Effects of IV iron treatment with ferumoxytol on health-related quality of life of patients with iron deficiency anemia

William E Strauss, MD, FACC,[a] Naomi V Dahl, PharmD,[a] Saroj Vadhan-Raj, MD,[b] Sarah Acaster, MSc,[c] Kristine Bernard, MPH,[a] Rene Dickerhoof, PhD,[c] Zhu Li, PhD,[a] and Lee F Allen, MD[a]

[a]AMAG Pharmaceuticals Inc, Waltham, Massachusetts; [b]The University of Texas MD Anderson Cancer Centre, Houston, Texas; and [c]Oxford Outcomes, San Francisco, California

Background Many patients with iron deficiency anemia (IDA) do not tolerate or adequately respond to oral iron and live with chronic anemia and related negative effects on health-related quality of life (HRQoL). However, data from double-blind, placebo-controlled trials exploring the effect of treatment on HRQoL in patients with IDA are lacking.
Objective To explore the HRQoL of IDA patients who are unresponsive to or intolerant of oral iron, and compare the effects of treatment with intravenous ferumoxytol or placebo in a double-blind randomized controlled trial.
Methods Unpublished HRQoL data using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), the Medical Outcomes Survey Short Form-36 (SF-36), and the Linear Analogue Scale Assessment (LASA) were collected from a previous study (NCT01114139). Between-group differences in change from baseline to the end of the study (week 5), evaluation of clinically meaningful change, and comparisons with population norms were analyzed.
Results Baseline HRQoL scores for ferumoxytol patients (n = 608) and placebo patients (n = 200) were notably below general population norms. Despite a substantial placebo effect, significant and clinically meaningful differences were found in favor of patients receiving ferumoxytol compared with those receiving placebo in FACIT-Fatigue improvement (10.6 vs 5.7; 95% CI for difference 3.1-6.71, $P < .0001$), all LASA domains: Energy ($P < .0001$), Activities of Daily Living ($P < .001$) and QoL ($P < .0001$) improvement, and all SF-36 domains (P's <.01- <.0001).
Limitations Short-term study, low number of cancer patients included (48 of 808)
Conclusions Patients with IDA who had been unsuccessfully treated with oral iron had poor baseline HRQoL scores. Ferumoxytol treatment resulted in clinically meaningful improvements in HRQoL, significantly greater than placebo, across all domains.
Funding/sponsorship AMAG Pharmaceuticals Inc, maker of the study drug

In the United States and worldwide, iron deficiency anemia (IDA) is one of the most common types of anemia.[1] In industrialized countries, most IDA cases are linked to abnormal uterine bleeding (AUB), gastrointestinal (GI) bleeding, cancer, postpartum bleeding, or chronic kidney disease.[2,3] The etiology of IDA in such patients represents the common pathophysiologic processes that lead to IDA, including blood loss, malabsorption, inadequate iron intake, and inflammatory disease. Iron is essential for the function of many key proteins including hemoglobin (Hb) and myoglobin (involved in oxygen transport and exchange), cytochromes (energy generation), various enzymes (cell proliferation and neurotransmission), and immune function. Iron deficiency can, therefore, have significant physiologic consequences that may have an impact on patients' health-related quality of life (HRQoL) .[4,5,6] The impact of disease on people and their experiences as they receive treatments are in many cases best captured through reports from the patients themselves using validated assessment instruments.[7] Many symptoms such as fatigue, depression, or discomfort and their degree of impact

Accepted for publication January 4, 2015. Correspondence: Naomi V Dahl; ndahl@amagpharma.com. Disclosures and conflicts of interest: William Strauss (executive director, medical affairs), Kristine Bernard, Naomi V Dahl, Zhu Li, and Lee F Allen are, or were at the time of the study, full-time employees of AMAG Pharmaceuticals Inc, the maker of the study drug. Dr Strauss, Dr Dahl, Ms Bernard, Dr Li, and Dr Allen, hold equity in the company. Sarah Acaster and Rene Dickerhoof are, or at the time of the study, were full-time employees of Oxford Outcomes Ltd, contracted by AMAG to design and execute the HRQoL analysis. Saroj Vadhan-Raj was the principal investigator of the AMAG-FER-IDA-301 study (NCT01114139), which forms the basis of the current study and which was sponsored by AMAG Pharmaceuticals and for which Dr Vadhan-Raj received research funding to support the clinical trial. JCSO 2016;14(8):342-350. doi: 10.12788/jcso.0232.

are only knowable by the patient.

Patient-reported outcomes (PROs) are commonly included in clinical trials to understand the impact of a treatment on symptoms, functioning or HRQoL and the full reporting of all PRO data associated with a clinical trial is being encouraged and more rigorously evaluated.[8] Currently available data from randomized controlled trials on the HRQoL of patients with IDA, and on whether treatment can improve their HRQoL, are sparse. Outcomes of patients with IDA have focused predominantly on fatigue, but the full picture of the impact on other HRQoL effects has rarely been reported, with open-label studies lacking placebo controls, and in some instances also lacking HRQoL domain mean scores, or baseline data, limiting the interpretation of those results.[9-15] Achieving a more comprehensive understanding of the impact of disease and its treatment on patients may be a valuable adjunct to clinical decision making in the case of IDA patients who are unresponsive to or intolerant of oral iron, because historically these patients have remained chronically undertreated.

