

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212320Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	505(b)2/NME
Application Number(s)	212320
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Division/Office	Division of Hematology Products (DHP)
Review Completion Date	June 15, 2019
Established Name	Ferric Maltol
(Proposed) Trade Name	ACCRUFER
Pharmacologic Class	Iron replacement product
Code name	ST10 or ST10-021
Applicant	Shield Therapeutics
Formulation(s)	Oral capsules
Dosing Regimen	30 mg twice daily (BID)
Applicant Proposed Indication(s)/Population(s)	Treatment of iron deficiency anemia (IDA)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of iron deficiency anemia (IDA) in adults.

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OPQ=Office of Pharmaceutical Quality

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OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
APTT	activated partial thromboplastin time
bid	twice daily
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CD	Crohn's disease
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CKD	Chronic kidney disease
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DB	double blind
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
ESA	erythropoiesis-stimulating agent
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ETASU	elements to assure safe use
F	female
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
Fe ³⁺	ferric iron
GCP	good clinical practice

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GLP	good laboratory practice
GRMP	good review management practice
Hb	hemoglobin
HD	high dose
ICH	International Conference on Harmonization
IBD	Inflammatory bowel disease
IDA	Iron deficiency anemia
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IV	Intravenous
ITT	intent to treat
Kg	kilogram
LD	low dose
LOCF	last observation carried forward
LS	least square
M	male
MAR	missing at random
Max	maximum
MD	medium dose
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
Mg	milligram
µg	microgram
MI	multiple imputation
Min	minimum
mITT	modified intent to treat
MMRM	mixed model repeated measures
MONO	monocytes
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OFP	Oral ferrous products
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCV	packed cell volume
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PLAT	platelet counts

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PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TSAT	transferrin saturation
T _{1/2}	time to half maximal concentration
UC	ulcerative colitis
UN	unstructured variance-covariance structure

1 Executive Summary

1.1. Product Introduction

Ferric maltol (ACCRUFER®) is an oral iron replacement product which contains 30 mg iron and 201.5 mg maltol. Its anatomical therapeutic classification (ATC) pharmaco-therapeutic group is an iron trivalent oral preparation and it is formulated as a 30 mg capsule. Ferric maltol delivers iron for uptake across the intestinal wall and transfer to transferrin and ferritin.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of ferric maltol for the indication, “treatment of iron deficiency anemia in adults.” This recommendation is based on the findings from three randomized, double-blind, placebo-controlled, multi-center Phase III pivotal studies which investigated ferric maltol treatment for the treatment iron deficiency anemia (ST10-01-301/302 and ST10-01-303). Studies ST10-01-301 and ST10-01-302 enrolled a patient population with inflammatory bowel disease (IBD) and concomitant iron deficiency anemia whereas ST10-01-303 enrolled patients with non-dialysis dependent chronic kidney disease (CKD) and iron deficiency anemia. For the purpose of this review, ST10-01-301 and ST10-01-302 were considered as one study since the protocols were identical and their safety and efficacy results are pooled in this review.

The determination of efficacy was based on the mean difference in hemoglobin (Hb) concentration from baseline to the conclusion of the double-blind phase in each study, (Week 12 for ST10-01-301/302 and Week 16 for ST10-01-303). There were improvements in mean Hb levels for subjects in the ferric maltol treatment arm from baseline to the end of the double-blind treatment phase (Least Square [LS] mean change from baseline: 2.25 g/dL in ST10-01-301/302 and 0.50 g/dL in ST10-01-303), whereas there was no improvement for subjects in the placebo groups (0.06 g/dL in ST10-01-301/302 and -0.02 g/dL in ST10-01-303). The treatment difference for ferric maltol versus placebo was statistically and clinically significant in each of the studies with LS mean difference of 2.18 g/dL with p value < 0.0001 in ST10-01-301/302 and LS mean difference of 0.52g/dL with p-value of 0.0149 in the ST10-01-303 study.

Supportive efficacy was demonstrated by an improvement in Hb concentration from baseline to Week 4 and Week 8 for the ferric maltol treatment arms, whereas Hb levels remained similar in the placebo groups. In addition, mean ferritin (µg/L) levels in the ferric maltol treatment arms improved from baseline over Weeks 4, 8 and to the end of the double-blind treatment phase, with a mean overall improvement of 17.3 µg/L in ST10-01-301/302 and 34.50 µg/L in ST10-01-303, respectively. Mean ferritin levels in placebo subjects showed a mean overall change of 1.2 µg/L in ST10-01-301/302 and 7.23 µg/L in ST10-01-303 compared to baseline, respectively.

All disciplines agreed with the approval recommendation of ferric maltol or did not identify any outstanding issues that precluded the approval recommendation. In conclusion, ferric maltol

treatment resulted in substantial improvement in Hb from baseline levels at study entry as well as increased ferritin in the pivotal studies. Although there may be different underlying etiologies for iron deficiency anemia, the treatment of IDA is similar and thus supports the approval for iron deficiency anemia irrespective of the background disease. Oral ferric maltol represents an effective therapeutic option for the treatment of iron deficiency and resultant iron deficiency anemia.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ferric maltol is a stable complex of ferric iron and maltol. Two randomized, double-blind, placebo-controlled, multicenter Phase III pivotal studies investigated ferric maltol treatment for the treatment iron deficiency anemia (ST10-01-301/302 and ST10-01-303). ST10-01-301 and ST10-01-302 enrolled patients with IBD who had failed other oral iron replacement products or otherwise could not tolerate other oral iron preparations due to adverse effects. Trials ST10-01-301/302 s enrolled 128 patients (age range 18-76 years, 45 males and 83 females) with quiescent IBD and baseline hemoglobin concentrations between 9.5g/dL and 12 to 13g/dL for female and males(respectively) and ferritin < 30g/dL. All patients had to discontinue prior oral ferrous product treatment due to lack of efficacy or inability to tolerate oral iron replacement products. Subjects were randomized 1:1 to receive either 30mg ferric maltol twice daily or matched placebo control for 12 weeks. The major efficacy outcome was mean difference in Hb concentration from baseline to week 12 between ferric maltol and placebo. The least Square mean difference from baseline was 2.18 g/dL ($p < 0.0001$). The mean ferritin (ug/L) levels in ferric maltol subjects at baseline were 8.6ug/L and mean ferritin (ug/L) levels at Week 12 were 26.0 ug/L with mean overall improvement of 17.3 ug/L.

ST10-01-303 enrolled a patient population with non-dialysis dependent CKD with concomitant iron deficiency anemia requiring treatment. This trial enrolled 167 patients (mean age 67.4 years, range 39-90 years) with non-dialysis dependent CKD and baseline hemoglobin concentrations between 8g/dL and 11g/DL and ferritin < 25ug/L with a TSAT < 25% or ferritin < 50ug/L with TSAT < 15%. Ferric maltol was administered a t a dose of 30 mg twice daily and subjects were randomized 2:1 to receive either 30 mg twice daily or matched placebo control for 16 weeks. The major efficacy outcome was mean difference in hemoglobin concentration from baseline to Week 16 and the LS mean difference was 0.52g/dL ($p = 0.0149$). The mean change in ferritin concentration from baseline to Week 16 was 49.3 ug/L for the ferric maltol group and 6.6 ug/L for the placebo group. The mean difference for ferric maltol versus placebo was 42.7 ug/L.

Pooled safety data from studies ST10-01-301, ST10-01-302, and ST10-01-303 have demonstrated the safety and tolerability of ferric maltol (30 mg BID) in patients with IDA. Overall, ferric maltol was well tolerated by patients with IDA in the pivotal clinical studies. The most common adverse reactions in the pivotal studies were flatulence, diarrhea, constipation, feces discolored, abdominal pain, nausea, vomiting, and abdominal discomfort/distention. This adverse reaction profile is consistent with other oral ferrous replacement products which are associated

with adverse gastrointestinal side effects. Caution should be exercised in patients with pre-existing IBD who are receiving ferric maltol for the treatment of iron deficiency anemia and in patients with evidence of iron overload or receiving intravenous iron as excessive iron therapy can lead to excess storage of iron with possibility of iatrogenic hemosiderosis. Ferric maltol should not be administered to patients with signs or symptoms of an active IBD flare as oral iron products may exacerbate the condition.

