Cost-effectiveness analysis of intravenous ferumoxytol for the treatment of iron deficiency anemia in adult patients with non-dialysis-dependent chronic kidney disease in the USA

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Objective: Ferumoxytol has demonstrated superior efficacy compared with oral iron in treating iron deficiency anemia in chronic kidney disease (CKD) patients. However, an economic evaluation of ferumoxytol has not been conducted. The aim of this study was to analyze the cost-effectiveness of treating iron deficiency anemia in adult non-dialysis-dependent CKD patients with ferumoxytol as compared with oral iron, alone or in combination with erythropoietin-stimulating agents (ESAs).

Methods: A decision analytic model compared health outcomes and costs associated with 5-week outpatient treatment of adult non-dialysis-dependent CKD patients with ferumoxytol or oral iron, each as monotherapy or in combination with ESAs in the USA. Direct costs include the following: drug acquisition and administration, adverse events, and medical management. Efficacy was determined as mean increase in hemoglobin (g/dL) from baseline over the 5-week period. Clinical inputs were derived from patient-level data from two Phase III randomized controlled trials of ferumoxytol vs. oral iron in non-dialysis-dependent CKD patients, and cost inputs from RED BOOK™ and Centers for Medicare and Medicaid Services data. Sensitivity analyses were performed to identify cost drivers and assess the stability of results.

Results: The 5-week treatment cost was $2,489, $5,216, $1,298, and $4,263 per patient for ferumoxytol, ferumoxytol with ESAs, oral iron, and oral iron with ESAs, respectively. The corresponding incremental costs per g/dL increase in hemoglobin, relative to ferumoxytol alone, were $398, $3,558, and $4,768 per patient. Efficacy was the main driver of cost-effectiveness for all treatments. Adverse event and medical management costs were the principal drivers of oral iron monotherapy costs, while drug acquisition substantially contributed to the overall cost for the remaining treatments.

Conclusion: These results suggest that ferumoxytol is a cost-effective treatment for iron deficiency anemia in non-dialysis-dependent CKD patients over a 5-week period compared with oral iron with or without ESAs. Ferumoxytol is more cost-effective as monotherapy.

Keywords: incremental cost-effectiveness ratio, ICER, health care costs, intravenous iron, iron therapy, erythropoietin

Introduction

Chronic kidney disease (CKD) affects more than 10% of adults and is the ninth leading cause of death in the USA.1,2 CKD can impair the production of erythropoietin (EPO), a hormone that regulates red blood cell (RBC) production, resulting in anemia.3,4 Iron deficiency anemia (IDA) represents the most severe stage of iron deficiency and is clinically diagnosed when hemoglobin (Hb) levels are more than 2 SDs below the mean.
for a normal individual of the same age and gender living at the same altitude. Among CKD patients, particularly those with severe kidney damage, IDA is associated with a range of symptoms characteristic of all anemias, and also serious complications such as compromised immune system, left ventricular hypertrophy, coronary heart disease, and even stroke. From 2007 to 2010, anemia prevalence was two times higher among adult CKD patients (15.4%) than in the general population (7.6%) and increased with severity (8.4% at stage 1 and 53.4% at stage 5). Standard initial IDA therapy in adults in the USA is orally administered iron (e.g., in the form of ferrous salts). Although oral iron is convenient and low in cost, benefits are often impaired by gastrointestinal (GI) side effects, poor treatment adherence (20% of patients develop GI distress and up to 30% discontinue oral treatment), and limited absorption. For patients who fail to respond to oral iron treatment due to noncompliance, chronic uncorrectable bleeding, oral iron intolerance, or intestinal malabsorption, intravenous (IV) administration is an alternative administration method. A recent systematic review and meta-analysis of 24 randomized controlled trials (RCTs), 13 of which included 2,369 patients with CKD stages 3–5, resulted in support for increased use of IV iron for patients with CKD stages 3–5 (not receiving dialysis). In addition, patients diagnosed with IDA due to CKD are often treated with EPO-stimulating agents (ESA) which further increases the demand for iron supplementation in these patients.

Ferumoxytol (FER) is a superparamagnetic iron oxide nanoparticle IV formulation approved by the US Food and Drug Administration (FDA) for the treatment of IDA in adult CKD patients. Clinical trials have demonstrated that FER significantly increases Hb levels in non-dialysis-dependent CKD (ND-CKD) patients compared with oral iron. FER in combination with ESA provides an incremental increase in Hb levels. Patients with lower baseline Hb levels respond better to FER treatment. Clinical trial results indicate that irrespective of concurrent ESA utilization, FER yields improved treatment outcomes as compared with oral iron in adult ND-CKD patients.