To address those questions, we analyzed HRQoL data collected from the previously reported phase 3 study of ferumoxytol safety and efficacy.[16] The initial trial results reported secondary endpoints associated with fatigue (using the Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-Fatigue), the Medical Outcomes Survey Short Form-36 (SF-36) Vitality domain, and the Linear Analogue Scale Assessment [LASA] Energy domain) in line with the study Statistical Analysis Plan, but did not comprehensively report all the HRQoL data captured. This current report presents all of the HRQoL data captured in that study, which included: fatigue, physical functioning, social functioning, and emotional well-being. The aim is to fully explore the breadth of differences in HRQoL improvement when comparing the treatment of IDA with ferumoxytol to placebo, the clinical meaningfulness of these changes and/or differences, and finally the impact of IDA on HRQoL outcomes compared with population norms where available.

Methods

Study design

The current report presents analysis of patient-reported outcomes data from a previously published phase 3 randomized, placebo-controlled, double-blind trial, which examined the safety and efficacy of intravenous (IV) ferumoxytol on HRQoL compared with IV placebo in IDA patients with a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used (NCT01114139).[16]

In the original trial, after a 2-week screening period, patients with IDA were randomized 3:1 to receive 510 mg ferumoxytol (volume 17 mL) or normal saline placebo at the baseline visit (day 1), followed by a second dose 2-8 days later (week 1). Patients were observed weekly until the end of the 5-week treatment period (weeks 2-5). The study was conducted with adherence to and compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The study protocol was reviewed and approved by an institutional review board at each study center, and patients provided written informed consent prior to study start.

Patients

A full description of the inclusion and exclusion criteria has been published previously.[16] Briefly, eligible patients were men and non-pregnant, non-breastfeeding women aged 18 years or older and with a serum Hb level of 7.0- <10.0 g/dL and a transferrin saturation (TSAT) level of less than 20%. Eligible patients had either failed oral iron therapy or were intolerant to oral iron. Patients were excluded if they had a history of allergy to IV iron (ferumoxytol is contraindicated in patients with history of allergic reaction to any intravenous iron product and has a Boxed Warning for risk for serious hypersensitivity/anaphylaxis reactions) or a serum ferritin level of more than 600 ng/mL, anemia due to known causes other than iron deficiency, hematologic malignancy, or were on dialysis or with an estimated glomerular filtration rate of less than 30 mL/min per 1.73 m^2 of body area. Those who received parenteral iron therapy or another investigational agent within 4 weeks prior to screening, or oral iron or a blood transfusion within 2 weeks prior to screening, were also excluded.

Patients were stratified by baseline Hb level (>7.0 to ≤8.5 g/dL or >8.5 to <10.0 g/dL) and by categories of underlying condition (AUB, cancer, GI disorders, postpartum, and other [eg, nutritional iron deficiency, rheumatoid arthritis, heart failure]). Patients with more than one underlying condition potentially contributing to IDA, were assigned to one category based on the investigator's assessment of the likely greatest contributor.

Patient-reported outcome measures

This study included 3 PRO measures: the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue)[17] the Medical Outcomes Survey Short Form-36 (SF-36)[18], and the Linear Analogue Scale Assessments (LASA).[19] The FACIT-Fatigue questionnaire was administered at baseline and every week thereafter to week 5. The SF-36 and LASA questionnaires were administered at baseline, week 3, and week 5 only.

FACIT-Fatigue. This is a 13-item patient-reported assessment of fatigue with a 7-day recall period. Items are scored on a scale of 0-4 (0, Not At All and 4, Very Much So). To score the FACIT-Fatigue, all items are summed to create a single fatigue score with a range of 0-52. Higher scores represent better functioning or less fatigue. The FACIT-Fatigue has shown good reliability and validity in non-

IDA populations[17] and more recently in IDA-specific populations.[20]

A clinically meaningful difference or minimal important difference (MID) in the FACIT-Fatigue score has been reported as 3.0.[21,22] US population norms have been reported as a mean of 43.6 (SD, 9.4), with a mean population value in anemic cancer patients of 23.9 (SD, 12.6).[21]

SF-36. This is a validated generic HRQoL instrument for use in a range of conditions as well as the general population. Thirty-six items assess patient health across 8 domains: Bodily Pain (BP), General Health Perceptions (GH), Mental Health (MH), Physical Functioning (PF), Role Limitations due to Emotional Health Problems (RE), Role Limitations due to Physical Health Problems (RP), Social Functioning (SF), and Vitality (VT). All items use categorical response options (range, 2-6 options). From the individual subscales, 2 component summary scores are generated for physical and mental health. The first 5 subscales (PF, RP, BP, GH, VT) produce the physical component score (PCS) and the last 5 subscales (GH, VT, SF, RE, MH) produce the mental component score (MCS); the GH and VT subscales overlap between the 2 overall components. The scores for each subscale are converted to norm-based scores (based on the 1998 US general population), with a mean of 50 and a standard deviation of 10. A score of 100 represents the best health. The validity and reliability of the SF-36 has been well established.[23] An MID of 5.0 has been reported for all SF-36 domains.[24]

The SF-36 is also useful to derive population-based utility values by applying the SF-6D algorithm[25]. Utility values represent preference-based weights of a health state with values ranging from 1 (full health) to 0 (dead), with some health states categorized as worse than dead (<0), and can be combined with survival data to produce a measure of quality-adjusted life-years (QALYs). The SF-6D is based on 11 items from the SF-36, representing 6 multilevel dimensions that describe 18,000 health states. Any patient who completes the SF-36 can be uniquely classified according to the SF-6D for economic analyses. The SF-6D can be regarded as a continuous outcome scored on a scale of 0.29-1.00, with 1.00 indicating "full health," with a reported mean MID of 0.041.[26] US population norms with a mean of 0.75-0.80 (varying by age group and gender) have been reported.[27]

LASA. The LASA consists of 3 visual analogue scales (VAS), 1 for each of the following domains: Energy Level, Activities of Daily Living (ADL), and Overall Quality of Life (QoL). Each VAS has a 7-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 are indicative of better functioning and HRQoL. VAS scales have been established as valid and reliable PRO tools.[28]

MID values associated with the LASA energy, ADL, and QoL domains have been reported as 9.61, 8.74, and 9.81, respectively.[19] No population norm data have been reported.

