite the significant internal validity issues, this secondary end point suggests that iron isomaltoside 1000 is associated with a significantly faster Hb response within the first two weeks compared with iron sucrose and that the difference in Hb response is noninferior by week 8.[14] Although the confidence in the reported FERWON-NEPHRO results is low[14], the end points studied in the FERWON-IDA trial were similar and supported by the FERWON-IDA findings.[16]

FERWON-IDA used the same co-primary efficacy end point as FERWON-NEPHRO (i.e., change in Hb from baseline to week 8). Iron isomaltoside 1000 was again found to be noninferior to iron sucrose for change in Hb levels from baseline to week 8 and the result was consistent across ITT, FAS, and PP datasets. Since no results for imputing missing data were made available, the robustness of the noninferiority claim could not be assessed. Testing was done for superiority but it was not found for the primary end point in FERWON-IDA.[16]

The secondary analysis in the FERWON-IDA trial evaluated the proportion of participants with an Hb increase of 2 g/dL or more (i.e., responders) from baseline to week 2. This showed that at two weeks from baseline, a significantly higher proportion of iron isomaltoside 1000 participants compared with iron sucrose participants were responders. The difference at eight weeks in the proportion of responders was non-significant between iron isomaltoside 1000 participants and iron sucrose participants. The mean changes seen in s-ferritin within the first two weeks were also statistically different between the iron isomaltoside 1000 group and iron sucrose group. Overall, these secondary results indicate that iron isomaltoside 1000 is associated with a faster Hb response within the first two weeks of treatment compared with iron sucrose.[16]

Interestingly, in FERWON-IDA, the median time to an Hb increase of 2 g/dL or more was identical for both iron isomaltoside 1000 and iron sucrose (28 days) and did not support the conclusion from the other secondary analyses that iron isomaltoside 1000 is associated with a faster response time within the first two weeks of treatment. However, this end point was not pre-specified in the study protocol and thus the confidence in the findings is low.[16] It is also important to note that this finding was different from the PROVIDE finding.[11,16] A possible explanation for why iron isomaltoside 1000 was associated with a statistically significant shorter time to an Hb increase of 2 g/dL or more compared with iron sucrose in PROVIDE and not in FERWON-IDA is likely due to the fact that the majority of iron isomaltoside 1000 participants in PROVIDE received a disproportionately higher cumulative iron dose (1,640.20 mg) compared with iron sucrose participants (1,127.9 mg).[11] As well, the cumulative iron dose was lower in FERWON-IDA treatment groups (iron isomaltoside 1000: 975 mg; iron sucrose: 905 mg).[16]

The maximum cumulative iron dose permitted in the included trials for review was administered to patients in the PROVIDE trial. Iron isomaltoside 1000 patients and iron sucrose patients were permitted up to 2,000 mg of iron.[11] The cumulative iron dose was lowest in the PROPOSE trial (500 mg)[9] and was up to 1,000 mg in the FERWON-NEPHRO[14] and FERWON-IDA trials.[16] This potentially explains why mean change in Hb levels remained statistically significant in favour of iron isomaltoside 1000 from baseline to week 2 and to the end of the PROVIDE study at week 5,[11] while the mean Hb change was non-significant at all study end points in PROPOSE[9] and noninferior by the end of the FERWON-NEPHRO[14] and FERWON-IDA trials.[16]

With the exception of FACIT-FS measured at week 1 in the FERWON-IDA trial, for all other QoL and patient-relevant symptom outcomes (fatigue and RLS) measured in the four included trials, iron isomaltoside 1000 was not found to be significantly different than iron sucrose. The clinical expert on this review suggested a possible reason for the non-significant differences in QoL, fatigue, and RLS was that the cumulative doses received by iron isomaltoside 1000 participants and iron sucrose participants was comparable between treatment groups, with the exception of PROVIDE.[9,11,14,16] The following summarizes the QoL, fatigue, and RLS results in the four included studies:

- PROPOSE: LASA (energy level, ability to do daily activities, and overall QoL) — There were no statistical differences at baseline, week 4, and week 6 between iron isomaltoside 1000 and iron sucrose.[9]
- PROPOSE: CH-RLSq — The average decrease was not statistically different between iron isomaltoside 1000 and iron sucrose from baseline to week 6.[9]
- PROVIDE: SF-36 — PCS and MCS scores improved for iron isomaltoside 1000 and iron sucrose treatment from baseline to week 2 and week 5. However, there were no differences in treatments in change from baseline to week 2 and week 5 in any of the eight health domains or two composite end points (PCS and MCS).[11]
- PROVIDE: FACIT-FS — Both iron isomaltoside 1000 and iron sucrose FACIT-FS scores improved with treatment. There were no differences between treatments in change (i.e., improvements) from baseline to week 2 and week 5 in fatigue scores.[11]
- FERWON-IDA: FACIT-FS — Both iron isomaltoside 1000 and iron sucrose FACIT-FS scores improved with treatment. There was a statistically significant difference in mean FACIT-FS from baseline to week 1 but not for week 2 and week 8.[16]

Harms

The overall incidence of participants reporting at least one TEAE was similar in the PROPOSE trial (iron isomaltoside 1000: 47.8%; iron sucrose: 41.2%)[9] and the PROVIDE trial (iron isomaltoside 1000: 43.2%; iron sucrose: 38.7%)[11] and both trials showed the proportion of TEAE reporting to be slightly greater for iron isomaltoside 1000 participants compared with iron sucrose participants. In contrast, the FERWON-IDA trial reported a lower and well-balanced incidence of TEAEs in both treatment groups (iron isomaltoside 1000: 12.5%; iron sucrose: 12.8%).[16] It is unclear why FERWON-IDA participants in both treatment groups reported fewer TEAEs as the cumulative dose of iron administered was lower than in PROVIDE and higher than in PROPOSE.[9,11,16]