In conclusion, ferric maltol treatment resulted in substantial improvement in Hb from baseline levels at study entry as well as increased ferritin in the pivotal studies. Although there may be different underlying etiologies for iron deficiency anemia, the treatment of IDA is similar and thus supports the approval for iron deficiency anemia irrespective of the background disease. Oral ferric maltol represents an effective therapeutic option for the treatment of iron deficiency and resultant iron deficiency anemia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Iron deficient states and iron deficiency anemia (IDA) impact a large proportion of individuals in the United States (U.S.) and internationally.	Iron deficiency and resultant IDA impacts a large number patients, particularly children, women of childbearing potential, and individuals with chronic conditions such as IBD and CKD.
Current Treatment Options	- Current treatment options for iron deficiency anemia include a variety of over the counter (OTC) oral iron replacement products that are readily available and do not require intravenous access. - If patients cannot tolerate available oral formulations of iron replacement products or have a lack of response without evidence of increasing iron stores or Hb levels, they are often treated with IV iron replacement products. IV iron treatments must be administered in a monitored healthcare setting and can take several hours to complete. While rare, some IV iron products have been associated with serious, life threatening side effects such as anaphylactic reactions.	Ferric maltol is a new oral formulation of iron that has been developed for the treatment of IDA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• In Study ST ST10-01-301/302, the major efficacy outcome was the mean difference in hemoglobin concentration from baseline to Week 12 between ferric maltol and placebo and the least square (LS) mean difference from baseline was 2.18 g/dL ($p < 0.0001$). The LS mean change in hemoglobin (Hb) concentration at the conclusion of the double-blind phase (Week 12 for ST10-01-301/302 was LS Mean was 2.25 (SE 0.12) in the ferric maltol arm compared to 0.06 (SE 0.13) in the placebo arm. • In Study ST ST10-01-301/302 the LS mean difference in change from baseline Hb to week 4 and 8 between ferric maltol and placebo were 1.04g/dL and 1.73g/dL, respectively. • In Study ST ST10-01-301/302 the mean ferritin (ug/L) levels in ferric maltol subjects at baseline were 8.6ug/L and mean ferritin (ug/L) levels at Week 12 were 26.0 ug/L with mean overall improvement of 17.3 ug/L. • In Study ST10-01-303 the major efficacy outcome was mean difference in hemoglobin concentration from baseline to week 16 between ferric maltol and placebo and the LS mean difference was 0.52 g/dL ($p=0.0149$). The LS mean change from baseline to week 16 was 0.50 in the ferric maltol arm and -0.02 in the placebo arm. • In Study ST10-01-303 An improvement was observed in Hb concentration from baseline to Week 4 and Week 8 for the ferric maltol treatment arms, whereas Hb levels remained similar in the placebo groups. • In addition, mean ferritin (µg/L) levels in the ferric maltol treatment arms improved from baseline over Weeks 4, 8 and to the end of the double-blind treatment phase, with a mean overall improvement of 17.3 µg/L in ST10-01-301/302 and 34.50 µg/L in ST10-01-303.	Ferric maltol treatment resulted in improvement in Hb from baseline levels at study entry as well as increased ferritin in the pivotal studies. Treatment with oral ferric maltol resulted in improvement in anemia secondary to iron deficiency and increased iron stores. Of note, the overall improvement in mean Hb from baseline at the conclusion of the ST10-01-303 double-blind phase was only 0.57 g/dL although statistically significant. The observed increase in mean Hb level can be only considered as a mild benefit. It is unclear why a more robust Hb response was not observed in this specific patient population. Anemia in patients with CKD is multi-factorial and driven by decreased erythropoietin (Epo) production, anemia of chronic disease, and decreased iron stores. There may have been additional confounding factors that resulted in the observed Hb response.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Pooled safety data from studies ST10-01-301, ST10-01-302 and ST10-01-303 (including data from the double-blind and open-label phases of ST10-01-301/302 and the double-blind phase of ST10-01-303) have demonstrated the safety and tolerability of ferric maltol (30 mg BID) in patients with IDA. • In the pooled safety population (N=222), a total of 165 (74.3%) patients who received ferric maltol experienced treatment emergent adverse events (TEAEs), 49 (22.1%) patients experienced drug-related TEAEs and 34 (15.3%) patients experienced SAEs. The most frequently reported TEAEs in the ferric maltol group were diarrhea (26 [11.7%]), abdominal pain (20 [9.0%]), and nasopharyngitis (21 [9.5%]). The most frequently reported drug-related TEAEs in the ferric maltol group were abdominal pain (9 [4.1%]), diarrhea (9 [4.1%]), and flatulence (9 [4.1%]). The majority of reported TEAEs were of mild to moderate intensity. • The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of the studies was 4.6% for patients taking ferric maltol and the most common adverse reaction leading to discontinuation • One death was reported in a patient treated with ferric maltol and was not related to study drug. Only 1 patient experienced a drug-related SAE (PT: abdominal pain). In total, 26 (11.7%) patients experienced TEAEs that led to study discontinuation, including 11 (5.0%) patients with drug-related TEAEs. The drug-related TEAEs leading to discontinuation were all gastrointestinal disorders and were reported at a low incidence (<2%).	Overall, ferric maltol was well tolerated by patients with IDA in the pivotal clinical studies. The most common adverse reactions in the pivotal studies were gastrointestinal conditions, including abdominal pain, diarrhea, and flatulence. This adverse reaction profile is consistent with other oral ferrous replacement products which are associated with gastrointestinal side effects. Caution should be exercised in patients with pre-existing IBD who are receiving ferric maltol for the treatment of iron deficiency anemia. Ferric maltol should not be administered to patients with signs or symptoms of an active IBD flare as oral iron products can exacerbate the condition.

1.4. **Patient Experience Data**

There was no patient experience data submitted with this application.

Cross-Disciplinary Team Leader
Tanya Wroblewski, MD

2 Therapeutic Context

2.1. Analysis of Condition

Iron deficiency affects a large proportion of the world's population including women of childbearing age, children, and individuals residing in low- and middle-income countries. The normal body iron content in an adult is approximately 3 to 4 grams.¹ The majority of iron is present in circulating red blood cells (RBCs), with additional iron stored in myoglobin and certain enzymes. Decreased dietary intake of iron, reduced absorption of iron, and acute or chronic blood loss are common etiologies of iron deficient states.¹

Iron deficiency occurs in several stages defined by the extent of iron depletion. Eventually, if negative iron balance is sustained, production of iron-deficient RBCs and ineffective hematopoiesis occur resulting in anemia. Changes in the peripheral blood count occur in proportion to the severity of iron deficiency and tend to lag behind changes in iron studies (i.e., reduced storage iron precedes anemia and microcytosis).² Thus, in early iron deficiency the complete blood count (CBC) may remain relatively normal.

As iron deficiency progresses and anemia develops, a low red blood cell (RBC) count, low hemoglobin (Hb) and hematocrit, low reticulocyte count, and low mean corpuscular volume (MCV) and low mean corpuscular hemoglobin (MCH) may be observed on routine peripheral blood counts. The platelet count may also be increased in patients with iron deficiency anemia. Iron deficiency anemia (IDA) is diagnosed when low serum levels of ferritin or transferrin saturation (TSAT) are measured in conjunction with decreased Hb levels.²

The presenting symptoms in adults with iron deficiency are primarily due to anemia. These may include fatigue, weakness, irritability, headaches, exercise intolerance, exertional dyspnea, angina pectoris, pica or ice cravings, and restless leg syndrome. Patients with concomitant cardiac or pulmonary conditions such as congestive heart failure, coronary artery disease and chronic respiratory failure may be more sensitive to decreasing hemoglobin levels and diminished oxygen carrying capacity. On physical exam, pallor, atrophic glossitis, angular cheilitis, and koilonychia may be observed although typically only in severe iron deficient states.