Statistical analysis

Analysis set and missing data. All analyses were conducted on the intent to treat (ITT) population, which included any randomized patient with exposure to the study drug (ferumoxytol) or placebo by randomized treatment assignment. PRO measures were scored in accordance with their user manual scoring algorithms. The change from baseline value was imputed to zero (0) for missing values at post-baseline visits. Sensitivity analyses were conducted with no imputation for missing values.

Patient-reported outcomes analyses. Mean change scores from baseline to each follow-up week (1-5) in the FACIT-Fatigue scale score, and baseline to week 5 for the SF-36 and LASA domains were compared across the treatment arms. The proportion of patients achieving or exceeding the MID from baseline to week 5 was calculated for the FACIT-Fatigue and all domains of the SF-36.

Differences between treatment groups in continuous outcomes were evaluated using analysis of covariance (ANCOVA), with the ANCOVA model adjusted for baseline Hb level and primary underlying condition (ie, AUB, postpartum anemia, cancer, GI disorders, or other conditions). Categorical outcomes were evaluated using the Cochran-Mantel-Haenszel test, adjusting for baseline Hb level and primary underlying condition. Within group change over time from baseline to the various post baseline assessment time points were assessed using paired *t* tests, expressed as 95% confidence interval (CI). Statistical significance was established if the *P* value was ≤.05.

Results

Patient characteristics

A total of 812 patients were randomized to 2 groups (ferumoxytol, 609; placebo, 203). The ITT population included 808 patients who had any exposure to study drug (ferumoxytol, 608; placebo, 200) and excluded 4 patients who withdrew from the study before administration of study drug. Detailed information about patient disposition, including the CONSORT patient flow diagram are available as part of the online supplementary information accompanying original study publication.[16] Baseline patient demographic and clinical characteristics of the 2 treatment groups were comparable (Table), including mean baseline Hb levels (ferumoxytol 8.8 g/dL; placebo, 8.9 g/dL) and mean baseline TSAT levels (ferumoxytol, 7.0%; placebo, 5.4%). Similarly, baseline mean patient-reported outcome scores were comparable across the 2 treatment

TABLE Baseline patients demographic and clinical characteristics

Characteristic	Treatment group	
	Ferumoxytol (n = 608)	Placebo (n = 200)
Mean age, y (SD)	44.8 (13.82)	46.0 (13.58)
Sex, n (%)		
Female	542 (89.1)	178 (89.0)
Male	66 (10.9)	22 (11.0)
Mean height, cm (SD)	163.2 (8.74)	163.3 (8.57)
Mean weight, kg (SD)	78.8 (24.42)	79.0 (23.81)
Race, n (%)		
American Indian/Alaskan Native	3 (0.5)	2 (1.0)
Asian	98 (16.1)	32 (16.0)
Black/African American	152 (25.0)	50 (25.0)
Native Hawaiian/other Pacific Islander	1 (0.2)	0 (0.0)
White	340 (55.9)	111 (55.5)
Other/multiracial	14 (2.3)	5 (2.5)
Ethnicity, n (%)		
Hispanic/Latino	110 (18.1)	34 (17.0)
Not Hispanic/Latino	498 (81.9)	166 (83.0)
Baseline measurements, mean (SD)		
Hb level, g/dL	8.9 (0.89)	8.8 (0.89)
TSAT, %	7.0 (12.9)	5.4 (4.9)
Serum ferritin level, ng/ml	22.6 (80.7)	20.7 (59.8)
Hb subgroups, n (%)		
>7.0 to ≤8.5 g/dL	189 (31.1)	62 (31.0)
>8.5 to <10.0 g/dL	419 (68.9)	138 (69.0)
Primary underlying condition subgroups, n (%)		
AUB	260 (42.8)	84 (42.0)
Cancer[a]	29 (4.8)	10 (5.0)
GI disorders	173 (28.5)	58 (29.0)
Postpartum anemia	4 (0.7)	0 (0.0)
Other[b]	142 (23.4)	48 (24.0)
Patient-reported outcomes measure, mean (SD)		
FACIT-Fatigue (population norm, 40.1 [10.4])	24.1 (11.8) (n = 593)	24.7 (11.3) (n = 195)
SF-6D Utility score (population norm, 0.75-0.80)	0.62 (0.15) (n = 595)	0.63 (0.14) (n = 197)
LASA domain		
Energy	35.5 (20.7) (n = 509)	36.2 (21.8) (n = 171)
Activities of daily living	43.3 (23.1) (n = 509)	42.5 (23.0) (n = 171)
Quality of life	46.9 (23.9) (n = 508)	48.6 (24.0) (n = 171)

AUB, abnormal uterine bleeding; FACIT, Functional Assessment Of Chronic Illness Therapy; GI, gastrointestinal; Hb, hemoglobin; LASA, Linear Analogue Scale Assessment; SF-36, Medical Outcomes Survey Short Form-36; SF-6D, 6-dimensional preference-based measure of health status derived from SF-36; TSAT, transferrin saturation

[a]There were 9 additional patients with cancer who were assigned to different categories based on the investigators' assessment that another comorbid condition was the likely greatest contributor to their IDA. [b]Included nutritional iron deficiency, heart failure, and rheumatoid arthritis.