The frequency of participants reporting at least one SAE was also higher in the PROPOSE and PROVIDE trials compared with the FERWON-IDA trial.[9,11,16] The proportion of iron isomaltoside 1000 participants and iron sucrose participants reporting one or more SAEs was similarly balanced between treatment groups for PROVIDE (3.3% and 3.6%, respectively)[11] and FERWON-IDA (0.5% and 0.4%, respectively).[16] However, the proportion of participants reporting one or more SAEs in PROPOSE was higher for iron isomaltoside 1000 participants (9.6%) compared with iron sucrose participants (5.3%), and it is unclear why this occurred.[9] The cumulative dose of iron administered in PROPOSE to both treatment groups was the lowest among the three included studies for review with SAE data. One possible explanation for this imbalance may relate to the administration rate of iron isomaltoside 1000.[9] In PROPOSE, iron isomaltoside 1000 was administered as a 500 mg IV bolus over approximately two minutes.[9] In comparison, single doses of iron isomaltoside 1000 were administered as IV infusions (dosing range: 1,000 mg to 2,000 mg) over 15 to 20 minutes.[11,14,16]

The incidence of participants withdrawing from a trial due to an AE was also higher in the PROPOSE and PROVIDE trials than in the FERWON-IDA trial.[9,11,16] The proportion of participants withdrawing from the study due to an AE was similarly balanced for iron isomaltoside 1000 participants and iron sucrose participants in PROVIDE (3.0% and 3.6%, respectively)[11] and FERWON-IDA (0.7% and 0.6%, respectively).[16] In contrast, more iron isomaltoside 1000 participants than iron sucrose participants withdrew from the PROPOSE trial (3.6% and 0%, respectively)[9] and it is unclear why this imbalance occurred. However, the clinical expert suggested that the imbalance may have been attributed to iron isomaltoside 1000 participants in the PROPOSE trial receiving the IV iron over a faster period of time (bolus injection over approximately two minutes) compared with the majority of iron isomaltoside 1000 participants in FERWON-NEPHRO, PROVIDE, and FERWON-IDA, who received IV infusions over 15 to 20 minutes.

Deaths were only reported in iron isomaltoside 1000 treatment groups for PROPOSE (1.3%),[9] PROVIDE (0.3%),[11] and FERWON-IDA (0.1%).[16] No deaths in iron sucrose treatment groups were reported.[9,11,16]

The incidence of hypersensitivity reactions was greater and slightly more frequent in iron isomaltoside 1000 participants compared with iron sucrose participants in the PROVIDE trial (8.4% and 6.0%, respectively).[11] In contrast, the PROPOSE trial reported that 0.4% and 0% of iron isomaltoside 1000 participants and iron sucrose participants, respectively, experienced a hypersensitivity reaction.[9] The higher and more frequent reporting of hypersensitivity reactions in PROVIDE may be attributed to the cumulative iron dose administered. PROVIDE participants were permitted up to a 2,000 mg dose of IV iron whereas the cumulative dose across the other three included trials was between 500 mg and 1,000 mg. Iron isomaltoside 1000 participants also received, on average, a higher cumulative dose during the PROVIDE trial compared with iron sucrose participants and this may explain the higher incidence of hypersensitivity reactions reported for iron isomaltoside 1000 participants.[11]

The incidence of serious or severe hypersensitivity reactions was consistently low across the included trials (PROPOSE: 0.4% for iron isomaltoside 1000 and 0% for iron sucrose[9]; FERWON-NEPHRO: 0.3% for iron isomaltoside 1000 and 0% for iron sucrose;[14] PROVIDE: 1.2% for iron isomaltoside 1000 and 1.2% for iron sucrose;[11] and FERWON-IDA: 0.3% for iron isomaltoside 1000 and 0.4% for iron sucrose).[16]

The indirect evidence from the NMA provided no additional evidence for harm-related outcomes.

Overall, the safety profiles of iron isomaltoside 1000 and iron sucrose are similar for three of the four included trials;[9,11,14,16] however, iron isomaltoside 1000 participants in PROPOSE had a slightly higher frequency of TEAEs, SAEs, and WDAEs compared with iron sucrose participants.[9] A possible explanation for this imbalance in event rates may be due to the faster iron isomaltoside 1000 administration rate in PROPOSE (500 mg IV bolus over approximately two minutes compared with IV infusions over 15 to 20 minutes).[9] The four included trials included in this review did not identify any new safety concerns.[9,11,14,16]

Conclusions

Four phase III, multi-centre, open-label, parallel group, active-controlled, noninferiority RCTs comparing iron isomaltoside 1000 to iron sucrose were identified and included in this systematic review (PROPOSE, FERWON-NEPHRO, PROVIDE, and FERWON-IDA).[9-17]

In all trials, noninferiority (assessed using different Hb measures from baseline to end of study time points) was demonstrated for maintenance and treatment with iron isomaltoside 1000 compared with iron sucrose. Overall, it also appeared iron isomaltoside 1000 was better than iron sucrose at producing a faster and greater rise in Hb .[9,11,14,16] However, considerable threats to internal validity were identified, and lowered the overall confidence in the findings. For example, three trials lacked data imputation methods to compensate for missing data,[11,14,16] three trials lacked sensitivity analyses to test the robustness of the noninferiority results,[11,14,16] one trial had a potential source of bias due to withdrawals,[9] and all trials had a risk of type I error due to multiple testing.[9,11,14,16] Lastly, there was a concern as to whether the findings were generalizable to the study populations due to a significant proportion of screened patients being excluded from the trials.

On average, iron isomaltoside 1000 participants received greater cumulative IV iron dose compared with iron sucrose participants in two of the four trials. Further, the dosing frequency required to achieve target cumulative IV iron dose was less for IIM participants in three of the four trials. [14,16,43,44]

The HRQoL outcomes of energy, fatigue, and overall QoL were identified as important to patients and found not to be different for either treatment group across three of the included trials. One trial found a statistically significant difference in fatigue, favouring iron isomaltoside at week 1; however, the effect was not sustained. [9,11,14,16]

Overall, the safety profiles of iron isomaltoside 1000 and iron sucrose were similar for three of the four included trials;[9,11,14,16] however, iron isomaltoside 1000 participants in PROPOSE had a slightly higher frequency of TEAEs, SAEs, and WDAEs compared with iron sucrose.[9] The review did not identify any new safety concerns and the overall incidence of serious or severe hypersensitivity reactions was low for both iron isomaltoside 1000 and iron sucrose.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 25, 2019
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(Monofer* or iron isomaltoside or iron isomaltose or monover* or Diafer* or ferric derisomaltose or isomaltose iron or 3M6325NY1R).ti,ab,ot,kf,hw,rn,nm.
2	1 use medall
3	*iron isomaltose/
4	(Monofer* or iron isomaltoside or iron isomaltose or monover* or Diafer* or ferric derisomaltose or isomaltose iron).ti,ab,kw,dq.
5	3 or 4
6	5 use oemezd
7	6 not (conference review or conference abstract).pt.
8	2 or 7
9	remove duplicates from 8

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: Monoferric OR iron isomaltoside OR Monofer	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: Monoferric OR iron isomaltoside OR Monofer	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Dates for Search:	July 17, 2019
Keywords:	Monoferric, iron isomaltoside, iron deficiency anemia
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug And Device Regulatory Approvals
- Advisories And Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (Free)
- Health Statistics.