For the purpose of this review, inflammatory bowel disease (IBD) and chronic kidney disease are 2 conditions that predispose patients to iron deficiency and IDA that frequently require treatment.

Iron deficiency and IDA affect a significant proportion of individuals with inflammatory bowel disease (IBD), especially those with ulcerative colitis and Crohn's disease. Iron deficiency in IBD

is typically caused by chronic blood loss. The resulting anemia is compounded by decreased erythropoietin production and alterations in iron metabolism secondary to release of inflammatory cytokines and reactive oxygen metabolites, which is referred to as anemia of chronic inflammation or anemia of chronic disease.³ Other potential contributors to anemia in patients with IBD include vitamin B12 deficiency, folic acid deficiency, or drug-induced anemia (caused by sulfasalazine or thiopurines).³ Patients with IBD present several challenges when considering oral iron supplementation. Oral iron replacement products are convenient and inexpensive, but their use is limited by the fact that many patients with IBD have severe intolerance to oral iron preparations. In addition, oral iron may worsen IBD disease activity and patients may have ongoing inflammation that interferes with enteral absorption of oral iron products. For these reasons, intravenous (IV) iron supplementation is appropriate for many patients with IBD, as suggested by several expert panels.⁴ Numerous studies have demonstrated the safety and efficacy of various IV iron preparations in these patients. In Europe, IV iron is standard frontline therapy for IBD-associated iron deficiency.⁴

Anemia is common among patients with chronic kidney disease (CKD). Anemia underlies many of the symptoms associated with reduced kidney function and is associated with increased mortality and hospitalizations.⁵ Anemia in patients with CKD is multifactorial with anemia of chronic disease, decreased erythropoietin production and iron deficiency contributing to observed levels of Hb. In addition to erythropoiesis stimulating agents (ESAs), a majority of individuals with CKD require correction of iron deficiency to optimize responses to therapy. Iron replacement may be given orally or intravenously. The route of administration is selected based upon the severity of anemia and iron deficiency, the patient's ability to tolerate oral iron, the response to prior oral iron therapy, history of adverse reactions to intravenous iron, and the availability of venous access.⁵

Oral iron replacement products are typically administered to non-dialysis dependent CKD patients who are selected for iron therapy. Oral iron is readily available and does not require intravenous access. Intravenous iron is utilized in select CKD patients who require more rapid repletion of iron, who cannot tolerate oral iron, or who are unlikely to be effectively treated with oral iron replacement.

2.2. Analysis of Current Treatment Options

Table 1: Summary of Treatments Relevant to Proposed Indication

Generic Name	Iron Dextran	Iron Dextran	Ferric Gluconate	Iron Sucrose	Ferumoxytol	Ferric Pyrophosphate	Ferric Carboxymaltose
Trade Name	INFeD®	Dexferrum®	Ferrlecit®	Venofer®	Feraheme®	Triferic®	Injectafer®
NDA Number	17441	40024	20955	21135	22180	206317*	203565
Sponsor	Allergan	Luitpold	Sanofi Aventis	Luitpold	AMAG	Rockwell Medical	Luitpold

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 Ferric Maltol, Accrufer®

Generic Name	Iron Dextran	Iron Dextran	Ferric Gluconate	Iron Sucrose	Ferumoxylol	Ferric Pyrophosphate	Ferric Carboxymaltose
Dosage Form	Injection	Injection	Injection	Injection	Injection	Injection (Intravenous Solution)**	Injection
Original Approval Date	April 29, 1974	February 23, 1996	February 18, 1999	November 6, 2000	June 30, 2009	January 23, 2015	July 25, 2013
Indication(s)	Intravenous or intramuscular injections of INFeD are indicated for treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.	Dexferrum is indicated for treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.	Ferrlecit is an iron replacement product for treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy.	Venofer is an iron replacement product indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease.	Feraheme is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease.	Triferic is an iron replacement product indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).	Injectafer is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients: • who have intolerance to oral iron or have had unsatisfactory response to oral iron • who have non-dialysis dependent chronic kidney disease.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ferric maltol is not currently marketed in the United States (U.S.).

On February 18, 2016, a Centralized Marketing Authorization in the European Union (EU/1/15/1075/001) was granted for ferric maltol 30 mg capsules (Feraccru®) for “the treatment of iron deficiency anemia (IDA) in adults with inflammatory bowel disease (IBD)”. On March 23, 2018, the European Committee for Medicinal Products for Human Use granted approval that the indication for ferric maltol in the EU be extended to “treatment of adults with iron deficiency”, irrespective of background disease.

Ferric maltol 30 mg capsules are commercially available in 12 countries under the trade name Feraccru®: United Kingdom (launched on June 6, 2016), Germany (launched September 2016), Austria (launched December 2016), Sweden (available August 2017), Denmark, Finland, Iceland, Norway, Poland, Bulgaria, Romania (available November 2017) and Hungary (available March 2018). Ferracru was granted a Marketing Authorization in Switzerland on September 22, 2017, it has not yet been launched in that country.

3.2. Summary of Presubmission/Submission Regulatory Activity

The key U.S. pre-submission regulatory activities are outlined in the table below.

Table 2: NDA 212320 Pre-Submission Regulatory History

Date	Meeting or Event
May 15, 2012	Pre-IND Meeting held to discuss ferric maltol clinical development program
June 3, 2016	Type C Written Responses Only Meeting to discuss clinical and non-clinical data packages to support a future NDA in conjunction with post-marketing data from the European Union (EU)
July 28, 2016	Type B Teleconference to address the ferric maltol CMC development program
November 2, 2017	Type C Teleconference to discuss NDA filing based on results of the pivotal ST10-01-301 and ST10-01-302 studies and QT Risk Evaluation Plan
March 14, 2018	Type B Pre-NDA Meeting to discuss topline results of the pivotal ST10-

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Ferric Maltol, Accrufer®

Date	Meeting or Event
	01-303 study
October 1, 2018	NDA 212320 in support of ferric maltol for the treatment of iron deficiency anemia was submitted to the Agency

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Two clinical sites were selected based on a high number of protocol violations in which patients who met withdrawal criteria were not appropriately withdrawn from study. From the review of Dr. Min Lu, “the final regulatory compliance classification of Dr. Block’s site is No Action Indicated (NAI). The preliminary regulatory compliance classification of Dr. Kharait’s site is Voluntary Action Indicated (VAI). Although protocol violations/deviations were noted, they appear unlikely to have significant impact on the primary efficacy endpoint of the study. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.”

Refer to the final report by Min Lu, M.D., M.P.H. in the Office of Scientific Investigations for the full detailed report.

4.2. Product Quality

Refer to CMC review for details.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

There are no devices or companion diagnostics associated with this drug product, hence this section is not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Ferric maltol (also known as ST10 or ST10-021) is stable complex formed between ferric iron (Fe^{3+}) and maltol (3-hydroxy-2-methyl-4-pyrone) that makes ferric iron bioavailable following oral administration. The applicant is seeking approval of ferric maltol for iron deficiency anemia (IDA) including patients who are intolerant to orally administered iron compounds. The iron of ferric maltol is chelated such that it cannot readily dissociate to undergo nonspecific reactions commonly found with other ferric or ferrous compounds. The iron of ferric maltol is also readily available to exchange with biomolecules, including the endogenous iron carriers transferrin and ferritin, with comparable binding affinity for ferric iron. This likely occurs in the mucosal enterocytes of the gastrointestinal tract. The established pharmacological class for ferric maltol is iron replacement product based on previously approved oral iron products with similar mechanisms of action.