A health economic analysis of FER compared with oral iron in treating IDA in the adult ND-CKD population is not available in the published literature. Such an evaluation would provide key insights into the cost-effectiveness of FER treatment and an assessment of health economic outcomes for adult ND-CKD patients diagnosed with IDA. Using results of two Phase III randomized controlled clinical trials (NCT00255424, NCT00255437), a health economic model was constructed to evaluate the cost-effectiveness of FER and oral iron, as monotherapy or in conjunction with ESA, for the treatment of IDA in adult ND-CKD patients was developed.

### Materials and methods

#### Model design

A multivariate cost-effectiveness model was developed in Microsoft Excel to evaluate the direct costs and health outcomes associated with IDA treatment over a 5-week evaluation period in adult ND-CKD patients from the US payers’ perspective. Four treatments were compared: FER monotherapy, oral iron monotherapy, FER in combination with ESA, and oral iron in combination with ESA. Direct costs associated with each IDA treatment considered in the model include therapy costs (drug acquisition and administration), adverse event (AE) costs, and medical management costs. The model is based on patient-level clinical data (patient characteristics, treatment efficacy, and safety) from two Phase III RCTs of FER compared with oral iron in ND-CKD patients. Treatment efficacy, defined as mean increase in Hb (g/dL) from baseline observed in the clinical trials, was used as an effectiveness measure in the model.

#### Model framework

The model follows an ND-CKD patient who receives one of four outpatient IDA treatments over a 5-week time horizon. During treatment, a patient gains clinical benefits in the form of Hb increase and incurs therapy acquisition and administration costs, AEs, and medical management specific to the treatment. A patient receives only one treatment and may not switch during the time horizon. The model accounts for the cost due to partial vial wasting (the number of vials needed per administration is rounded up to the nearest integer). Partial vial wasting was relevant to the weight-based dosing of the ESAs. A patient may discontinue treatment at the end of each week up to week 4 (according to treatment-specific discontinuation observed in trials in intent-to-treat [ITT] population) with therapy costs accrued during a week reduced proportionally to the discontinuation rate in that week.

Model inputs include patient characteristics, therapy efficacy, and the cost of therapy acquisition and administration, medical management, and management of therapy-associated AEs. Model outputs include the average cost per g/dL increase in Hb for each treatment (to standardize for differences in effectiveness), incremental cost compared to FER monotherapy, and incremental cost per incremental change in Hb level.

The model also considers selected patient subgroups that reflect quartiles of baseline Hb levels observed in the
trials (<9.55 g/dL, 9.55–10.05 g/dL, 10.05–10.45 g/dL, and ≥10.45 g/dL). In each subgroup, efficacy of each treatment is assumed equal to the efficacy observed in clinical trials.

**Model inputs and data sources**

**Clinical inputs**

Clinical inputs, including patient weight and baseline Hb, treatment efficacy, vial size/pill strength, ESA utilization distribution, and clinical safety data inclusive of AE types and rates, were obtained from data pooled from two Phase III clinical trials – NCT00255424 (N = 304) and NCT00255437 (N = 303).3,16 Trial summaries are presented in Table 1 and key clinical input values in Table 2.

Patient weight and baseline Hb level were determined as the mean baseline weight and Hb level of all patients pooled from both trials regardless of treatment. Treatment efficacy is not dependent on pill strength/vial size used and is determined as the mean increase in Hb from baseline through day 35 (week 5) among ITT patients who received that treatment.

Utilization rates of ESAs considered in the model were based on clinical trial data (42% of patients had darbepoetin alfa and 58% had epoetin alfa). For a patient receiving a treatment that includes an ESA, outcomes are determined for the treatment with darbepoetin alfa and epoetin alfa separately and then weighted based on their utilization rates.

All AEs observed in the clinical trials, regardless of assessment of causality, were included in this analysis and were categorized as serious or nonserious. Serious AEs (SAEs) include any patient outcome that is life-threatening, resulted in death, patient disability, inpatient admission or prolonged hospitalization, congenital anomaly, birth defect, or permanent damage. Non-SAes include any AEs observed that were otherwise not classified as an SAE in the clinical trials. Due to similar occurrence rates and a large difference between costs of SAE management and of non-SAE management, the effect of non-SAes on the cost of AE management was assumed negligible compared with that of SAes. Additional analysis of AEs confirmed that the effects of AEs on the model were minimal for various levels of individual AE costs. The SAE rate is calculated as the number of events over total number of patients on a specific treatment among all patients pooled from the two trials (Table 3).