Appendix 2: Excluded Studies

Table 12: Excluded Studies

Reference	Reason for exclusion
Auerbach (2019)[16]	Duplicate
Auerbach (2019)[16]	Duplicate
Derman (2017)[13]	Duplicate
Bhandari (2015)[10]	Duplicate

Appendix 3: Detailed Outcome Data

Table 13: Detailed Outcome Data — CKD Study Populations

	PROPOSE		FERWON-NEPHRO N = 1,538	
	IIM N = 226	IS N = 115	IIM	IS
Hb (g/dL)				
Change in Hb				
Week 1				
FAS				
Number of patients contributing to the analysis	-	-	-	-
Baseline, mean (SD)	-	-	-	-
End of treatment time point (**1 week**), mean (SD)	-	-	-	-
Change from baseline, mean (SD)	-	-	0.43	0.21
LS mean estimate	-		-	
Treatment group difference vs. control (95% CI)	-		-	
SE	-		-	
P value	-		< 0.0001	
Week 2				
FAS				
Number of patients contributing to the analysis	219	115	-	-
Baseline, mean (SD)	11.20 (0.83)	11.08 (0.93)	-	-
End of treatment time point (**2 weeks**), mean (SD)	11.24 (0.88)	11.03 (0.89)	-	-
Change from baseline, mean (SD)	0.04 (0.71)	–0.05 (0.69)	0.75	0.50
LS mean estimate	0.1072	–0.0066	-	-
Treatment group difference vs. control (95% CI)	0.1138 (–0.031 to 0.259)		-	-
SE	0.0737		-	-
P value	0.1239		< 0.0001	
Week 4				
FAS				
Number of patients contributing to the analysis	213	114	-	-
Baseline, mean (SD)	11.20 (0.83)	11.08 (0.93)	-	-
End of treatment time point (**4 weeks**), mean (SD)	11.22 (1.07)	11.05 (0.95)	-	-
Change from baseline, mean (SD)	0.01 (0.91)	–0.03 (0.68)	-	-
LS mean estimate	0.0631	0.0085	-	-
Treatment group difference vs. control (95% CI)	0.0546 (–0.113 to 0.223)		-	
SE	0.0854		-	
P value	0.5233		-	
End of study — Week 6				
FAS				

	PROPOSE		FERWON-NEPHRO N = 1,538	
	IIM N = 226	IS N = 115	IIM	IS
Number of patients contributing to the analysis	216	113	-	-
Baseline, mean (SD)	11.20 (0.83)	11.08 (0.93)	-	-
End of treatment time point (**6 weeks**), mean (SD)	11.13 (1.22)	11.01 (1.12)	-	-
Change from baseline, mean (SD)	–0.07 (1.11)	–0.06 (0.99)	-	-
LS mean estimate	–0.0069	–0.0277	-	
Treatment group difference vs. control (95% CI)	–0.0069 (–0.204 to 0.246)		-	
SE	0.1143		-	
P value	0.8557		-	
End of study — Week 8				
P value	-	-	IIM noninferior to IS	
Subjects who maintained Hb between 9.5 g/dL and 12.5 g/dL (both values) at 6 weeks				
FAS				
n (%)	187 (82.7)	95 (82.6)	-	-
RD (95% CI) [a]	1.0 (–7.4 to 9.4)		-	-
P value	0.0106		-	-
PP				
n (%)	167 (83.9)	88 (82.2)	-	-
RD (95% CI) [a]	2.2 (–6.4 to 10.9)		-	
P value	0.0057		-	
Subjects who maintained Hb ≥ 9.5 at 6 weeks				
FAS, unadjusted analysis				
n (%)	200 (92.6)	104 (92.0)	-	-
RD (95% CI)	0.6 (–5.5 to 6.6)		-	-
P value[d]	0.0006		-	-
FAS, unadjusted analysis with LOCF method				
n (%)	209 (92.5)	106 (92.2)	-	-
RD (95% CI)	0.3 (–5.7, 6.3)		-	
P value	0.0008		-	
FAS, unadjusted analysis with imputed missing value as failure method				
n (%)	200 (88.5)	104 (90.4)	-	-
RD (95% CI)	–1.9 (–8.7 to 4.9)		-	
P value	0.0202		-	
PP, unadjusted analysis				
n (%)	180 (92.8)	96 (91.4)		
RD (95% CI)	1.4 (–5.1 to 7.8)	9 (8.6)		
P value[d]	0.0006			

	PROPOSE		FERWON-NEPHRO N = 1,538	
	IIM N = 226	IS N = 115	IIM	IS
PP, unadjusted analysis with LOCF method				
n (%)	184 (92.5)	98 (91.6)		
RD (95% CI)	0.9 (–6.3 to 7.3)			
P value	0.0008			
PP, unadjusted analysis with imputed missing value as failure method				
n (%)	180 (90.5)	96 (89.7)		
RD (95% CI)	0.7 (–6.3 to 7.8)			
P value	0.0028			
S-ferritin (mcg/L)				
Change in s-ferritin			-	-
Week 2				
FAS				
Number of patients contributing to the analysis	220	115	-	-
Baseline, mean (SD)	350.88 (186.17)	357.74 (192.98)	-	-
End of treatment time point (**2 weeks**), mean (SD)	492.25 (278.53)	379.18 (198.68)	-	-
Change from baseline, mean (SD)	142.58 (187.82)	20.85 (94.84)	-	-
LS mean estimate	134.6967	11.3367	-	-
Treatment group difference vs. control (95% CI)	123.3600 (96.449 to 150.271)		-	
SE	13.6719		-	
P value	< 0.0001		-	
Week 4				
FAS				
Number of patients contributing to the analysis	212	114	-	-
Baseline, mean (SD)	350.88 (186.17)	357.74 (192.98)	-	-
End of treatment time point (**4 weeks**), mean (SD)	477.87 (247.20)	444.98 (211.84)	-	-
Change from baseline, mean (SD)	128.04 (157.75)	126.79 (76.95)	-	-
LS mean estimate	125.7422	76.4029	-	-
Treatment group difference vs. control (95% CI)	49.3393 (18.174 to 80.505)		-	
SE	15.8282		-	
P value	0.0020		-	
End of study				
FAS				
Number of patients contributing to the analysis	216	114	-	-
Baseline, mean (SD)	350.88 (186.17)	357.74 (192.98)	-	-
End of treatment time point (**6 weeks**), mean (SD)	487.80 (256.11)	511.77 (267.66)	-	-
Change from baseline, mean (SD)	136.20 (154.59)	156.30 (183.63)	-	-
LS mean estimate	129.8617		-	-