Ferric maltol as a single 7 mg oral dose of iron was administered to rats, resulting in complete donation of iron to the transport and storage proteins and separate absorption of maltol. Studies in rats intraduodenally administered radiolabeled ferric maltol demonstrated that it was not found as an intact complex in the plasma, likely due to the previously described carrier exchange occurring in the mucosal enterocytes. Radiolabeled iron from ferric maltol in the rat intraduodenal administration studies was found bound to transferrin with a time to half maximal concentration ($T_{1/2}$) of 133 minutes. Ferric maltol as single 1000 μg or 1 mg IV doses of iron was administered to rats, resulting in highest iron concentrations in the liver and bone marrow, with the iron being bound to proteins. Plasma levels of maltol peaked between 10 minutes and 1 hour, dependent on dose, and was rapidly excreted in the urine as glucuronidated and/or sulphated species. Only 3% of administered iron was found in urine. Overall plasma iron levels did not increase by oral ferric maltol administration, likely due to the saturable process of uptake and transfer of iron to endogenous carriers.

Twenty-eight-day repeat dose oral administration toxicity studies were conducted in dogs with initial ferric maltol doses of 0, 250, 500, and 1000 mg/kg. Tolerability issues led to a change in administration method for all treated animals (powder gavage to capsule) and dose modifications in the high dose group (1000 $\rightarrow$ 750 $\rightarrow$ 125 mg/kg) by the end of the first week. The post-modification high dose group (500 mg/kg) exhibited vomiting with reductions in rate of weight gain and food intake. By the end of the study, this group also had an increase in platelet count, reduced red blood cell parameters, reduced alkaline phosphatase activity and increased bilirubin levels associated with liver histology changes, increased liver, kidney, thyroid, and adrenal weights. Middle dose animals (250 mg/kg) had increased bilirubin levels; and liver, kidney, and spleen weights. Low dose dogs (125 mg/kg) had increased liver weights by the end of the study but no other notable effects.

Embryo-fetal development studies have not been conducted with ferric maltol. Embryo-fetal development studies have been conducted in mice and rats treated with ferrous sulfate and ferric sodium pyrophosphate. Ferrous sulfate showed no maternal toxicity or adverse developmental outcomes at dose levels up to 160 mg/kg in mice and 200 mg/kg in rats. Ferric sodium pyrophosphate showed no maternal toxicity or adverse developmental outcomes at dose levels up to 160 mg/kg in mice or rats. A 3-generation fertility and reproduction study was conducted in the Crl: COBS-CD (SD) BR rat with dietary maltol administered daily at doses of 0, 100, 200, and 400 mg/kg. Oral administration of maltol to pregnant rats during organogenesis at doses 6 times the recommended human dose resulted in no adverse developmental outcomes. Overall, maltol had no effect on rat fertility, pregnancy, or lactation. The high dose caused a significant reduction in rate of weight gain in males.

Carcinogenicity studies have not been conducted with ferric maltol. Ferric maltol was mutagenic in vitro in bacterial reverse mutation (Ames) assays. Ferric maltol increased revertant frequency in the absence and presence of metabolic activation. Fertility studies have not been conducted with ferric maltol. Maltol was mutagenic in the Ames assay and increased micronuclei in an in vivo clastogenicity assay in mice. Maltol was not carcinogenic in an 18-month study in mice at doses up to 400 mg/kg (approximately 5 times the human daily dose). Maltol was also not carcinogenic in a 2-year study in rats at doses up to 400 mg/kg (approximately 10 times the human daily dose). Based on the available information the carcinogenic potential of ferric maltol under the proposed use scenario appears low.

The nonclinical pharmacology/toxicology studies submitted to the NDA are adequate and there are no outstanding issues from a nonclinical perspective that would prevent approval of ferric maltol for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary Pharmacology

The scientific literature includes an exhaustive characterization of the presence and pharmacological effects of iron in the human body. Iron deficiency and iron overload situations have also been the subject of decades of study and review. Studies with radiolabeled iron in rats, confirmed in dogs and humans, demonstrate that intact ferric maltol is found in the gastrointestinal tract, but not in the blood. Ferric iron is exchanged via a saturable process from maltol to transferrin and ferritin at the enterocytes of the duodenum. In iron overload conditions in rats, ferric maltol was associated with less iron-induced damage than ferrous sulfate.

Safety Pharmacology

No standalone safety pharmacology studies were conducted for ferric maltol, which is scientifically justified as the active moiety is iron.

5.4. ADME/PK

Table 3: ADME/PK

Type of Study	Major Findings
Absorption	
Dissociation of ferric maltol complex and its subsequent metabolism during absorption across the small intestine of the rat (Barrand & Callingham 1991)	Single 7 mg oral dose of iron to male Wistar rats. Complete donation of iron to the transport and storage proteins and separate absorption of maltol.
Distribution	
Dissociation of ferric maltol complex and its subsequent metabolism during absorption across the small intestine of the rat (Barrand & Callingham 1991)	Single 1000 µg or 1 mg IV doses of iron to male Wistar rats. Highest concentration in liver and bone marrow, iron bound to proteins, maltol conjugated.
Excretion	
Dissociation of ferric maltol complex and its subsequent metabolism during absorption across the small intestine of the rat (Barrand & Callingham 1991)	Single 0.7 to 700 µg IV doses of iron to male Wistar rats. Maltol is rapidly excreted in urine, but only 3% of iron was found in urine.

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: Iron Maltol: 28 Day Oral (Gavage/Capsule) Sub-Chronic Toxicity Study in the Beagle/6148-148/40

Key Study Findings

- Doses of 125, 250, and 500 mg/kg/day administered as capsules after day 6 of the treatment phase due to gavage-related vomiting.
- Test article-related toxicities included reduced food intake, increased platelet counts, alkaline phosphatase activity, and bilirubin concentrations. Liver, kidney, adrenals, and thyroid weights increased. Liver and kidney cells stained for the presence of iron.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: Initial protocol: 250, 500, and 1000 mg/kg/day for 28 days.
 Changed to 250, 500, and 750 mg/kg/day on day 2; then 125, 250, and 500 mg/kg/day on day 6 (750 mg/kg/day group changed to 125 mg/kg/day on day 6). Dosing continued to day 30.

Route of administration: Oral gavage on days 1 through 5 then oral capsule from day 6 onward.

Formulation/Vehicle: Gavage: (b) (4)
 Capsules: gelatin.

Species/Strain: Dog/beagle.

Number/Sex/Group: 3.

Age: Four to 6 months.

Satellite groups/ unique design: No.

Deviation from study protocol affecting interpretation of results: Yes. Change from gavage to capsule due to vomiting.