Dose and administration frequency of each treatment were extracted from prescribing information for FER and both ESAs, while clinical trial data were used for oral iron.14,15,17 Oral iron (ferrous fumarate) was prescribed at a dose of 100 mg of elemental iron twice daily for the first 21 days of the time horizon. The model assumes a starting dose for adult ND-CKD patients as recommended by the prescribing information of each ESA: 50 units/kg three times weekly subcutaneously for epoetin alfa and 0.45 µg/kg subcutaneously at 4-week intervals for darbepoetin alfa.14,15 FER administration follows the recommended schedule of 510 mg on day 1 and a second 510 mg dose 3–8 days later.

### Table 1 Summary of clinical data sources

| Clinical data | NCT00255424 | NCT00255437 |
|---------------|-------------|-------------|
| **Study design** | 5-week Phase III, RCT | 5-week Phase III, RCT |
| **Study size, n** | 304 | 303 |
| **FER, n (%)** | 228 (75) | 226 (75) |
| **Oral iron, n (%)** | 76 (25) | 77 (25) |
| **N (%) with ESA use at baseline in ITT population** | 116 (38) | 129 (43) |
| **Administration schedule** | | |
| **FER** | 83 (36) | 95 (42) |
| **Oral iron** | 33 (43) | 34 (44) |
| **Day 21 efficacy, mean, g/dL** | | |
| **FER** | 0.48 | 0.65 |
| **FER + ESA** | 0.98 | 1.24 |
| **Oral iron** | 0.09 | 0.28 |
| **Oral iron + ESA** | 0.34 | 0.50 |
| **Day 35 efficacy, mean, g/dL** | | |
| **FER** | 0.62 | 0.91 |
| **FER + ESA** | 1.16 | 1.64 |
| **Oral iron** | 0.13 | 0.25 |
| **Oral iron + ESA** | 0.19 | 0.86 |

**Notes:** 1. Treatment randomization of FER vs. oral iron was 3:1. 2. Efficacy is defined as the change in Hb from baseline.

**Abbreviations:** ESA, erythropoietin-stimulating agent; FER, ferumoxytol; Hb, hemoglobin; ITT, intent-to-treat; IV, intravenous; RCT, randomized controlled trial.
Vial size or pill strength determines the number of vials or pills required in each administration. FER vial size and oral iron pill strengths, 510 mg/17 mL and 50 mg, respectively, are equivalent to those used in the trials. Vial sizes of 100 µg/mL and 2,000 units/mL/vial are assumed for darbepoetin alfa and epoetin alfa, respectively.

Medical management events consider routine medical procedures associated with IDA treatment and include relevant laboratory tests, blood draw (i.e., venipuncture), nurse consultation, and physician visit. Relevant laboratory tests include complete blood count (CBC), absolute reticulocyte count, Hb, transferrin saturation (TSAT), and serum ferritin. All tests occurring in the same week are assumed to be measured in a single blood draw. The frequency of medical management events, expressed as the number of events occurring over 5 weeks, was determined from the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Anemia Guidelines and prescribing information for both ESAs and is specific to each treatment.14,15,18

Cost inputs
Cost inputs include drug acquisition and administration costs, cost of treating SAEs, and medical management cost. Key cost inputs used in the model are presented in Table 4. Drug acquisition cost inputs are considered on a per vial or per pill basis and are equivalent to those used in the trials. Vial sizes of 100 µg/mL and 2,000 units/mL/vial are assumed for darbepoetin alfa and epoetin alfa, respectively.

Medical management events consider routine medical procedures associated with IDA treatment and include relevant laboratory tests, blood draw (i.e., venipuncture), nurse consultation, and physician visit. Relevant laboratory tests include complete blood count (CBC), absolute reticulocyte count, Hb, transferrin saturation (TSAT), and serum ferritin. All tests occurring in the same week are assumed to be measured in a single blood draw. The frequency of medical management events, expressed as the number of events occurring over 5 weeks, was determined from the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Anemia Guidelines and prescribing information for both ESAs and is specific to each treatment.14,15,18