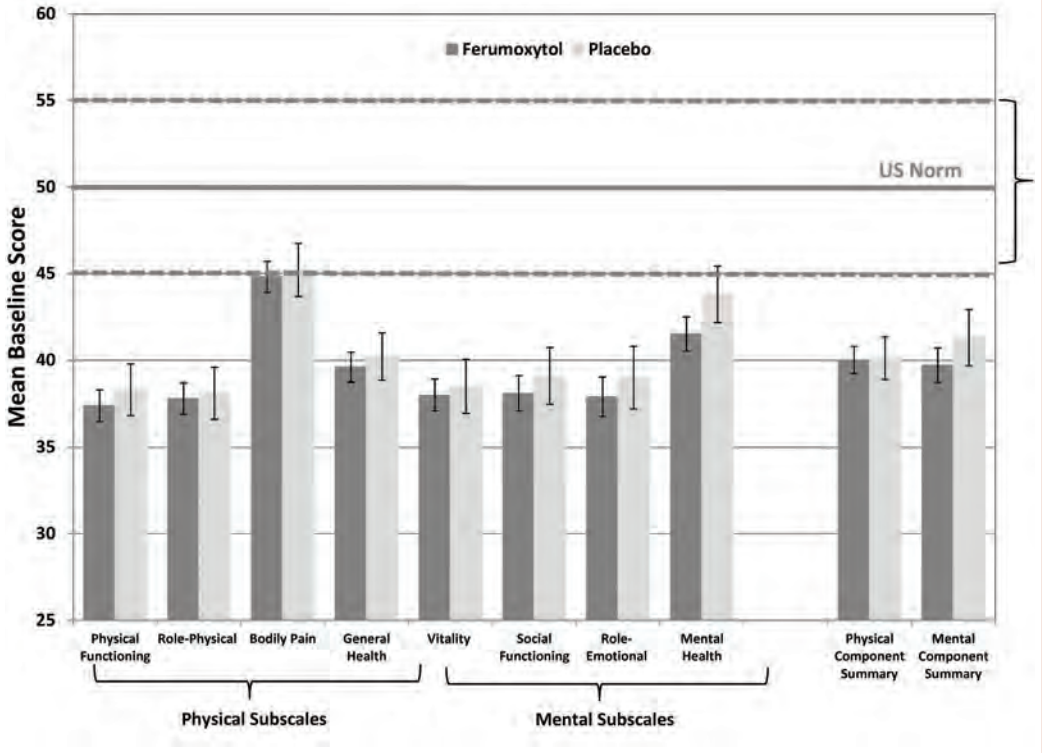

FIGURE 1 Mean baseline SF-36 scores.

Note: Error bars represent 95% confidence intervals (1.96 x standard error).

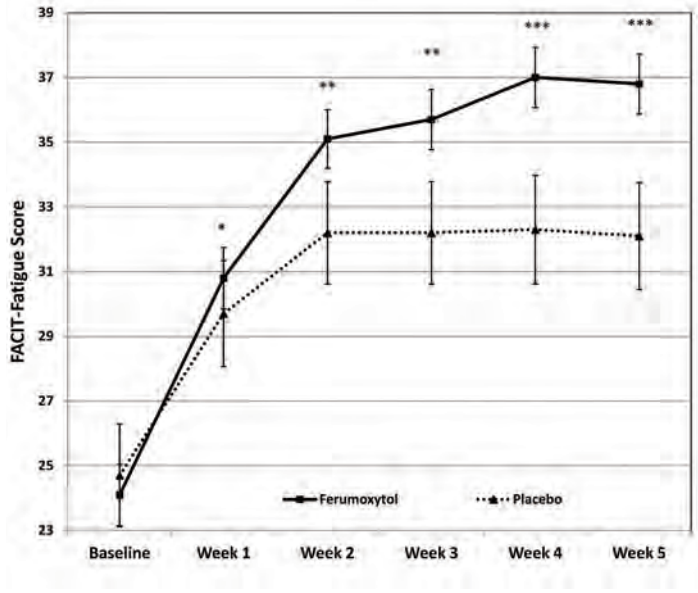

FIGURE 2 FACIT-Fatigue mean scores.

FACIT, Functional Assessment of Chronic Illness Therapy

Note: Between group difference in change scores: *P < .05; **P < .001; ***P < .0001. P-value was derived from the least squares means and an analysis of covariance model, adjusted for baseline hemoglobin and underlying condition. Error bars represent 95% confidence intervals (1.96 x standard error).

groups for all domains and HRQoL concepts (Table, Figure 1). All baseline scores were clinically meaningfully lower than the population norms for FACIT-Fatigue (MID, 3.0), SF-36 domains (MID, 5.0; Figure 1) and SF-6D utility score (MID, 0.04).