	PROPOSE		FERWON-NEPHRO N = 1,538	
	IIM N = 226	IS N = 115	IIM	IS
Treatment group difference vs. control (95% CI)	–15.0585 (–54.196 to 24.079)		-	
SE	19.8434		-	
P value	0.4489		-	
TSAT (%)				
Change in TSAT				
Week 2				
FAS				
Number of patients contributing to the analysis	220	115	-	-
Baseline, mean (SD)	22.20 (17.90)	22.57 (8.49)	-	-
End of treatment time point (**2 weeks**), mean (SD)	24.63 (12.88)	23.93 (11.45)	-	-
Change from baseline, mean (SD)	2.45 (20.75)	1.44 (9.62)	-	-
LS mean estimate	0.1370	–1.0622	-	-
Treatment group difference vs. control (95% CI)	1.1992 (–1.350 to 3.748)		-	
SE	1.2940		-	
P value	0.3550		-	
End of study				
FAS				
Number of patients contributing to the analysis	216	113	-	-
Baseline, mean (SD)	22.20 (17.90)	22.57 (8.49)	-	-
End of treatment time point (**6 weeks**), mean (SD)	24.66 (11.35)	24.96 (9.17)	-	-
Change from baseline, mean (SD)	19.43 (2.00)	8.62 (2.00)	-	-
LS mean estimate	–0.0497	–0.0290	-	-
Treatment group difference vs. control (95% CI)	–0.0207 (–2.118 to 2.077)		-	
SE	1.0654		-	
P value	0.9845		-	
S-iron (µmol/L)				
Week 2				
FAS				
Number of patients contributing to the analysis	220	115	-	-
Baseline, mean (SD)	10.36 (4.02)	10.78 (4.01)	-	-
End of treatment time point (**2 weeks**), mean (SD)	11.38 (4.55)	11.34 (6.63)	-	-
Change from baseline, mean (SD)	1.07 (4.12)	0.64 (5.75)	-	-
LS mean estimate	0.9650	0.5889	-	-
Treatment group difference vs. control (95% CI)	0.3761 (–0.797 to 1.549)		-	
SE	0.5943		-	
P value	0.5277		-	
End of study				
FAS				
Number of patients contributing to the analysis	216	113	-	-

	PROPOSE		FERWON-NEPHRO N = 1,538	
	IIM N = 226	IS N = 115	IIM	IS
Baseline, mean (SD)	10.36 (4.02)	10.78 (4.01)	-	-
End of treatment time point (**6 weeks**), mean (SD)	11.23 (5.37)	11.50 (4.65)	-	-
Change from baseline, mean (SD)	0.82 (5.21)	0.76 (4.18)	-	-
LS mean estimate	0.7297	0.7232	-	-
Treatment group difference vs. control (95% CI)	0.0066 (–0.965 to 0.978)		-	
SE	0.4932		-	
P value	0.9894		-	
Reticulocyte count				
Week 2				
FAS				
Number of patients contributing to the analysis	211	111	-	-
Baseline, mean (SD)	1.33 (0.60)	1.26 (0.55)	-	-
End of treatment time point (**2 weeks**), mean (SD)	1.39 (0.63)	1.27 (0.56)	-	-
Change from baseline, mean (SD)	0.05 (0.45)	0.02 (0.40)	-	-
LS mean estimate	0.0933	0.0494	-	-
Treatment group difference vs. control (95% CI)	0.0439 (–0.047 to 0.135)		-	
SE	0.0464		-	
P value	0.3448		-	
Week 4				
FAS				
Number of patients contributing to the analysis	213	114	-	-
Baseline, mean (SD)	1.33 (0.60)	1.26 (0.55)	-	-
End of treatment time point (**4 weeks**), mean (SD)	1.41 (0.70)	1.29 (0.59)	-	-
Change from baseline, mean (SD)	0.05 (0.47)	0.03 (0.36)	-	-
LS mean estimate	0.0949	0.0647	-	-
Treatment group difference vs. control (95% CI)	0.0302 (–0.061 to 0.122)		-	
SE	0.0465		-	
P value	0.5171		-	
End of study				
FAS				
Number of patients contributing to the analysis	207	109	-	-
Baseline, mean (SD)	1.33 (0.60)	1.26 (0.55)	-	-
End of treatment time point (**6 weeks**), mean (SD)	1.40 (0.69)	1.26 (0.63)	-	-
Change from baseline, mean (SD)	0.06 (0.53)	–0.00 (0.40)	-	-
LS mean estimate	0.1054	0.0327	-	-
Treatment group difference vs. control (95% CI)	0.0727 (–0.028 to 0.173)		-	
SE	0.0512		-	
P value	0.1564		-	