Table 4: Observations and Results: changes from control

Parameters	Major findings																																							
Mortality	One female at 1000 mg/kg, one male at 750 mg/kg, and one male at 250 mg/kg. All likely related to vomit inhalation.																																							
Clinical Signs	Vomiting following gavage at all doses reduced when capsular administration was introduced on day 6. Intermittent dose-dependent vomiting continued throughout the dosing period. Low dose (125 mg/kg) animals ceased vomiting after capsule introduction and no control animals vomited.																																							
Body Weights	Weight loss occurred by week 4 in high dose animals while weight gain in the low and middle dose animals was less than for the control animals. <table><tr><td></td><td colspan="3">Week 4 Weight Change % of Controls</td></tr><tr><td>Dose</td><td>LD</td><td>MD</td><td>HD</td></tr><tr><td>M</td><td>-12.96</td><td>-9.82</td><td>-22.88</td></tr><tr><td>F</td><td>-5.29</td><td>-1.81</td><td>-17.55</td></tr></table>		Week 4 Weight Change % of Controls			Dose	LD	MD	HD	M	-12.96	-9.82	-22.88	F	-5.29	-1.81	-17.55																							
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Dose	LD	MD	HD																																					
M	-12.96	-9.82	-22.88																																					
F	-5.29	-1.81	-17.55																																					
Ophthalmoscopy	Unremarkable																																							
Hematology	While there were no dose-related changes, notable high-dose-associated changes included reduced red cell parameters, increased platelet counts and activated partial thromboplastin times, and reduced monocyte counts. <table><tr><td></td><td colspan="12">Hematology Week 4 % Difference from Control</td></tr><tr><td></td><td colspan="2">Hb</td><td colspan="2">RBC</td><td colspan="2">PCV</td><td colspan="2">PLAT</td><td colspan="2">APTT</td><td colspan="2">MONO</td></tr><tr><td></td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr></table>		Hematology Week 4 % Difference from Control													Hb		RBC		PCV		PLAT		APTT		MONO			M	F	M	F	M	F	M	F	M	F	M	F
	Hematology Week 4 % Difference from Control																																							
	Hb		RBC		PCV		PLAT		APTT		MONO																													
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	LD	-3.01	-2.99	-8.57	-1.02	-3.69	-3.92	-23.42	7.56	-8.33	9.84	-54.55	-89.36
	MD	-3.76	4.48	-1.11	2.04	-4.18	2.45	4.96	9.30	-8.33	12.30	-39.39	-72.34
	HD	-14.29	-2.99	-22.22	-4.41	-14.25	-2.21	52.89	96.51	18.33	50.00	-39.39	-42.55
Clinical Chemistry	Reduced ALP levels. High dose (500 mg/kg) total bilirubin increase (M: ↑33%, F ↑82% at 4 weeks relative to predose).												
Urinalysis	No significant differences in the urine parameters at week 4.												
Gross Pathology	Unremarkable												
Organ Weights	Kidney: Increased in high dose (500 mg/kg) males and females by 24% and 29% respectively. Liver: Increased in high dose males and females by 28% and 47% respectively. Thyroid: Increased in all dosed males by 22% and high dose females by 26%. Adrenals: Increases observed in low dose males, mid dose females, and all high dose animals at levels up to 39% greater than controls.												
Histopathology Adequate battery: Yes	Generally unremarkable with sporadic findings. Leukocyte foci in liver and lung, mineralization in kidney, immature testes and cysts in the thyroid and parathyroid. Iron accumulation was demonstrable in the cytoplasm of hepatocytes, Kupffer cells, and proximal tubular epithelial cells of high dose animals.												

LD: low dose; MD: mid dose; HD: high dose.

:- indicates reduction in parameters compared to control.

General toxicology; additional studies

The NDA contains toxicology study reports that characterize the toxicity for orally administered maltol. These include 6-month studies in mice (Report 79029) and rats (Report 79031) at doses of 0, 100, 200 or 400 mg/kg/day by dietary administration, and a 3-month study in dogs (Report 79032) at doses of 0, 100, 200 or 300 mg/kg/day by administration of capsules. The general conclusions from these studies were that oral administration of maltol in the context of the maximum daily intake of the proposed drug product are not toxicologically significant or are not appreciably different than the results of the 28-day repeat dose toxicology study in dogs administered iron maltol described above.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Ferric Maltol Bacterial Mutation Assay/ETP 2A/921557

Key Study Findings:

- In a first round of testing ferric maltol at 50, 150, 500, 1500, and 5000 µg/plate, increased revertants were observed at the high dose for strains TA 1535 and TA 100.
- In a second round of testing only the TA 1535 strain with 1500, 2500, 5000, and 7500 µg/plate, increased revertant rates were observed in all conditions. Increase revertant in both rounds of testing occurred independent of S-9 liver extract.

GLP compliance: Yes

Test system: Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100.

Ferric maltol was tested on all strains at 50, 150, 500, 1500, and 5000 µg/plate and on the TA

1535 strain with 1500, 2500, 5000, and 7500 µg/plate. All testing was carried out with and without S-9.

Study is valid: Yes

Study title/ number: Maltol, Maltol β D Glucoside, Ferric Maltol, 3-0 Methyl Maltol Bacterial Mutation Assay/VPL1/SX

Key Study Findings:

- Maltol and ferric maltol caused increased revertants in the absence of S-9, while ferric maltol alone caused increased revertants in the presence of S-9.
- Maltol β D Glucoside and 3-0 Methyl Maltol did not increase the revertant induction rate.

GLP compliance: Yes

Test system: Salmonella typhimurium strain TA 1535, Maltol (1.6, 8, 40, 200, 1000, and 5000 µg/plate), ferric maltol (5.476, 27.378, 136.89, 684.44, 3422.2, and 4363.3 µg/plate), Maltol β D Glucoside, 3-0 Methyl Maltol, S-9.

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: Study to Evaluate the Potential of Maltol to Induce Micronuclei in the Polychromatic Erythrocytes of CD-1 Mice/RLG 1/MNT

Key Study Findings:

- Maltol induced increased micronuclei with the high dose of 774 mg/kg 24 hours after administration.
- No elevated presence of micronuclei was observed at any other time points for the highest dose or for any of the other doses tested.

GLP compliance: Yes

Test system: CD-1 mice received single intraperitoneal doses of Maltol at 193.5, 387, and 774 mg/kg. The animals were killed 24, 48, and 72 hours after administration. Marrow was aspirated from the femur and cells were isolated and used to prepare slide that was stained for micronuclei scoring.

Study is valid: Yes

5.5.3. Carcinogenicity

The NDA contains a study report for a mouse 18-month carcinogenicity study of maltol at doses of 0, 100, 200 or 400 mg/kg/day by dietary administration (Report 75009). The only tumor types found were those commonly occurring in mice of this strain and age. The incidence of tumors, whether benign or malignant or total, was similar in all groups. The high dose of 400 mg/kg/day in mice is approximately 5 times the human daily dose. The NDA also contains a study report for a 3-generation study of maltol in rats administered maltol mixed on the diet at

concentrations to give doses of 0, 100, 200, or 400 mg/kg/day (Report 74107). The F1 generation was exposed to maltol, at first in utero and then via the mother's milk, and finally for two years by dietary administration. There was no evidence of tumorigenicity in rats at doses up to 400 mg/kg (approximately 10 times the human daily dose).

5.5.4. Reproductive and Developmental Toxicology

Extended Reproductive and Development Study of Maltol

Study title/ number: Maltol Rat 3-Generation Fertility and Reproduction Study/74107

Key Study Findings:

- Maltol had no effect on rat fertility, pregnancy, or lactation.
- Growth and survival of offspring born from 2 successive matings were normal.

Conducting laboratory and location

(b) (4)

GLP compliance:

Pre-GLP (1978)

Methods

Dose and frequency of dosing:

100, 200, and 400 mg/kg/day

Route of administration:

Oral (in food)

Formulation/Vehicle:

Powdered maltol mixed with the powdered basic diet/powdered basic diet.

Species/Strain:

Rat/Sprague-Dawley

Number/Sex/Group:

50

Satellite groups:

20

Study design:

F0 animals were treated starting post-weaning prior to day 70 mating, with sacrifice occurring after weaning of F1. F1 animals were exposed in utero and throughout development, mating, and the rest of the lifespan. F2 animals were exposed throughout development and killed either at weaning or post mating and weaning of F3. F3 animals were exposed through sacrifice at weaning.