FACIT-Fatigue

Ferumoxytol was superior to placebo in the mean improvement in fatigue score from baseline to each follow-up assessment (Figure 2). Although both treatment arms showed improvement in fatigue at weeks 1 and 2, only the ferumoxytol-treated group continued to show an increase in FACIT-Fatigue scores from weeks 3-5, whereas the placebo group demonstrated no further improvement. By week 5, the mean increase in FACIT-Fatigue scores for ferumoxytol-treated patients was 11.7 (SD,11.7), compared with 6.8 (SD, 9.5) for those receiving placebo. After controlling for baseline Hb and underlying condition, the lower bound confidence interval of the between-group difference (mean, 4.9; 95% CI, 3.1-6.7; P < .001) was above the MID, indicating a clinically meaningful between-group difference. Similarly, at week 5, the proportion of patients achieving or exceeding the MID was significantly higher for ferumoxytol patients (72%) than for the placebo-treated patients (59%; P < .001). The correlation of FACIT-Fatigue scores with hemoglobin level (grouped in 0.5 g/dL categories) across the treatment period was high (r = 0.97, P = .002). The week-by-week changes from baseline in FACIT-Fatigue scores and the mean weekly values for Hb levels and measures of iron status, TSAT and CHr (reticulocyte Hb content) are shown in Figure 3.

SF-36

Patients in the ferumoxytol group showed greater mean improvement of all HRQoL domains from baseline to week 5 than did placebo patients (Figure 4). Both groups demonstrated some improvement from baseline. However, only in ferumoxytol-treated patients did the level of change reported in almost all domains (VT, PF, RP, SF, RE, MH, and MCS) correspond with clinically meaningful improve-

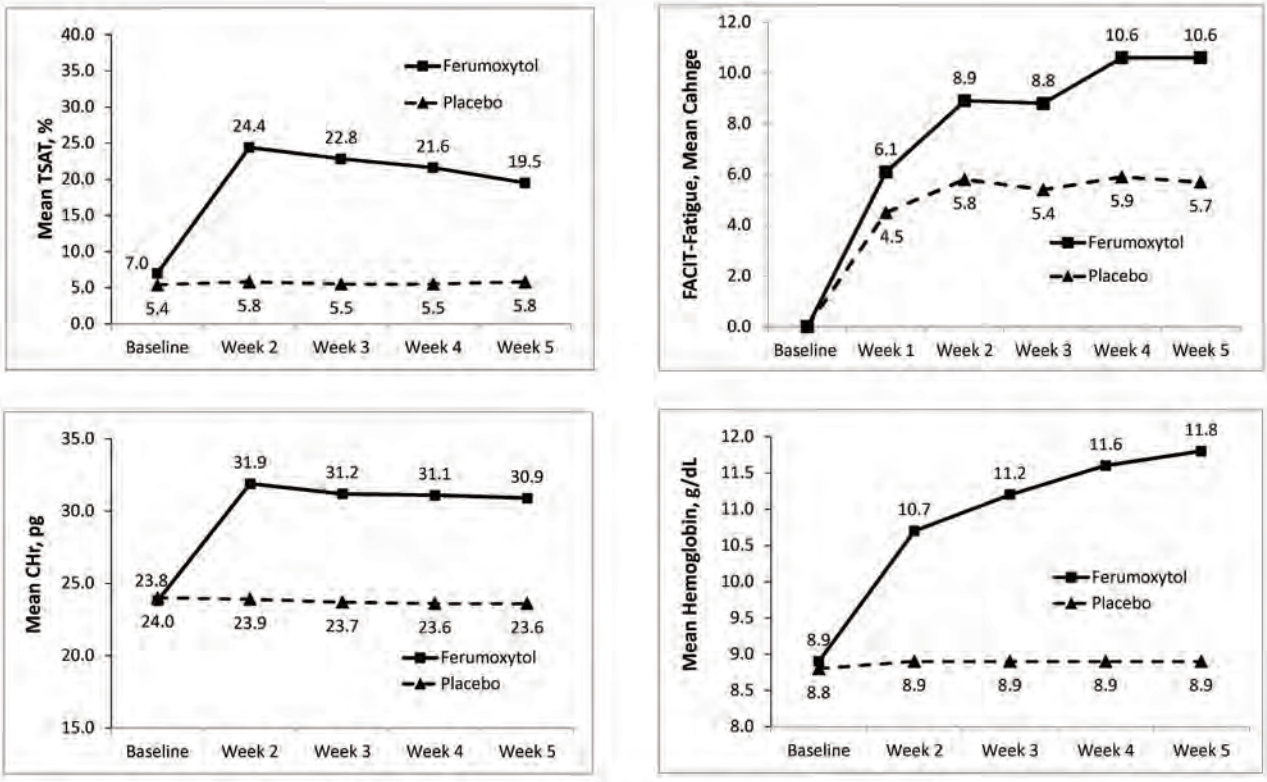

FIGURE 3 Weekly laboratory values and FACIT-Fatigue change from baseline.

CHr, reticulocyte hemoglobin content; FACIT, Functional Assessment of Chronic Illness Therapy; TSAT, transferrin saturation

P < .05 at each time point for mean difference between treatment groups in change from baseline.

ment. The lower bound 95% CI in all these cases was greater than the MID of 5.0. By those criteria, none of the changes in the placebo-treated patients exceeded the MID.

SF-6D

From baseline to week 5, there was significantly greater improvement in SF-6D utility scores in patients in the ferumoxytol group compared with those in the placebo group (mean change, 0.11 vs 0.04, respectively; *P* < .0001). After controlling for baseline covariates, the lower bound CI of the between-group difference (mean, 0.07; 95% CI, 0.05-0.09) was higher than the MID of 0.041, indicating a clinically meaningful between-group difference. Likewise, the level of improvement reported in the ferumoxytol-treated patients was clinically meaningful (95% CI, 0.10-0.12), which was not true of the level of improvement reported by placebo-treated patients (95% CI, 0.02-0.06).