	PROPOSE		FERWON-NEPHRO N = 1,538	
	IIM N = 226	IS N = 115	IIM	IS
QoL measures				
LASA — Energy level				
End of study				
FAS				
Number of patients contributing to the analysis	204	113	-	-
Baseline, mean (SD)	57.98 (21.31)	62.14 (20.30)	-	-
End of treatment time point (**6 weeks**), mean (SD)	62.20 (22.21)	64.46 (19.96)	-	-
Change from baseline, mean (SD)	3.9 (18.91)	2.3 (17.54)	-	-
LS mean estimate	4.0874	3.8895	-	-
Treatment group difference vs. control (95% CI)	0.1111 (–3.667 to 3.889)		-	
SE	1.9182		-	
P value	0.9539		-	
LASA — Ability to do daily activities				
End of study				
FAS				
Number of patients contributing to the analysis	204	113	-	-
Baseline, mean (SD)	61.34 (23.57)	65.43 (22.51)	-	-
End of treatment time point (**6 weeks**), mean (SD)	64.94 (23.16)	68.26 (23.02)	-	-
Change from baseline, mean (SD)	3.3 (19.60)	2.8 (17.91)	-	-
LS mean estimate	4.9889	4.8968	-	-
Treatment group difference vs. control (95% CI)	–0.8519 (–4.829 to 3.125)		-	
SE	2.0186		-	
P value	0.6734		-	
LASA — Overall QoL				
End of study				
FAS				
Number of patients contributing to the analysis	204	113	-	-
Baseline, mean (SD)	64.46 (20.99)	68.31 (20.24)	-	-
End of treatment time point (**6 weeks**), mean (SD)	66.40 (21.13)	68.34 (20.99)	-	-
Change from baseline, mean (SD)	2.0 (18.56)	0.1 (15.65)	-	-
LS mean estimate	0.6786	0.1254	-	-
Treatment group difference vs. control (95% CI)	0.4718 (–3.125 to 4.069)		-	
SE	1.8264		-	
P value	0.7964		-	
RLS symptoms				
CH-RLSq				
End of study				
FAS				
Number of patients contributing to the analysis	68	40	-	-

	PROPOSE		FERWON-NEPHRO N = 1,538	
	IIM N = 226	IS N = 115	IIM	IS
Baseline, mean (SD)	15.4 (8.34)	17.7 (7.83)	-	-
End of treatment time point (**6 weeks**), mean (SD)	17.3 (8.41)	16.6 (6.74)	-	-
Change from baseline, mean (SD)	–0.7 (7.60)	–1.3 (5.37)	-	-
LS mean estimate	–2.3621	–2.7599	-	-
Treatment group difference vs. control (95% CI)	0.4033 (–1.880 to 2.686)		-	
SE	1.1507		-	
P value	0.7267		-	

CH-RLSq = Cambridge–Hopkins Restless Legs Syndrome Questionnaire; CI = confidence interval; CKD = chronic kidney disease; FAS = full analysis set; Hb = hemoglobin; IIM = iron isomaltoside 1000; IS = iron sucrose; LASA = Linear Analog Scale Assessment; LOCF = last observation carried forward; LS = least squares; PP = per-protocol; QoL = quality of life; RD = risk difference; RLS = restless legs syndrome; s-ferritin = serum ferritin; s-iron = serum iron; SD = standard deviation; SE = standard error; TSAT = transferrin saturation; vs. = versus.

[a] PROPOSE: Noninferiority was achieved if lower boundary of the 95% CI was greater than –10% points.

Source: Clinical Study Report for PROPOSE[9] and publication for FERWON-NEPHRO.[14]

Table 14: Detailed Outcome Data — IDA Study Populations

	PROVIDE		FERWON-IDA	
	IIM N = 342	IS N = 169	IIM N = 1,009	IS N = 503
Hb (g/dL)				
Change in Hb				
Week 2				
FAS (PROVIDE), ITT (FERWON-IDA)				
Number of patients contributing to the analysis	318	157	1,009	503
Baseline, mean (SD)	9.39 (1.15)	9.39 (1.31)	9.25 (1.28)	9.17 (1.27)
Change from baseline, mean (SD)	1.56 (1.03)	0.87 (0.90)	-	-
Treatment group difference vs. control (95% CI)	0.70 (0.53 to 0.86)		-	
P value	< 0.0001		< 0.001	
Week 4				
FAS				
Number of patients contributing to the analysis	317	148		
Baseline, mean (SD)	9.39 (1.15)	9.39 (1.31)		
Change from baseline, mean (SD)	2.35 (1.32)	1.74 (1.17)		
Treatment group difference vs. control (95% CI)	0.60 (0.44 to 0.77)			
P value	< 0.0001			
End of study — Week 5				
FAS				
Number of patients contributing to the analysis	322	155	-	-
Baseline, mean (SD)	9.39 (1.15)	9.39 (1.31)	-	-
Change from baseline, mean (SD)	2.52 (1.41)	2.05 (1.27)	-	-
Treatment group difference vs. control (95% CI)	0.46 (0.30 to 0.62)		-	
P value	< 0.0001		-	

	PROVIDE		FERWON-IDA	
	IIM N = 342	IS N = 169	IIM N = 1,009	IS N = 503
End of study — Week 8				
ITT				
Number of patients contributing to the analysis	-	-	1,009	503
Baseline, mean (SD)	-	-	9.25 (1.28)	9.17 (1.27)
LS mean (95% CI)	-	-	2.49 (2.41 to 2.56)	2.49 (2.38 to 2.59)
Treatment group difference vs. control (95% CI)	-	-	0.00 (–0.13 to 0.13)	
P value	-	-	0.977	
FAS				
Number of patients contributing to the analysis	-	-	972	485
Baseline, mean (SD)	-	-	9.25 (1.28)	9.17 (1.27)
LS mean (95% CI)	-	-	2.51 (2.43 to 2.58)	2.49 (2.39 to 2.60)
Treatment group difference vs. control (95% CI)	-		0.01 (–0.12 to 0.14)	
P value	-		0.834	
PP				
Number of patients contributing to the analysis	-	-	901	437
Baseline, mean (SD)	-	-	9.25 (1.28)	9.17 (1.27)
LS mean (95% CI)	-	-	2.58 (2.50 to 2.65)	2.57 (2.46 to 2.68)
Treatment group difference vs. control (95% CI)	-		0.01 (–0.12 to 0.14)	
P value	-		0.871	
Subjects with Hb increase ≥ 2 g/dL				
FAS				
Any time from week 1 to week 5				
Responders/n (%)	226/330 (68.5)	83/161 (51.6)	-	-
RD (95% CI)[a]	16.7 (7.5 to 25.7)		-	
Superiority test, P value	< 0.0001		-	
PP				
Any time from week 1 to week 5				
Responders/n (%)	218/311 (70.1)	77/143 (53.8)	-	-
RD (95% CI)[a]	15.9 (6.3 to 25.4)		-	
Superiority test, P value	0.0002		-	
Subjects with Hb increase ≥ 2 g/dL				
ITT				
Week 2				
Responders/n (%)	-	-	297/912 (32.6)	94/452 (20.8)
OR (95% CI)	-		2.42 (1.80 to 3.26)	
P value	-		< 0.0001	
Subjects with Hb increase ≥ 2 g/dL				
Week 8				
Responders/n (%)	-	-	606/903 (67.1)	
OR (95% CI)	-		1.05 (0.80 to 1.38)	