Deviation from study protocol

No

affecting interpretation of results:

Observations and Results

Table 5: Results

Parameters	Major findings
Mortality	Unremarkable
Clinical Signs	Unremarkable
Body Weights	A dose-dependent impairment in growth rate was noted in HD males.
Necropsy findings	LD: Unremarkable MD: Unremarkable HD: Unremarkable

LD: low dose; MD: mid dose; HD: high dose

Embryo-Fetal Development

The effects of ferrous sulfate and ferric sodium pyrophosphate on embryo-fetal development have been reported in the literature. Ferrous sulfate showed no maternal toxicity or teratogenic effect at dose levels up to 160 mg/kg in mice and 200 mg/kg in rats (Food and Drug Research Laboratories, 1974). Ferric sodium pyrophosphate showed no maternal toxicity or teratogenic effects at dose levels up to 160 mg/kg in mice or rats (Food and Drug Research Laboratories, 1975). These doses are 13 to 32 times the recommended human dose.

5.5.5. Other Toxicology Studies

The local tolerance of ferric maltol was evaluated in the Barrand & Callingham (1991) study. Wistar rats were administered daily oral doses of ferric maltol (14 mg iron). There were no signs of gastrointestinal irritation in the areas examined by light microscopy or electron microscopy.

Simon Williams, PhD
Primary Reviewer

Christopher M. Sheth, PhD
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking approval of ferric maltol for the treatment of iron deficiency in adults. The proposed dosing regimen is 30 mg by mouth (PO) twice daily (BID) taken one hour before or two hours after a meal. The primary evidence of efficacy to support the proposed dosing regimen was based on the change in hemoglobin (Hb) concentration from baseline observed in multiple Phase 3, randomized, placebo-controlled clinical trials. In patients with both iron deficiency anemia and quiescent inflammatory bowel disease (IBD; ST10-01-301/302) and in patients with both iron deficiency anemia and chronic kidney disease (CKD; ST10-01-303), treatment with ferric maltol 30 mg PO BID for 12 or 16 weeks, respectively, resulted in statistically significant increases in Hb compared to placebo ($p < 0.05$). The safety evaluation shows ferric maltol was tolerated with primarily gastrointestinal adverse events.

The Clinical Pharmacology Review evaluated the acceptability of the proposed dosing regimen as well as the food effect, drug-drug interaction, and PK and PD analyses for safety and efficacy.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 212320. This NDA is approvable from a Clinical Pharmacology perspective. The key review issues with specific recommendations/comments are summarized below.

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from pivotal studies ST10-01-301/302 and ST10-01-303 in the target population. Treatment with ferric maltol 30 mg PO BID for 12 or 16 weeks, respectively, resulted in mean difference between change from baseline Hb for ferric maltol compared to placebo of 2.18 g/dL for patients with iron deficiency anemia and IBD and 0.52 g/dL for patients with iron deficiency anemia and CKD.
General dosing instructions	The proposed dosing regimen is 30 mg PO BID taken one hour before or two hours after a meal. Treatment duration will depend on the severity of iron deficiency but generally at least 12 weeks of treatment is required. The treatment should be continued as long as necessary until ferritin levels are within the normal range.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose modifications are recommended for intrinsic factors. Ferric maltol should be separated from other oral medications for a sufficient duration to allow for absorption of either medication when a reduction in bioavailability for either ferric maltol or the concomitant oral medication may cause a clinically meaningful change in safety or efficacy. A PMR will be issued to the Applicant to conduct a nonclinical study to evaluate the risk of and support recommended management strategies for drug-drug interactions between ferric maltol and other oral medications.
Labeling	Modifications were made to the proposed Drug Interactions section to reflect the lack of available data and provide management strategies for

	potential interactions with concomitant oral medications. The Pharmacokinetics section (section 12.3) was also modified (b) (4)
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed 30 mg capsule formulation was used in the pivotal studies (ST10-01-301/302 and ST10-01-303) and Phase 1 study (ST10-01-101).

Post-Marketing Requirement (PMR) or Commitment (PMC)

The following issue should be addressed as a PMR: Conduct in vitro binding studies to evaluate the potential for ferric maltol to bind commonly used concomitant oral medications. The studies should be performed under conditions that mimic the physicochemical conditions of the gastrointestinal tract. The list of drugs to be evaluated should be inclusive of alendronate, atorvastatin, calcium carbonate, ciprofloxacin, doxycycline, levothyroxine, lisinopril, metoprolol, mycophenolate, and warfarin. Submit the protocol and the list of drugs to be evaluated for review and concurrence prior to starting the study. The results of this study will identify drugs with significant or potentially clinically meaningful binding that require further in vivo evaluation.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Ferric maltol contains iron in a ferric state as a complex with a trimaltol ligand. Ferric maltol delivers iron for uptake across the intestinal wall and transfer to transferrin and ferritin. In subjects with iron deficiency (with or without anemia), total serum iron concentrations increase in a less than dose proportional manner with increasing ferric maltol doses (30 mg, 60 mg, or 90 mg PO BID).

Ferric maltol dissociates upon uptake from the gastrointestinal tract allowing iron and maltol to be absorbed separately. Total serum iron peak values were reached 1.5 to 3 hours after administration of ferric maltol. Food has been shown to decrease the bioavailability of iron after administration of ferric maltol. Absorbed iron is physiologically regulated in the systemic iron pool where it is stored in ferritin or incorporated into heme. There is no specific metabolism or excretion of iron in humans.

Absorbed maltol is rapidly metabolized via UGT1A6 to maltol glucuronide, which is excreted in urine. There was no accumulation of maltol after administration of ferric maltol 30 mg PO BID x 16 weeks in patients with non-dialysis dependent CKD (eGFR ≥ 15 mL/min/1.73 m² and <60 mL/min/1.73 m²).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing regimen is 30 mg PO BID taken one hour before or two hours after a meal. Treatment duration will depend on the severity of iron deficiency but generally at least 12 weeks of treatment is required. The treatment should be continued as long as necessary until ferritin levels are within the normal range.

Therapeutic Individualization

Iron binds to a large number of medications to form iron-drug complexes. These complexes may precipitate, resulting in reduced absorption (Campbell 1991). There is insufficient data to evaluate which drugs may need to be separated from ferric maltol. However, given the potential for interactions, ferric maltol should be separated from other oral medications for a sufficient duration to allow for absorption of either medication when a reduction in bioavailability for either ferric maltol or the concomitant oral medication may cause a clinically meaningful change in safety or efficacy.

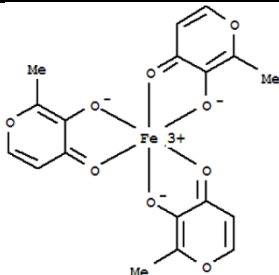
Outstanding Issues

We have issued one PMR, as presented in the PMR/PMC Section above. There are no other outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The general overview of ferric maltol ADME and clinical PK information are presented in the table below.

General Information	
Chemical structure and aqueous solubility	 - Chemical Name: 3-hydroxy-2-methyl-4H-pyran-4-one iron (III) complex (3:1) - MW: 431.2 g/mol
Solubility in Media	(b) (4)

	Medium		Solubility (%w/v)
	Water		0.6
	pH 4.0		0.8
	pH 6.5		0.5
	Fasted simulated small intestinal fluid (pH 6.5)		0.6
	Fed simulated small intestinal fluid (pH 5)		0.6
	Fasted simulated gastric fluid (pH 1.6)		1.9
	Source: 2.3.S Quality overall summary, Drug Substance		
Mechanism of action	Ferric maltol delivers iron for uptake across the intestinal wall and transfer to transferrin and ferritin.		
Dose and Adverse Events			
Therapeutic dose	The recommended dosage of ferric maltol is 30 mg PO BID taken one hour before or two hours after a meal.		
Major adverse events	The most common adverse events (>1%) were flatulence, diarrhea, constipation, feces discolored, abdominal pain, nausea, vomiting, abdominal discomfort, and abdominal distension. Drug-related gastrointestinal disorders led to discontinuation of ferric maltol in 4.6% of patients during the double-blind period.		
Pharmacokinetics of Iron			
Dose range tested in clinical trials	Single Dose	30, 60, or 90 mg PO BID	
	Multiple Dose	30, 60, or 90 mg PO BID x 7 days 30 mg PO BID x up to 64 weeks (12 weeks double-blind + 52 weeks open-label)	
Dose proportionality	Serum iron increased in a less than dose-proportional manner following administration of 30, 60, or 90 mg ferric maltol in patients with iron deficiency (with or without anemia).		
Absorption	T _{max}	Median (min, max): 2 hr (0.97, 4)	
Metabolism and Elimination	Iron is not metabolized or eliminated in humans.		
Extrinsic Factors	Drug interactions (including gastric acid reducing agents)	No DDI studies have been completed (see PMR). Iron may bind to other drugs, resulting in decreased bioavailability of iron, the concomitant medication, or both.	
	Food effects	In a non-standard food effect study using a different formulation of ferric maltol, administration of ferric maltol with food (maize porridge and toast) resulted in ~75% reduction of iron absorbed relative to fasting. Ferric maltol was administered one	