### Table 2 Key clinical input values

| Clinical inputs                        | Value (in USD) | Reference                                      |
|---------------------------------------|----------------|-----------------------------------------------|
| Weight, mean (SD), kg                 | 88.46 (23.63)  | NCT00255424, NCT00255437                      |
| Baseline Hb, mean (SD), g/dL          | 9.90 (0.73)    | NCT00255424, NCT00255437                      |
| ESA utilization distribution, %       |                |                                               |
| FER vial size/pill strength           |                |                                               |
| FER, mg/17 mL                         | 510            | Feraheme PI17                                  |
| Oral iron, mg                         | 50             | Assumption                                    |
| Darbepoetin alfa, µg/mL               | 100            | Assumption                                    |
| EPA, units/mL                         | 2,000          | Assumption                                    |
| Treatment efficacy, mean (SD), g/dL   |                |                                               |
| CBC                                   | 0.76 (1.03)    | KDOQI Anemia Guidelines, Aranesp PI, Procrit PI14,15,18 |
| Absolute reticulocyte count           | 1.42 (1.44)    | KDOQI Anemia Guidelines, Aranesp PI, Procrit PI14,15,18 |
| TSAT                                  | 0.19 (0.75)    | KDOQI Anemia Guidelines, Aranesp PI, Procrit PI14,15,18 |
| Serum ferritin                        | 0.53 (1.20)    | KDOQI Anemia Guidelines, Aranesp PI, Procrit PI14,15,18 |
| Hb                                    | 0.76 (1.03)    | Aranesp PI, Procrit PI14,15,18                |
| Blood draw                            | 1.42 (1.44)    | KDOQI Anemia Guidelines, Aranesp PI, Procrit PI14,15,18 |
| Nurse consultation                     |                | Assumption                                    |
| Physician visit                       | 0.19 (0.75)    | Assumption                                    |
| No. of medical management events      |                |                                               |
| CBC                                   | 2.00           | Assumption                                    |
| Absolute reticulocyte count           | 4.00           | Assumption                                    |
| TSAT                                  | 0.53 (1.20)    | Assumption                                    |
| Serum ferritin                        | 0.19 (0.75)    | Assumption                                    |
| Hb                                    | 0.76 (1.03)    | Assumption                                    |
| Blood draw                            | 1.42 (1.44)    | Assumption                                    |
| Nurse consultation                     | 0.19 (0.75)    | Assumption                                    |
| Physician visit                       | 0.76 (1.03)    | Assumption                                    |

Note: Efficacy is defined as the change in Hb from baseline. 
Abbreviations: CBC, complete blood count; DPA, darbepoetin alfa; EPA, epoetin alfa; ESA, erythropoietin-stimulating agent; FER, ferumoxytol; Hb, hemoglobin; KDOQI, Kidney Disease Outcomes Quality Initiative; PI, prescribing information; TSAT, transferrin saturation.
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of occurrences of that event within the 5-week treatment period. Individual medical management event costs were derived from the Clinical Diagnostic Laboratory Fee Schedule and Physician Fee Schedule published by the CMS and Medical Expenditure Panel Survey (MEPS) Statistical Briefs.22,23

Table 3 SAE rate input values, costs referenced from IPPS FY 2016 Correction Notice,21 rates from NCT00255424 and NCT0025543721,16