	PROVIDE		FERWON-IDA	
	IIM N = 342	IS N = 169	IIM N = 1,009	IS N = 503
P value	-		0.703	
Time to increase Hb ≥ 2 g/dL (days)				
Number of patients contributing to the analysis	330	161	1,009	503
Median time (range)	26 (21.0 to 28.0)	37 (32.0 to 42.0)	28	28
HR (95% CI)	2.488 (1.916 to 3.230)		-	
P value	< 0.0001		0.088	
S-ferritin (mcg/L)				
Change in s-ferritin				
Week 2				
FAS				
Number of patients contributing to the analysis	322	159	1,009	503
Baseline, mean (SD)	14.3 (32.8)	15.6 (47.2)	14.4 (42.6)	11.9 (37.6)
Change from baseline, mean (SD)	825.4 (5,548.1)	126.2 (87.2)	-	-
Treatment group difference vs. control (95% CI)	702.9 (313.9 to 1,091.9)		-	
P value	0.0004		< 0.0001	
End of study — Week 5				
FAS				
Number of patients contributing to the analysis	323	155	-	-
Baseline, mean (SD)	14.3 (32.8)	15.6 (47.2)	-	-
Change from baseline, mean (SD)	241.2 (209.3)	185.7 (166.8)	-	-
Treatment group difference vs. control (95% CI)	58.5 (–333.7 to 450.6)		-	
P value	0.7700		-	
End of study — Week 8				
ITT				
Number of patients contributing to the analysis	-	-	1,009	503
Baseline, mean (SD)	-	-	14.4 (42.6)	11.9 (37.6)
Change from baseline, mean (SD)	-	-	-	-
Treatment group difference vs. control (95% CI)	-		-	
P value	-		NS	
TSAT (%)				
Change in TSAT				
Week 2				
FAS (PROVIDE), ITT (FERWON-IDA)				
Number of patients contributing to the analysis	322	152	1,009	503
Baseline, mean (SD)	5.8 (5.0)	6.4 (5.9)	7.43 (10.93)	6.69 (7.44)
Change from baseline, mean (SD)	17.9 (9.8)	5.7 (6.8)	-	-
Treatment group difference vs. control (95% CI)	11.98 (10.37 to 13.59)		-	
P value	< 0.0001		0.0001	
End of study — Week 5				

	PROVIDE		FERWON-IDA	
	IIM N = 342	IS N = 169	IIM N = 1,009	IS N = 503
FAS				
Number of patients contributing to the analysis	323	155		
Baseline, mean (SD)	5.8 (5.0)	6.4 (5.9)		
Change from baseline, mean (SD)	15.6 (8.6)	11.8 (9.5)		
Treatment group difference vs. control (95% CI)	3.50 (1.89 to 5.10)			
P value	< 0.0001			
End of study — Week 8				
ITT				
Number of patients contributing to the analysis	-	-	1,009	503
Baseline, mean (SD)	-	-	7.43 (10.93)	6.69 (7.44)
Change from baseline, mean (SD)	-	-	-	-
Treatment group difference vs. control (95% CI)	-		-	
P value	-		NS	
S-iron (µmol/L)				
Week 2				
FAS				
Number of patients contributing to the analysis	322	154	-	-
Baseline, mean (SD)	-	-	-	-
Change from baseline, mean (SD)	10.94 (7.41)	3.71 (5.64)	-	-
Treatment group difference vs. control (95% CI)	6.94 (5.84 to 8.04)		-	
P value	< 0.0001		-	
End of study — Week 5				
Number of patients contributing to the analysis	321	155	-	-
Baseline, mean (SD)	-	-	-	-
Change from baseline, mean (SD)	7.75 (5.84)	6.71 (7.37)	-	-
Treatment group difference vs. control (95% CI)	0.76 (0.34 to 1.85)		-	
P value	0.1777		-	
QoL				
Change in overall QoL (SF-36, 8 health domains) at 2 weeks and 5 weeks			-	-
P value	NS		-	
Change in overall QoL (SF-36, 2 composite scores) at 2 weeks and 5 weeks			-	-
P value	NS		-	
Fatigue symptoms				
Change in FACIT-FS at week 5				
Baseline median FACIT-FS (25th quartile, 75th quartile)	22.0 (15.0 to 32.0)	23.0 (15.0 to 36.0)	-	-
End of study (week 5) median FACIT-FS (25th quartile, 75th quartile)	42.0 (35.0 to 49.0)	43.0 (34.0 to 48.0)	-	-
P value	NS		-	
Change in FACIT-FS at week 8				
Baseline mean FACIT-FS	-	-	25.72	24.63

	PROVIDE		FERWON-IDA	
	IIM N = 342	IS N = 169	IIM N = 1,009	IS N = 503
End of study (week 8) mean FACIT-FS	-	-	39.98	39.93
P value	-		NS	

CI = confidence interval; FACIT-FS = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; FAS = full analysis set; Hb = hemoglobin; HR = hazard ratio; IDA = iron deficiency anemia; IIM = iron isomaltoside 1000; IS = iron sucrose; ITT = intention-to-treat; LS = least squares; NS = non-significant; QoL = quality of life; OR = odds ratio; PP = per-protocol; RD = risk difference; s-ferritin = serum ferritin; s-iron = serum iron; SD = standard deviation; SF-36 = Short Form (36) Health Survey; TSAT = transferrin saturation; vs. = versus.

[a] PROVIDE: Noninferiority was achieved if lower boundary of the 95% CI was 12.5% points or more.