		hour before or two hours after a meal in the pivotal studies.
Pharmacokinetics of Maltol		
Maltol content	Each 30 mg capsule of ferric maltol contains 201.5 mg maltol.	
Absorption	Maltol is absorbed separately from iron after administration of ferric maltol with a Tmax of ~1 hr.	
Metabolism	Maltol is glucuronidated by UGT1A6 to maltol glucuronide.	
Elimination	39.8 – 60% of the maltol administered was recovered in urine as maltol glucuronide within 6 hours of administration. Less than 0.1% of maltol was recovered in urine unchanged. In patients with non-dialysis dependent chronic kidney disease (eGFR $\geq$ 15 mL/min/1.73 m ² and <60 mL/min/1.73 m ²), there was no accumulation of maltol after administration of ferric maltol 30 mg PO BID x 16 weeks.	
Pharmacodynamic (PD) Features		
PD Studies	Serum iron indices, including ferritin and TSAT, increase after administration of ferric maltol at the recommended dosage.	

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. Supportive evidence of effectiveness was obtained from pivotal studies ST10-01-301/302 and ST10-01-303. Additional supportive evidence was obtained from study ST10-01-101 and PK sub-study ST10-01-102.

The pivotal studies were randomized, double-blind, placebo-controlled Phase 3 trials. ST10-01-301/302 included patients with iron deficiency anemia and IBD who were treated with placebo or ferric maltol 30 mg PO BID x 12 weeks. ST10-01-303 included patients with iron deficiency anemia and CKD who were treated with placebo or ferric maltol 30 mg PO BID x 16 weeks. In ST10-01-301/302 and ST10-01-303, treatment with ferric maltol 30 mg PO BID for 12 or 16 weeks, respectively, resulted in difference between least squares mean change from baseline Hb for ferric maltol compared to placebo of 2.18 g/dL and 0.52 g/dL, respectively. See **Section 8.1** for additional information on studies ST10-01-301/302 and ST10-01-303, including analysis of the primary and secondary endpoints.

Secondary endpoints in the pivotal trials included clinically relevant iron indices such as serum iron, ferritin, and transferrin saturation. In both ST10-01-301/302 and ST10-01-303 treatment with ferric maltol 30 mg PO BID resulted in improvement from baseline to end of the double-blind period in iron indices. The changes in iron indices from baseline to the end of the double-blind period are summarized in **Table 6** for ST10-01-301/302 and in **Table 7** for ST10-01-303.

Table 6: Iron Indices in ST10-01-301/302

Iron Index			Ferric Maltol		Placebo	
			Absolute Value	Change from Baseline	Absolute Value	Change from Baseline
Iron (µmol/L)	Baseline	n	64		64	
		Mean (SD)	7.8 (8.83)		7.1 (5.99)	
	Week 12	n	59		52	
		Mean (SD)	18.0 (10.57)	10.2 (13.21)	7.2 (5.66)	-0.4 (6.96)
Ferritin (µg/L)	Baseline	n	64		64	
		Mean (SD)	8.6 (6.77)		8.2 (6.46)	
	Week 12	n	59		53	
		Mean (SD)	26.0 (30.57)	17.3 (28.30)	9.8 (9.55)	1.2 (7.85)
Transferrin Saturation (%)	Baseline	n	64		64	
		Mean (SD)	10.6 (11.69)		9.5 (7.50)	
	Week 12	n	59		52	
		Mean (SD)	28.5 (17.19)	18.0 (20.17)	9.8 (8.13)	-0.4 (7.82)

Source: ST10-01-301/ST10-01-302 CSR, Table 19

Table 7: Iron Indices in ST-10-01-303

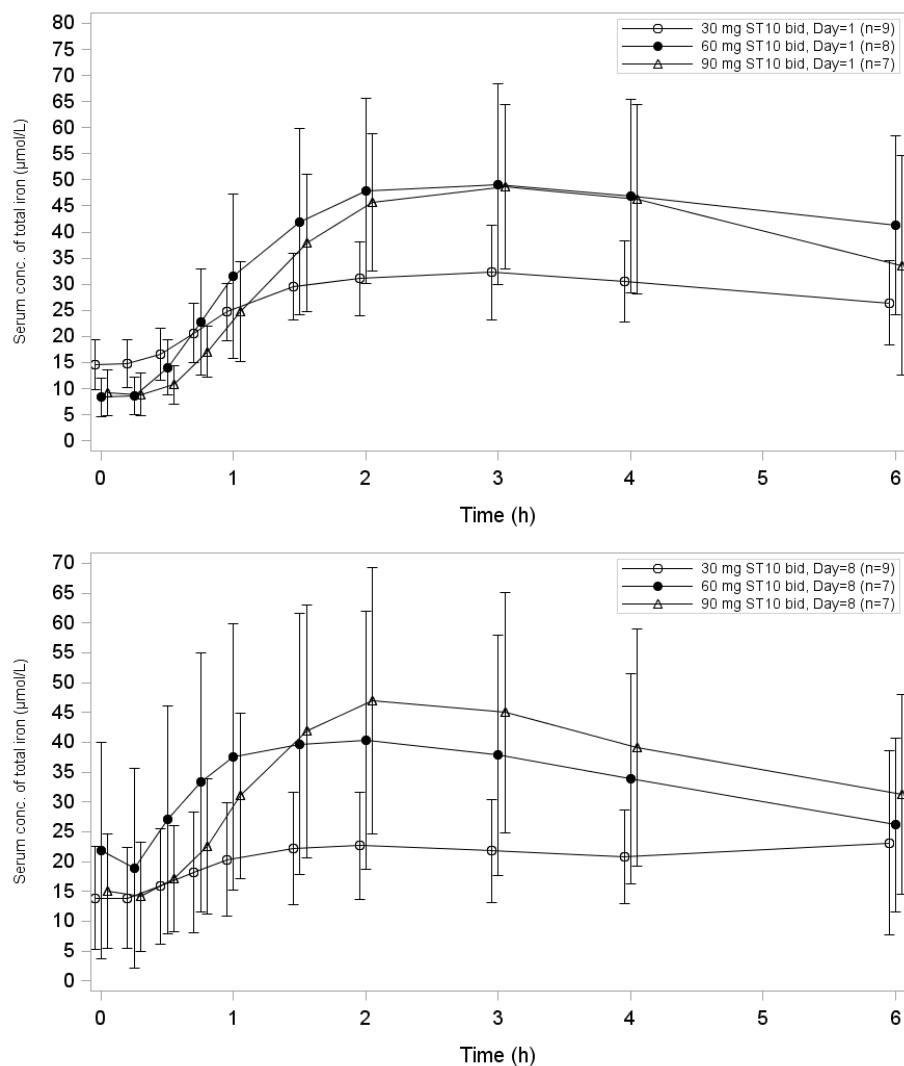
Iron Index			Ferric Maltol		Placebo	
			Absolute Value	Change from Baseline	Absolute Value	Change from Baseline
Iron (µmol/L)	Baseline	n	111		56	
		Mean (SD)	8.87 (3.476)		8.86 (3.778)	
	Week 16/ET	n	102		50	
		Mean (SD)	10.61 (4.082)	1.61 (4.444)	8.93 (3.831)	0.30 (3.184)
Ferritin (µg/L)	Baseline	n	111		56	
		Mean (SD)	97.0 (88.50)		104.2 (80.03)	
	Week 16/ET	n	102		50	
		Mean (SD)	147.5 (180.09)	49.3 (150.10)	107.9 (82.63)	6.3 (56.77)
Transferrin Saturation (%)	Baseline	n	111		56	
		Mean (SD)	15.7 (6.44)		15.6 (5.94)	
	Week 16/ET	n	102		50	
		Mean (SD)	19.9 (8.15)	3.9 (7.95)	15.4 (6.74)	0.3 (5.28)

Source: ST10-01-303 CSR, Table 14.3.4.2

Fifteen patients enrolled in ST10-01-301/302 had intensive PK sampling after at least one week of treatment with open-label ferric maltol 30 mg PO BID (PK sub-study ST10-01-105). Serum iron and TSAT increased after administration of ferric maltol and reached maximum values 1 – 3 hours post-dose.