| SAEs                                           | Cost per event (USD) | FER, n (%) | FER + ESA, n (%) | Oral iron, n (%) | Oral iron + ESA, n (%) |
|------------------------------------------------|----------------------|------------|------------------|------------------|------------------------|
| Acute coronary syndrome                        | $3,795.88            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Acute tubular necrosis                         | $5,555.32            | 0 (0)      | 0 (0)            | 0 (0)            | 1 (1.56)               |
| Adrenal insufficiency                          | $5,978.79            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Alteration in mental status                    | $4,344.56            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Anemia                                         | $5,062.74            | 0 (0)      | 0 (0)            | 1 (1.18)         | 3 (4.69)               |
| Angina pectoris                                | $3,597.43            | 0 (0)      | 0 (0)            | 1 (1.18)         | 0 (0)                  |
| Azotemia                                       | $4,095.32            | 0 (0)      | 0 (0)            | 1 (1.18)         | 0 (0)                  |
| Bradycardia                                    | $4,636.91            | 0 (0)      | 0 (0)            | 0 (0)            | 2 (3.13)               |
| Cardiac arrest                                 | $3,831.90            | 1 (0.37)   | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Cardiac failure chronic                        | $3,733.09            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Cardiac failure congestive                     | $5,733.09            | 3 (1.12)   | 1 (0.59)         | 1 (1.18)         | 0 (0)                  |
| Cardio-pulmonary arrest                        | $3,831.90            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Chest pain                                     | $3,910.46            | 2 (0.75)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Cholelithiasis                                 | $6,232.75            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Chronic obstructive airways disease            | $5,505.11            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Coronary artery disease                        | $3,795.88            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Diverticulitis                                 | $4,370.54            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Dyspnea                                        | $4,306.17            | 0 (0)      | 0 (0)            | 0 (0)            | 1 (1.56)               |
| Gangrene                                       | $5,902.60            | 0 (0)      | 1 (0.59)         | 0 (0)            | 1 (1.56)               |
| Gastritis                                      | $4,370.54            | 0 (0)      | 0 (0)            | 1 (1.18)         | 0 (0)                  |
| Gastroenteritis                                | $4,370.54            | 0 (0)      | 0 (0)            | 1 (1.18)         | 0 (0)                  |
| Gastroparesis                                  | $4,370.54            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Grand mal seizure                              | $4,690.66            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Hypercalcemia                                  | $4,264.82            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Hyperkalemia                                   | $4,264.82            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Hypertensive crisis                            | $3,913.41            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Hypovolemia                                    | $4,264.82            | 0 (0)      | 0 (0)            | 1 (1.18)         | 0 (0)                  |
| Hypoglycemia                                   | $4,998.37            | 1 (0.37)   | 0 (0)            | 0 (0)            | 1 (1.56)               |
| Hypoglycemic shock                             | $4,998.37            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Hypotension                                    | $4,506.38            | 1 (0.37)   | 0 (0)            | 0 (0)            | 1 (1.56)               |
| Hypothermia                                    | $4,344.56            | 0 (0)      | 0 (0)            | 0 (0)            | 1 (1.56)               |
| Hypovolemia                                    | $4,264.82            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Hypoxia                                        | $4,821.77            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Hypoxic encephalopathy                         | $5,952.80            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Ischemic cardiomyopathy                        | $3,795.88            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Loss of consciousness                          | $4,506.38            | 0 (0)      | 0 (0)            | 0 (0)            | 1 (1.56)               |
| Lower back pain                                | $5,107.63            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Nausea                                         | $4,370.54            | 0 (0)      | 0 (0)            | 1 (1.18)         | 0 (0)                  |
| Pancreatitis                                   | $5,210.99            | 0 (0)      | 0 (0)            | 1 (1.18)         | 0 (0)                  |
| Peripheral vascular disease                    | $5,902.60            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Pneumonia                                      | $5,726.00            | 1 (0.37)   | 1 (0.59)         | 1 (1.18)         | 2 (3.13)               |
| Pulmonary edema                                | $7,243.88            | 1 (0.37)   | 0 (0)            | 2 (2.35)         | 0 (0)                  |
| Renal failure                                  | $5,555.32            | 1 (0.37)   | 1 (0.59)         | 1 (1.18)         | 1 (1.56)               |
| Scrotal swelling                               | $4,629.23            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Supraventricular tachycardia                   | $4,636.91            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Syncope                                        | $4,506.38            | 0 (0)      | 2 (1.18)         | 0 (0)            | 0 (0)                  |
| Transient ischemic attack                      | $4,268.37            | 0 (0)      | 1 (0.59)         | 0 (0)            | 0 (0)                  |
| Ulcerative esophagitis                         | $4,370.54            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Ventricular fibrillation                       | $4,636.91            | 1 (0.37)   | 0 (0)            | 0 (0)            | 0 (0)                  |
| Vomiting                                       | $4,370.54            | 0 (0)      | 0 (0)            | 1 (1.18)         | 0 (0)                  |

Abbreviations: ESA, erythropoietin-stimulating agent; FER, ferumoxytol; FY, financial year; IPPS, inpatient prospective payment system; SAEs, serious adverse events.
Analyses
The primary outcomes analyzed were overall cost and cost-effectiveness (expressed as average cost per g/dL increase in Hb) for each treatment, and the incremental cost and incremental cost-effectiveness of each treatment compared to FER monotherapy.

Overall cost is calculated as the sum of total therapy cost, average AE cost per patient, and total medical management cost. Treatment cost-effectiveness is determined as the ratio of the overall treatment costs and its efficacy. Incremental cost is the cost difference, while incremental efficacy is the difference in Hb increase (from baseline) between a treatment of interest and FER monotherapy. Incremental cost-effectiveness is the ratio of the incremental cost and incremental efficacy. These outcomes are stratified by cost components, including therapy costs, SAE costs and medical management costs for each treatment.

One-way sensitivity analyses were performed to identify cost drivers and multivariate probabilistic sensitivity analysis (PSA) to assess the stability of the results. One-way sensitivity was analyzed as a series of univariate variations in key parameters (weight, baseline Hb level, efficacy, cost per vial or per pill, administration costs, costs due to SAE management, and medical management costs). Each key parameter is varied (increased/decreased) by 20% of its default value, while all other parameters are kept constant at their default values. The multivariate sensitivity analysis utilized 1,000 iterative Monte Carlo simulations for each treatment pathway to examine the effects of simultaneous variation in multiple input parameters based on random sampling from the following distributions: normal (patient weight, baseline Hb level, efficacy), gamma (therapy acquisition, administration costs), and uniform (AEs).