Source: Clinical Study Report for PROVIDE[11] and publication for FERWON-IDA.[16]

Table 15: Subgroup/Sensitivity Analyses With Key Efficacy Outcomes — IDA Study Population From the PROVIDE Trial

Stratum/subgroup (FAS)	Total N	Subjects with Hb ≥ 2 g/dL		
		Responders/n (%)	RD (95% CI)[a]	P value
PROVIDE				
Hb < 10 g/dL and gastroenterology				
IIM	330	49/58 (84.5)	15.5 (–3.7 to 34.8)	0.0940
IS	161	20/29 (69.0)		
Hb < 10 g/dL and gynecology				
IIM	330	93/108 (86.1)	15.0 (1.0 to 28.9)	0.0236
IS	161	37/52 (71.2)		
Hb < 10 g/dL and oncology				
IIM	330	2/3 (66.7)	66.7 (13.3 to 100.0)	0.1824
IS	161	0/2 (0.0)		
Hb < 10 g/dL and other				
IIM	330	26/30 (86.7)	15.2 (–11.4 to 41.8)	0.2276
IS	161	10/14 (71.4)		
Hb ≥ 10 g/dL and gastroenterology				
IIM	330	23/53 (43.4)	10.1 (–13.0 to 33.2)	0.4074
IS	161	8/24 (33.3)		
Hb ≥ 10 g/dL and gynecology				
IIM	330	19/50 (38.0)	8.4 (–13.5 to 30.2)	0.4656
IS	161	8/27 (29.6)		
Hb ≥ 10 g/dL and oncology				
IIM	330	2/3 (66.7)	66.7 (13.3 to 100.0)	0.3173
IS	161	0/1 (0.0)		
Hb ≥ 10 g/dL and other				
IIM	330	12/25 (48.0)	48.0 (28.4 to 67.6)	0.0040
IS	161	0/12 (0.0)		

CI = confidence interval; FAS = full analysis set; Hb = hemoglobin; IDA = iron deficiency anemia; IIM = iron isomaltoside 1000; IS = iron sucrose; RD = risk difference.

[a] PROVIDE: Noninferiority was achieved if lower boundary of the 95% CI was 12.5% points or more.

Source: Clinical Study Report for PROVIDE.[11]

Table 16: Subgroup and Sensitivity Analyses With Key Efficacy Outcomes — IDA Study Population From the PROVIDE Trial

Stratum/subgroup: Cause of IDA (FAS dataset)	Total N	Subjects with Hb ≥ 2 g/dL		
		Responders/n (%)	RD (95% CI)	P value
PROVIDE				
Gastroenterology				
IIM	330	72/111 (64.9)	12.0% points (–4.1 to 28.1)	• IIM noninferior to iron sucrose • P = 0.1407
IS	161	28/53 (52.8)		
Gynecology				
IIM	330	112/158 (70.9)	13.9% points (0.9 to 26.9)	• IIM noninferior to iron sucrose • IIM superior to iron sucrose, P = 0.0330
IS	161	45/79 (57.0)		
Oncology				
IIM	330	4/6 (66.7)	66.7% points (28.9 to 100.0)	• IIM noninferior to iron sucrose • P = 0.0736
IS	161	0/3 (0.0)		
Other				
IIM	330	38/55 (69.1)	30.6% points (8.3 to 53.0)	• IIM noninferior to iron sucrose • IIM superior to iron sucrose, P = 0.0092
IS	161	10/26 (38.5)		

CI = confidence interval; FAS = full analysis set; Hb = hemoglobin; IDA = iron deficiency anemia; IIM = iron isomaltoside 1000; IS = iron sucrose; RD = risk difference.

Source: Clinical Study Report for PROVIDE.[11]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MCID):

- SF-36
- FACIT-FS
- LASA
- CH-RLSq.

Table 17: Outcome Measures Included in Each Study

Outcome measure	Study P-IDA-01	Study P-CKD-03
SF-36	Secondary efficacy end points	
FACIT-FS	Secondary efficacy end points	
LASA		Secondary efficacy end points
CH-RLSq		Secondary efficacy end points

CH-RLSq = Cambridge–Hopkins Restless Legs Syndrome Questionnaire; CKD = chronic kidney disease; FACIT-FS = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; IDA = iron deficiency anemia; LASA = Linear Analog Scale Assessment; SF-36 = Short Form (36) Health Survey.

Findings

Table 18: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MCID/MID
SF-36	This is a general health status instrument for assessing HRQoL.	The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.	2.5 points to 5 points[a]
FACIT-FS	This is a self-administration HRQoL questionnaire for patients with chronic illness. FACIT-FS, a subscale of FACIT, is used to assess the fatigue symptom related to HRQoL.	The validity, reliability, and responsiveness of FACIT-FS has been assessed in patients with IDA due to various underlying diseases in the US.	Unknown
LASA	This is a self-administered questionnaire for assessing HRQoL. LASA consists of 3 domains assessed with visual analogue scales.	The validity of LASA was assessed in patients with newly diagnosed high-grade gliomas. The validity of information from LASA in the IDA population was not identified.	Unknown
CH-RLSq	This is a self-completed questionnaire to assess RLS.	The validity of the CH-RLSq was assessed in 2,005 people who were blood donors in England. The validity of information from CH-RLSq in the IDA population was not identified.	Unknown

CH-RLSq = Cambridge–Hopkins Restless Legs Syndrome Questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; FACIT-FS = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; HRQoL = health-related quality of life; IDA = iron deficiency anemia; LASA = Linear Analog Scale Assessment; MCID = minimal clinically important difference; MID = minimal important difference; RLS = restless legs syndrome; SF-36 = Short Form (36) Health Survey.

[a] No MCID information was reported in the IDA population.

Short Form (36) Health Survey

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[45] The SF-36 consists of eight health domains — physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[39] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries, the PCS and the MCS, derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100 with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a SD of 10 in the general US population. Therefore, all scores above or below 50 are considered above or below average for the general US population.

The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 points and 5 points.[40-42] No MCID of SF-36 was identified in the IDA population.