LASA

The mean improvement of all LASA domain scores from baseline to week 3 and week 5 was better among ferumoxytol-treated patients that among those who received placebo (**Figure 5**). The level of improvement reported for all LASA domains was clinically meaningful in ferumoxytol-treated patients. At week 5, the lower bound 95% CI of each ferumoxytol mean change score was greater than the associated Energy, ADL, and QoL domain MIDs (9.61, 8.74, and 9.81, respectively). No changes in LASA domain scores in placebo-treated patients achieved this definition of clinical meaningfulness.

Discussion

Capturing the impact of disease and treatment on patients' HRQoL by using patient-reported outcome measures is a useful adjunct to clinical decision making for patients, physicians, and other health care providers. It is essential to fully understand the impact of IDA on patients' HRQoL in order to evaluate the benefits and value an IV therapy could offer. This study aimed to explore the impact of IDA on HRQoL outcomes, and further, to assess the magnitude of the impact of ferumoxytol compared with placebo on these important HRQoL endpoints.

Ferumoxytol is an IV iron therapy approved by the FDA for treatment of IDA in patients with chronic kidney disease. A recent study demonstrated that ferumoxytol was effective in patients with IDA and a history of unsatisfactory oral iron therapy or in whom oral iron cannot not be used. In that study, the proportion of ferumoxytol

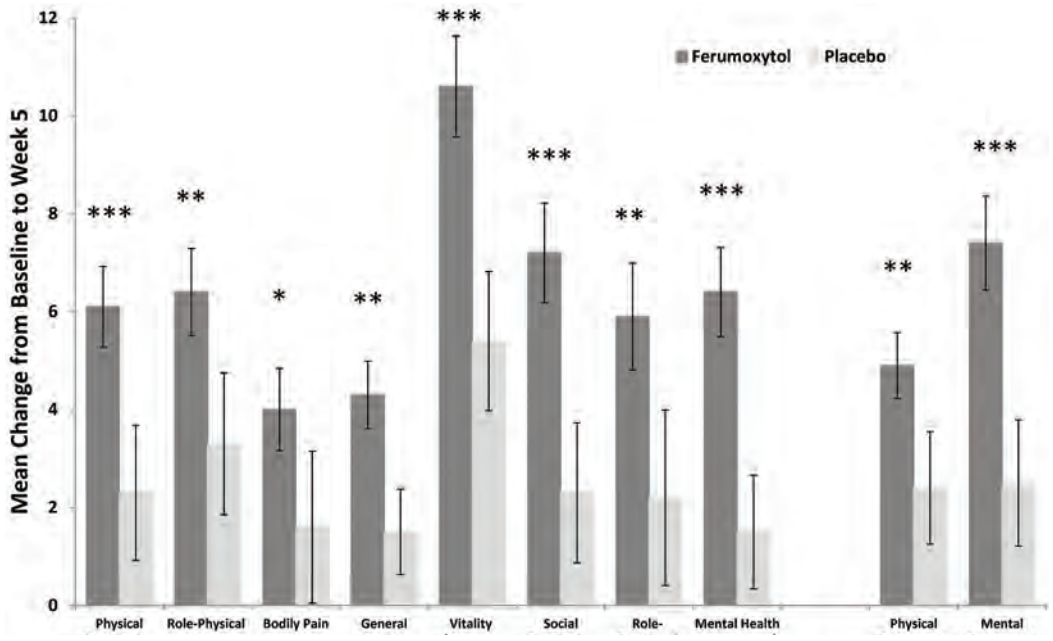

FIGURE 4 SF-36 Mean change from baseline to week 5.

Notes: Between group difference in change scores: *P < .05; **P < .001; ***P < .0001. P-value was derived from the least squares means and an analysis of covariance model, adjusted for baseline hemoglobin and underlying condition. Error bars represent 95% confidence intervals (1.96 x standard error).

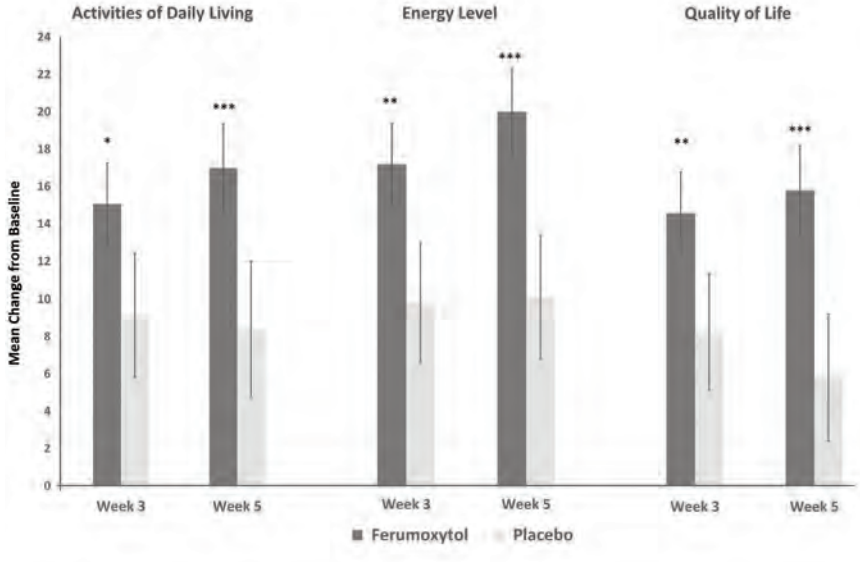

FIGURE 5 LASA mean change from baseline to week 3 and week 5.