Results
Base case
The total direct cost for FER monotherapy was $2,489 as compared with $1,298 for oral iron monotherapy. The majority of the overall cost of the FER monotherapy treatment was attributed to drug acquisition cost (51.9%), while the total cost of oral iron monotherapy was mostly composed of AE costs (64.7%). The concurrent use of ESA resulted in an incremental cost of $2,727 for FER and $2,965 for oral iron, with the majority of the cost increase in product acquisition cost. Comparison of the results for the analyzed treatments is presented in Table 5.

FER is the most cost-effective treatment compared to oral iron with or without ESA use. FER monotherapy is approximately two times more cost-effective than oral iron monotherapy ($3,275 vs. $6,833 per 1 g/dL increase in Hb, respectively). In combination with ESA, FER remains more cost-effective than oral iron ($3,673 vs. $8,044 per 1 g/dL increase in Hb, respectively).

At base case, the model reflects general clinical practice where vials with remaining drug volume are discarded. Vial

### Table 4 Key cost input values

| Cost inputs                                           | Value (in USD) | Reference                                      |
|-------------------------------------------------------|----------------|-----------------------------------------------|
| Therapy acquisition cost, WAC per vial/pill           |                |                                               |
| FER, mean (SD)                                        | $645.36 ($64.54) | RED BOOK™ 201619                              |
| Oral iron, mean (SD)                                  | $0.18 ($0.02)   | RED BOOK™ 201619                              |
| Darbepoetin alfa, mean (SD)                           | $744.80 ($74.48)| RED BOOK™ 201619                              |
| Epoetin alfa, mean (SD)                               | $44.62 ($4.46)  | RED BOOK™ 201619                              |
| Therapy administration cost, per administration       |                |                                               |
| FER, mean (SD)                                        | $152.44 ($15.24)| Physician Fee Schedule 2015B, CMS20           |
| Oral iron, mean (SD)                                  | $0.00 ($0.00)   | Assumption                                    |
| Darbepoetin alfa, mean (SD)                           | $53.54 ($5.35)  | Physician Fee Schedule 2015B, CMS20           |
| Epoetin alfa, mean (SD)                               | $53.54 ($5.35)  | Physician Fee Schedule 2015B, CMS20           |
| Cost per medical management event                     |                |                                               |
| CBC                                                   | $10.59          | Clinical Diagnostic Laboratory Fee Schedule 2016, CMS23 |
| Absolute reticulocyte count                           | $5.45           | Clinical Diagnostic Laboratory Fee Schedule 2016, CMS23 |
| TSAT                                                  | $17.39          | Clinical Diagnostic Laboratory Fee Schedule 2016, CMS23 |
| Serum ferritin                                        | $18.57          | Clinical Diagnostic Laboratory Fee Schedule 2016, CMS23 |
| Hb                                                    | $3.23           | Clinical Diagnostic Laboratory Fee Schedule 2016, CMS23 |
| Blood draw                                            | $3.00           | Clinical Diagnostic Laboratory Fee Schedule 2016, CMS23 |
| Nurse consultation                                    | $74.45          | Physician Fee Schedule 2015B, CMS20           |
| Physician visit                                       | $169.48         | MEPS Statistical Brief #484: Expenses for Office-Based Physician Visits by Specialty, 201322 |

Abbreviations: CBC, complete blood count; CMS, Centers for Medicare and Medicaid Services; FER, ferumoxytol; Hb, hemoglobin; MEPS, Medical Expenditure Panel Survey; TSAT, transferrin saturation; WAC, wholesale acquisition cost.
wasting increases the cost of therapy acquisition in strategies with ESA. When vial wasting is not considered, FER remains more cost-effective than oral iron with or without ESA use (without ESA: $3,275 vs. $6,833; with ESA: $3,192 vs. $6,755).

Analysis of the treatment discontinuation showed minimal impact due to low discontinuation rates observed in the trials underlying the model, with FER remaining cost-effective compared with oral iron with or without concurrent ESA use (without ESA: $3,266 vs. $6,831; with ESA: $3,641 vs. $7,810).

FER, with or without ESA, was more cost-effective than oral iron irrespective of baseline Hb levels (Table 5). The cost-effectiveness of FER-based treatment does not greatly differ across the baseline Hb subgroups, while the difference in cost-effectiveness of oral iron treatment across subgroups is more pronounced. The difference in cost-effectiveness of oral iron-based treatment across the subgroups was primarily due to difference in recorded treatment efficacies – with the g/dL increase in Hb in the ≥10.45 g/dL baseline Hb subgroup reaching negative values, indicating a decrease in Hb. The outcomes for each subgroup are presented in Table 5.

### Sensitivity analyses

The results of one-way sensitivity analyses are illustrated in the tornado graphs in Figure 1. Among the varied parameters, the primary driver of cost per g/dL increase in Hb for all treatments was week 5 efficacy. With the exception of oral iron monotherapy, the acquisition cost per vial/pill was the second strongest driver of cost per g/dL increase. For oral iron monotherapy, cost is significantly influenced by AE costs and medical management costs.