FACIT-FS

The FACIT is a commonly used HRQoL questionnaire in international research settings for patients with chronic illness.[38] The FACIT scales are designed for patient self-administration.[38] Higher scores for the scales and subscales indicate better QoL.[38] FACIT-FS is a subscale of FACIT used to assess the fatigue symptom related to QoL.[34,35] It is a self-administered questionnaire that was completed by patients at baseline, at various time points throughout the trial, and at the end of the trial. The FACIT- FS[36,37] is a 13-item instrument designed to assess fatigue and tiredness and their impact on daily activities and functioning (HRQoL) in many chronic diseases. The FACIT-FS assesses symptoms such as tiredness, weakness, listlessness, lack of energy, and the impact of HRQoL (e.g., sleeping and social activities). The FACIT-FS (previously called the Functional Assessment of Cancer Therapy-Fatigue) was originally developed to assess cancer-related fatigue and has shown good reliability and validity in a sample of cancer patients.[37] The content validity and/or psychometric properties of the FACIT-FS have been established in many chronic conditions such as systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, chronic immune thrombocytopenia, and Parkinson disease.[34] The response options of the FACIT-FS range from 0 (indicating no improvement at all in fatigue symptom) to 4 (much improved — namely, decreased in fatigue symptom). All 13 items, except item 7 (I have energy) and item 8 (I am able to do my usual activities) are reverse scored from 4 to 0; i.e., a low score indicates more fatigue. The total score range is 0 to 52.[34] The higher the score, the better the HRQoL. A score of less than 30 indicates severe fatigue.[11]

Acaster et al. evaluated the content validity (N = 15 patients) and psychometric validity (N = 808) of the FACIT-FS in patients with IDA.[34] The content validity study was conducted in a cross-sectional study, which was developed to gather information on the nature of fatigue and its impact on HRQoL experienced by patients with IDA due to various underlying diseases in the US.[34] The psychometric properties of the FACIT-FS were investigated using data from a phase III clinical trial assessing ferumoxytol in patients with a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used.[46 47] The trial, which lasted seven weeks, consisted of a screening period of up to two weeks and a five-week treatment period. The FACIT-FS questionnaire was administered at baseline and every week thereafter to week 5. In addition, the FACIT-FS,[37] SF-36,[45] and LASA[48] were

also administered. The statistical analysis assessed the reliability, validity, and responsiveness of the FACIT-FS. In the study by Acaster,[34] the reliability of FACIT-FS was assessed by evaluating internal consistency and test–re-test reliability. Internal consistency reliability was assessed with Cronbach's alpha (α) coefficient and item to total correlations: an α greater than or equal to 0.80 and item to total correlations greater than or equal to 0.20 were used as a guide for determining that the FACIT-FS was internally consistent. Test–re-test reliability was examined with intraclass correlation coefficient. An intraclass correlation coefficient greater than or equal to 0.80 was used as a guide to determine test–re-test reliability. Validity was evaluated based on correlations between the FACIT-FS and other related patient-reported outcome scales (SF-36 and LASA), and several known groups comparisons. Responsiveness was assessed based on Hb level and SF-36 vitality score (i.e., changes from baseline to week 3). Three Hb groups were created and defined as "improved" (≥ 1 g/dL), "stable" (0 to < 1 g/dL), and "worsened" (< 0 g/dL). Five SF-36 vitality groups were created and defined as "much improved" (≥ 20), "moderately improved" (10 to < 20), "minimally improved" (5 to < 10), "stable" (0 to < 5), and "worsened" (< 0). Change from baseline FACIT-FS within each group was assessed using repeated sample t-tests.

The content validity assessment demonstrated that the FACIT-FS sufficiently assessed the fatigue symptom, which is the major symptom in patients with IDA. The FACIT-FS reliability assessment showed that the FACIT-FS was stable over time (intraclass correlation coefficient = 0.87) and internally consistent (Cronbach's α = 0.93). The FACIT-FS validity assessment demonstrated convergence with SF-36 vitality (r = 0.74), and LASA energy domain (r = 0.71) and LASA activities of daily living domain (r = 0.71). The LASA and SF-36 physical and SF-36 domains all showed similar correlations with the FACIT-FS (r = 0.68, r = 0.67, and r = 0.66, respectively). The SF-36 MCS and PCS scores showed lower levels of association with the FACIT-FS scale (r = 0.62 and r = 0.59, respectively). The validity of the FACIT-FS was also supported by the validity data of the known groups (i.e., patients with different Hb levels or patients in different treatment groups). It demonstrated that patients with higher Hb levels and patients receiving active treatment rather than placebo reported significantly lower levels of fatigue (higher FACIT-FS scores) at week 3. The FACIT-FS also showed good responsiveness (i.e., ability to detect change). Observed changes in the FACIT-FS were directly linked to the changes in the SF-36 vitality domain from baseline to week 3.

In summary, Acaster's study[34] suggested that the FACIT-FS was an appropriate and interpretable HRQoL scale for patients with IDA. However, as the author acknowledged, a potential limitation of this study was the nature of the post-hoc analysis based on clinical trial data. No MCID of FACIT-FS was identified in the IDA population.

Linear Analog Scale Assessment

LASA is a self-administered questionnaire for assessing QoL.[31] LASA consists of three domains assessed with VASs. The three domains include energy level, activities of daily living, and overall QoL. Each VAS has a seven-day recall period and consists of a 100 mm line with a left anchor representing the worst possible score (0) and the right anchor representing the best possible score (100). Higher scores indicate better functioning and HRQoL. The VAS scale has been established as a valid and reliable patient-reported outcome tool. [31]

The validity (psychometric properties) of LASA was assessed in patients with high-grade gliomas.[49,50] The findings from this study suggested that LASA was a valid instrument for

assessing the HRQoL of cancer patients.[50] However, no MCID information was reported in this study. The validity and MCID information of LASA in patients with IDA was not identified.

Cambridge-Hopkins-Restless Leg Syndrome Questionnaire

RLS is a condition that negatively affects patients' QoL.[51] The prevalence of clinically significant RLS was 23.9% in patients with IDA and nine times higher than in the general population.[51] The CH-RLSq is a self-completed 22-item questionnaire with seven of the items used to make the diagnosis and the remaining items used to further characterize the condition.[9,32] CH-RLSq includes items covering the basic diagnostic and differential diagnostic features of RLS.[32] Allen et al. assessed the validity of the CH-RLSq in 2,005 people who were blood donors. Of the 2,005 participants, a total of 185 participants who completed the CH-RLSq agreed to be selected for expert clinical diagnosis using a validated questionnaire (Hopkins telephone diagnostic interview). A telephone diagnosis by the expert was obtained on 183 of 185 participants. It was reported that the CH-RLSq's normalized sensitivity and specificity were 87.2% (for participants with RLS) and 94.4% (for participants without RLS), respectively. The positive predictive values were 85.5%. The author concluded that the CH-RLSq provided a reasonable level of sensitivity and specificity for diagnosis of RLS in population-based studies.

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