LASA, Linear Analogue Scale Assessment

Notes: Between group difference in change scores: *P < .05; **P < .01; ***P < .001. P-value was derived from the least squares means and an analysis of covariance model, adjusted for baseline hemoglobin and underlying condition. Error bars represent 95% confidence intervals (1.96 x standard error).

patients achieving an Hb increase of ≥2.0 g/dL at week 5 was 81.1%, compared with 5.5% of placebo patients (P < .0001); the mean increase in Hb in was 2.7 g/dL compared with 0.1 g/dL, respectively (P < .0001); and the increases in TSAT were 11.4% and 0.4% respectively (P < .0001).[16]

As demonstrated by the baseline PRO characteristics of this patient population, IDA has a significant impact on patient HRQoL. The baseline levels of patient-reported fatigue as measured by the FACIT-Fatigue scale were more than 15 points (1.5 SDs) below the population norm, with 3 points considered to indicate a clinically meaningful decrement. This level of fatigue is in line with that previously reported in anemic cancer patients (mean, 23.9; SD, 12.6).[21] Likewise, the baseline LASA Energy, Activity, and QoL mean scores were similar to those reported by anemic cancer patients who were undergoing cytotoxic chemotherapy in 2 large clinical trials involving more than 3,500 patients (38.6-39.4, 38.8-40.8, and 45.4-46.4, respectively),[29,30] and the SF-36 Vitality domain scores were more than 10 points (1 SD) below the population norm. Notably, decrements of this level and greater (5-10) on the Vitality domain of the SF-36 have been associated with an inability to work, job loss in the subsequent year, and hospitalization over the next year in analyses performed on a large population data set of 3,445 patients from the Medical Outcomes Study.[31]

Based on the findings of the present study, it is evident that the impact of IDA is not limited to fatigue, but also affects many other aspects of patients' HRQoL. At baseline, all SF-36 domains were clinically, meaningfully lower than the population norm (MID, 5.0); almost all domains, with the exception of Bodily Pain, were around 1 SD below the population norm. This global impact of IDA on patients' HRQoL was also reflected in the SF-6D utility values, which were around 0.15 points below the population mean of 0.75-0.80, exceeding a clinically meaningful decrement of 0.041.[26] These findings are consistent with many previous studies dem-

onstrating the relationship between decreased work capacity, and endurance, with both non-anemic iron deficiency and iron deficiency anemia.[5] In the IDA patient population with this poor baseline HRQoL profile, ferumoxytol demonstrated superiority over a strong placebo response in all HRQoL domains. Ferumoxytol provided significantly greater, and clinically meaningful, improvement in FACIT-Fatigue from baseline to week 5; almost restoring fatigue levels to population norms over that period. FACIT-Fatigue improvements were mirrored in the alternative measures of fatigue using specific domains in the LASA and SF-36 instruments. The LASA Energy domain and SF-36 Vitality domain both demonstrated significantly greater improvement in fatigue with ferumoxytol than placebo. Furthermore, ferumoxytol consistently showed clinically meaningful levels of improvement; while placebo-treated patients showed some improvement, the level of change was not considered clinically meaningful based on published MIDs.

This pattern of results and clinically meaningful improvement was consistently reported across almost all SF-36 domains. All domains demonstrated ferumoxytol's superiority over placebo. In the ferumoxytol treatment arm, 7 of the 10 domains (VT, PF, RP, SF, RE, MH, MCS) also showed clinically meaningful improvement, whereas no clinically meaningful improvements were reported for placebo. Correspondingly, 9 of the 10 domains (VT, PF, RP, SF, RE, MH, GH, PCS, MCS) showed a significantly higher proportion of patients achieving the MID in the ferumoxytol treatment arm. The only SF-36 domain not demonstrating clinically meaningful improvement or a higher proportion of MID level response was the Bodily Pain domain. These results parallel the previously reported potential impact of treatment for IDA, with fatigue demonstrating the largest improvement consistent with a highly significant association with Hb[16] and the impact fatigue may have on patients' physical, social, and emotional well-being, but not their experience of pain.

The SF-36 findings were also mirrored in the LASA domains of ADL and QoL, adding further support to the global HRQoL improvement demonstrated by ferumoxytol over placebo. Finally, this global HRQoL superiority was also supported by the results of SF-6D analysis. These data not only provide further evidence of the clinically meaningful improvement in the ferumoxytol-treated patients, with significantly greater improvement than placebo, they also provide potentially valuable utility data. The mean utility score at week 5 in ferumoxytol-treated patients was close to the US population norm at 0.73, compared with the placebo group mean of 0.67. In addition to being statistically and clinically significant, this 0.06 difference could also be used in economic analysis to consider the HRQoL benefit offered by ferumoxytol over placebo in the calculation of quality adjusted life years associated with each treatment option.

Most, if not all, previous studies exploring the relationship between anemia treatment and changes in HRQoL were open label studies. When patients think they are receiving an active treatment, and therefore improvement is anticipated, PRO results can be confounded by social desirability responding. The pronounced placebo response seen in this study reinforces the importance of a placebo control when evaluating PRO results from clinical trials.

A limitation of this study was the relatively short time frame. It remains unknown how long the observed improvements would last beyond the 5-week study period. Future research should include longer term studies to assess the durability of response, and also to explore the effects, if any, on objective outcomes such as work productivity and use of health care.