The mean values of all simulated 1,000 iteration outcomes from the PSA for incremental cost and efficacy of

### Table 5 Overall cost and cost-effectiveness results for each treatment strategy, in the overall patient population and in different baseline Hb patient subgroups

| Results                                      | FER  | FER + ESA | Oral iron | Oral iron + ESA |
|----------------------------------------------|------|-----------|-----------|-----------------|
| Overall patient population                   |      |           |           |                 |
| Total therapy costs                          | $1,595.60 | $3,896.59 | $15.12   | $2,316.11       |
| Therapy acquisition cost                     | $1,290.72 | $3,080.93 | $15.12   | $1,805.33       |
| Therapy administration cost                  | $304.88  | $815.65   | $0.00    | $510.77         |
| AE costs                                     | $450.10  | $553.03   | $839.62  | $1,180.73       |
| Medical management costs                     | $443.51  | $766.23   | $443.51  | $766.23         |
| Physician and nurse costs                    | $338.96  | $636.76   | $338.96  | $636.76         |
| Laboratory test costs                        | $104.55  | $129.47   | $104.55  | $129.47         |
| Total costs                                  | $2,489.21 | $5,215.85 | $1,298.25 | $4,263.07       |
| Efficacy, a g/dL Hb increase                 | 0.76    | 1.42      | 0.19     | 0.53            |
| Cost per 1 g/dL Hb increase                  | $3,275.27 | $3,673.13 | $6,832.89 | $8,043.53       |
| Baseline Hb patient subgroups                |      |           |           |                 |
| <9.55 g/dL baseline Hb                       |      |           |           |                 |
| Overall costs                                | $2,037.95 | $3,966.60 | $1,298.25 | $3,465.08       |
| Efficacy, a g/dL Hb increase                 | 1.09   | 1.53      | 0.48     | 0.99            |
| Cost per 1 g/dL Hb increase                  | $1,874.84 | $2,587.48 | $2,676.80 | $3,466.00       |
| 9.55–10.05 g/dL baseline Hb                  |      |           |           |                 |
| Overall costs                                | $2,037.95 | $3,966.60 | $1,298.25 | $3,465.08       |
| Efficacy, a g/dL Hb increase                 | 0.77   | 1.80      | 0.12     | 0.36            |
| Cost per 1 g/dL Hb increase                  | $2,657.04 | $2,206.12 | $11,096.15 | $9,679.00      |
| 10.05–10.45 g/dL baseline Hb                 |      |           |           |                 |
| Overall costs                                | $2,037.95 | $3,966.60 | $1,298.25 | $3,465.08       |
| Efficacy, a g/dL Hb increase                 | 0.57   | 0.99      | 0.22     | 0.82            |
| Cost per 1 g/dL Hb increase                  | $3,575.35 | $4,002.63 | $5,982.72 | $4,230.87       |
| ≥10.45 g/dL baseline Hb                      |      |           |           |                 |
| Overall costs                                | $2,037.95 | $3,966.60 | $1,298.25 | $3,465.08       |
| Efficacy, a g/dL Hb increase                 | 0.63   | 1.12      | 0.00     | –0.03           |
| Cost per 1 g/dL Hb increase                  | $3,255.51 | $3,529.00 | –        | N/A             |

**Notes:** aEfficacy values were determined as the mean of pooled g/dL increase (rounded to two decimals) in Hb values observed in individual patient data of two Phase III RCTs of FER vs. oral iron in ND-CKD patients (NCT00255424 and NCT00255437). bDue to the demonstrated negative efficacy, cost per 1 g/dL increase is not applicable. **Abbreviations:** AE, adverse event; CKD, chronic kidney disease; ESA, erythropoietin-stimulating agent; FER, ferumoxytol; Hb, hemoglobin; N/A, not applicable; ND-CKD, non-dialysis-dependent CKD; RCTs, randomized controlled trials.
other treatments with respect to FER demonstrated that FER is more cost-effective than oral iron. Similar patterns were observed across all patient subgroups, therefore validating the cost-effectiveness of FER.

**Discussion**

This analysis, which was primarily based on patient-level clinical trial data, strongly suggests that FER is associated with superior clinical and economic benefits in the
treatment of IDA in adult ND-CKD patients compared to oral iron.