This analysis found that patients with IDA, who had been unsuccessfully treated with oral iron, had very poor baseline HRQoL scores. Treatment with ferumoxytol, administered as a 510-mg dose followed by a second 510-mg dose 2-8 days later, resulted in significant and clinically meaningful improvement in HRQoL outcomes over placebo, which were consistently seen across all HRQoL domains. These findings add important information to the recently published clinical data on efficacy and safety of the use of ferumoxytol in this patient population.[16]

Acknowledgment

Authorship contribution: William Strauss, Kristine Bernard, and Lee F Allen contributed to the study design and acquisition of data. Sarah Acaster and Rene Dickerhoof developed the HRQoL specific statistical analysis plan and executed the analysis. William Strauss, Kristine Bernard, Saroj Vadhan-Raj, Naomi V Dahl, Zhu Li, and Lee F Allen contributed to interpretation of the data. Sarah Acaster, Rene Dickerhoof, and Naomi V Dahl drafted the manuscript. All authors reviewed, revised and contributed to the final manuscript.

References

1. World Health Organization. In: de Benoist B, McLean E, Egli I, Cogswell M (eds). Worldwide prevalence of anaemia 1993-2005: WHO global database on anaemia. Geneva, Switzerland: World Health Organization; 2008.
2. Croker JR, Beynon G. Gastro-intestinal bleeding – a major cause of iron deficiency in the elderly. Age Ageing. 1981;10:40-43.
3. Niv E, Elis A, Zissin R, Naftali T, Novis B, Lishner M. Iron deficiency anemia in patients without gastrointestinal symptoms: a prospective study. Fam Pract. 2005;22(1):58-61.
4. Lieu PT, Heiskala M, Peterson PA, Yang Y. The roles of iron in health and disease. Mol Aspects Med. 2001;22(1-2):1-87.
5. Haas JD, Brownlie T IV. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr. 2001;131(2 suppl):676S-88S; discussion 688S-90S
6. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr. 2001;131(2S-2):568S-579S.
7. Food and Drug Administration. Guidance for industry. Patient-reported outcome measures: use in medical product development

to support labeling claims. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Published December 2009. Accessed May 15, 2015.
8. Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: The CONSORT PRO Extension. JAMA. 2013;309(8):814-822.
9. Anthony LB, Gabrail NY, Ghazal H, et al. IV iron sucrose for cancer and/or chemotherapy-induced anemia in patients treated with erythropoiesis-stimulating agents. Comm Oncol. 2011;8(6):270-278.
10. Ando K, Morita S, Higashi T, et al. Health-related quality of life among Japanese women with iron-deficiency anemia. Qual Life Res. 2006;15(10):1559-1563.
11. Kaltwasser JP, Kessler U, Gottschalk R, Stucki G, Möller B. Effect of recombinant human erythropoietin and intravenous iron on anemia and disease activity in rheumatoid arthritis. J Rheumatol. 2001;28(11): 2430-2436.
12. Patterson AJ, Brown WJ, Powers JR, Roberts DC. Iron deficiency, general health and fatigue: results from the Australian Longitudinal Study on Women's Health. Qual Life Res. 2000;9(5):491-497.
13. Van Wyck DB, Mangione A, Morrison J, et al. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. Transfusion. 2009;49(12):2719-2728.
14. Zhou SJ, Gibson RA, Crowther CA, Baghurst P, Makrides M. Effect of iron supplementation during pregnancy on the intelligence quotient and behavior of children at 4 yrs of age: long-term follow-up of a randomized controlled trial. Am J Clin Nutr 2006;83(5):1112-1117.
15. Henry DH, Dahl NV, The Ferrlecit Cancer Study Group. Does quality of life improvement precede anemia correction in patients with chemotherapy-induced anemia treated with intravenous iron? J Clin Oncol. 2007;(18S):abstract 9082.
16. Vadhan-Raj S, Strauss W, Ford D, et al. Efficacy and safety of IV ferumoxytol for adults with iron deficiency anemia previously unresponsive to or unable to tolerate oral iron. Am J Hematol. 2014; 89(1):7-12.
17. Yellen SB, Cella D, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage. 1997;13(2):63-74.
18. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-483.
19. Patrick DL, Gagnon DD, Zagari MJ, et al. Assessing the clinical significance of health-related quality of life (HrQoL) improvements in anaemic cancer patients receiving epoetic alfa. Euro J Cancer. 2003;39(3):335-345.
20. Acaster S, Dickerhoof R, DeBusk K, Bernard K, Strauss W, Allen LF. Qualitative and quantitative validation of the FACIT-fatigue scale in iron deficiency anemia. Health Qual Life Outcomes. 2015;13:60.
21. Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002;94(2):528-538.
22. Cella D, Eton D, Lai J, Peterman AH, Merkel DE. Combining anchor and distribution based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) Anemia and Fatigue Scales. J Pain Symptom Manage. 2002;24(6):547–561.
23. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993;31(3):247-263.
24. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41(5):582-592.
25. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21(2):271-292.
26. Walters S, Brazier J. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005;14(6):1523-1515.
27. Fryback DG, Dunham NC, Palta M, et al. US Norms for six generic health related quality of life indexes from the national health measurement study. Med Care. 2007;45(12):1162-1170.
28. Maxwell C. Sensitivity and accuracy of the visual analogue scale: A psychophysical classroom experiment. Br J Clin Pharmacol. 1978;6(1):15-24.
29. Glaspy J, Bukowski R, Steinberg D, et al. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. J Clin Oncol. 1997;15(3):1218-1234.
30. Demetri GD, Kris M, Wade J, Degos L, Cella D. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. J Clin Oncol. 1998;16(10):3412-3425.
31. Bjorner JB, Wallenstein GV, Martin MC, et al. Interpreting score differences in the SF-36 vitality scale: using clinical conditions and functional outcomes to define the minimally important difference. Curr Med Res Opin. 2007;23(4):731-739.