With or without ESA, FER is cost-effective compared with oral iron in treating IDA due to higher treatment efficacy and lower AE rates. ESA use in ND-CKD patients has recently decreased in response to new anemia guidelines.\textsuperscript{24} FER as a monotherapy is more cost-effective than in combination with ESA, likely reducing the need for ESA in ND-CKD patients when ESA use is optional. The impact of discontinuation on cost is negligible due to low discontinuation rates observed in the clinical trials. Vial wasting has no pronounced effect on the total treatment cost and only influences treatments that utilize ESAs. An analysis of vial size variation showed the same trends in cost-effectiveness.

The cost of oral iron-based treatments is predominantly driven by AE costs; AE management costs in FER-based treatments are approximately half of those in oral iron-based treatments. Different AE rates reported in the trials directly contribute to this AE management cost difference between oral iron- and FER-based treatments.

Both FER treatments are consistently more cost-effective than oral iron across all baseline Hb level subgroups. The superior cost-effectiveness of FER, with or without concurrent ESA, compared with oral iron treatments is more pronounced among patient subgroups with higher baseline Hb. FER is the most cost-effective in the subgroup with the lowest baseline Hb ($<9.55$ g/dL) due to the high efficacy observed.

Results were robust to the variation in costs and patient and therapy characteristics. Treatment efficacy, followed by therapy acquisition cost, is the main factor in determining the cost-effectiveness.

This analysis may be subject to limitations. The model is based on data from 5-week clinical trials; however, the 5-week treatment period was long enough for effects to be observed and achieve statistical significance, reflecting FER’s advantage in providing more rapid IDA correction. After 5 weeks of treatment, the difference in the observed efficacy of FER and oral iron was larger than the difference in cost, further reinforcing FER’s superior cost-effectiveness. While treatment with oral iron extending beyond 5 weeks may lead to better effectiveness, the extended treatment period may also be associated with additional medical management and AE costs that counteract the potential cost-effectiveness improvements. It is generally accepted that an increase in Hb of $1$ g/dL after 1 month of treatment indicates an adequate response to treatment and that, while IV therapy can restore iron stores in a single course of treatment, oral iron therapy should be continued for 3 months after the anemia is corrected to allow iron stores to become replenished.\textsuperscript{12,14,15,25} In a 6-month extension study, patients with IDA and a history of unsatisfactory oral iron therapy or in whom oral iron could not be used who had completed a randomized, double-blind, placebo-controlled trial were evaluated for IDA monthly. Those with persistent or recurrent IDA at any monthly evaluation received a further course of treatment. Overall, 61% of the patients did not require a second course of FER over the 6-month period.\textsuperscript{26} The two RCTs in this study did not measure the quality of life. However, the effect of IDA and its treatment on patient reported outcomes, especially fatigue, has been studied. In a double-blind, placebo-controlled trial, patients with a history of unsatisfactory oral iron therapy, or in whom oral iron could not be used, had very poor baseline health-related quality of life (HRQoL) scores (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], LASA-QOL), showing the levels of fatigue similar to those previously reported in anemic cancer patients. FER treatment resulted in clinically meaningful improvements in HRQoL, significantly greater than placebo, across all domains. The correlation of FACIT-Fatigue scores with Hb level (grouped in 0.5 g/dL categories) across the treatment period was high ($r = 0.97, P = 0.002$).\textsuperscript{27,28} These results were also observed among the subgroup of patients in this study with kidney disease.\textsuperscript{29} The two RCTs used in the cost-effectiveness model reported in this study recruited just over 600 patients; however, the sample size met the power calculation and the sample size of these studies is consistent with the majority of studies investigating treatments for IDA. The analysis specifically studied the cost-effectiveness of FER and oral iron and may not be generalizable to other IV iron preparations, which may require more infusions and venipunctures to administer $1$ g elemental iron. Finally, the model utilizes a snapshot of 2016 US cost data and does not take into consideration price fluctuations or regional variations; however, one-way sensitivity analysis evaluated 20% changes in each of the cost parameters assessing for possible price increases or decreases.

The model reflects practices observed in clinical trials. The results were determined from patient and treatment characteristics, including efficacies and AE occurrences, directly sourced from the trials. The analysis is based on patient data from the trials that have compared oral iron and FER treatments in a controlled environment with identical criteria for both treatment populations, which adds to the validity of the input values used while reducing potential biases and the number of assumptions.
Conclusion
This study strongly suggests that FER is a more cost-effective treatment for IDA in adult ND-CKD patients over a 5-week treatment period as compared with oral iron with or without ESA. FER as monotherapy is a more cost-effective option than in combination with ESA.

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Disclosure
Naomi V Dahl, William E Strauss, and Robert F Kaper are employees of AMAG Pharmaceuticals. William E Strauss and Naomi V Dahl own stock in AMAG Pharmaceuticals. Frank Corvino and Marko Zivkovic have current consulting agreements with AMAG Pharmaceuticals. The authors report no other conflicts of interest in this work.

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