In study ST10-01-101, 24 adults with iron deficiency (with or without anemia) were randomized to receive ferric maltol 30, 60, or 90 mg PO BID for 7 days with a final morning dose on Day 8 (15 total doses). Serum iron and TSAT increased after administration of ferric maltol, reaching maximum values 1.5 – 3 hours post-dose. Increases in serum iron and TSAT were larger following ferric maltol doses of 60 or 90 mg compared to 30 mg but changes in iron indices were not dose proportional. These results are consistent with the known physiologic regulation of iron absorption. **Figure 1** shows the serum iron concentration vs time profile on Day 1 and Day 8.

Figure 1: Serum Iron Concentration vs Time Profile on Day 1 (Top) and Day 8 (Bottom)



Source: ST10-01-101 CSR, Figures 11 and 12

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen is supported by the observed PK, safety, and efficacy data from studies ST10-01-301/302 (including PK sub-study ST10-01-102), ST10-01-303, and ST10-01-101. The PK and efficacy of ferric maltol are described above. Frequently observed adverse events included gastrointestinal effects [flatulence (4.6%), diarrhea (4%), constipation (4%), feces discolored (4%), abdominal pain (2.9%), nausea (1.7%), vomiting (1.7%), abdominal discomfort (1.1%), and abdominal distension (1.1%)]. Discontinuation due to adverse events was uncommon (4.6%). See **Section 8.3** for detailed safety review.

The proposed dosing regimen was evaluated in patients with iron deficiency and varying comorbidities (IBD or CKD) and across a broad age range (18 – 90 years). The Applicant's proposed dosing regimen of 30 mg PO BID taken one hour before or two hours after a meal is therefore appropriate for the intended patient population of adults with iron deficiency.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Response to treatment with ferric maltol as measured by change in Hb from baseline differed between patients with differing comorbidities (ST10-01-301/302 vs ST10-01-303) and in patients with varying degrees of renal impairment (ST10-01-303). However, these differences in response to ferric maltol may be related to the multifactorial nature of anemia in patients with CKD. Furthermore, treatment with ferric maltol should continue as long as necessary until ferritin levels are within the normal range. Response to ferric maltol as measured by both Hb and ferritin can be readily monitored consistent with clinical practice and therefore ferric maltol 30 mg PO BID with the duration of dosing based on the individual patient's iron stores is an appropriate regimen regardless of other intrinsic patient factors.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-Drug Interaction:

Yes. Ferric maltol should be taken one hour before or two hours after a meal.

A non-standard, two phase, crossover food effect study that evaluated the effect of food on ferric maltol was conducted in 21 adult females with mild anemia. In the first phase (Fed), subjects were randomized to receive 30 mg ferric maltol or 30 mg ferrous sulfate with food (maize porridge with milk and sugar plus a slice of toast with margarine) on Day 1 followed by the opposite treatment on Day 2. In the second phase (Fasted), the same subjects were randomized to receive 30 mg ferric maltol or 30 mg ferrous sulfate following a 10 hour fast on Day 1 followed by the opposite treatment on Day 2.

In this food effect study, the mean absorption of iron from a 30 mg dose of ferric maltol fasted was 5.3 ± 2.7 mg compared with 1.3 ± 1.3 mg when taken with food. As such, there was an absolute reduction in iron absorbed of 4.0 mg (relative reduction of approximately 75%) when ferric maltol was taken with food compared with fasting. However, it is noted that the formulation of ferric maltol used was a gelatin capsule containing ferric maltol (b) (4) (see CMC review) and that no details on the caloric and nutritional content of the meal was available.

Though this food effect study was not consistent with guidance, the results are consistent with established knowledge of the food effect on absorption of orally administered iron and the study was therefore included in the assessment of food-drug interaction.

In the pivotal (ST10-01-301/302 and ST10-01-303) and supportive (ST10-01-101) studies, patients were instructed to take ferric maltol before breakfast and at night before bed on an empty stomach with a glass of water. Therefore, pivotal safety and efficacy information as well as PK and PD data was obtained from patients taking ferric maltol separately from meals. In the label, the recommended dosage is 30 mg (b) (4) twice daily, (b) (4) taken one hour before or two hours after a meal. The labeled recommendations are an appropriate management strategy for food-drug interaction.

Drug-Drug Interactions

Concomitant Oral Medications

Positively charged iron ions interact with electron pairs in other drugs, resulting in formation of iron-drug complexes. Drugs containing phenol, catechol, carboxyl, amine, or sulfhydryl groups may strongly bind to iron (Campbell 1991). Multiple published studies demonstrate reduced drug bioavailability in the presence of orally administered iron and the potential for significant drug interactions between iron and other medications is widely recognized.

The Applicant did not provide sufficient data to assess the risk of or support recommended management strategies for potential drug-drug interactions between ferric maltol and other oral medications. Based on published literature, oral iron products may interact with a large number of concomitant therapies resulting in decreased bioavailability of iron, the concomitantly administered drug, or both. These potential interactions may impact the safety and efficacy of both ferric maltol and the concomitantly administered drug.

The Applicant conducted a single *in vitro* study evaluating Caco-2 permeability of ciprofloxacin and ofloxacin in the absence and presence of ferrous sulfate or ferric maltol. This study found no significant effect of either ferrous sulfate or ferric maltol on the permeability of ciprofloxacin or ofloxacin. As this study failed to identify the known *in vivo* interaction between ferrous sulfate and the fluoroquinolones, the lack of observed interaction for ferric maltol was not considered informative.

Given the lack of information and the potential for clinically significant drug interactions with a known mechanism (formation of iron-drug complexes), the label includes recommendations to separate the administration of ferric maltol from other oral medications for a sufficient duration to allow for absorption of either medication when a reduction in bioavailability for either ferric maltol or the concomitant oral medication may cause a clinically meaningful change in safety or efficacy. A PMR, as detailed in **Section 6.1**, will be issued to the Applicant to conduct a nonclinical study to evaluate the risk of and support recommended management strategies for drug-drug interactions between ferric maltol and other oral medications.

Gastric Acid Reducing Agents

Uptake of non-heme iron from the GI tract involves reduction of Fe^{3+} to Fe^{2+} by a ferric reductase (duodenal cytochrome B) followed by absorption via divalent metal transporter (DMT-1). Ferric reductase activity is pH-dependent with lower pH leading to higher activity. Gastric acid reducing agents may reduce the efficacy of oral iron replacement therapy by reducing absorption of iron from the gastrointestinal tract.

To assess the impact of gastric acid reducing agents on the efficacy of ferric maltol, the Applicant provided additional *post hoc* analyses of changes in serum iron, ferritin, and TSAT through Week 4 of the double-blind period of Studies ST10-01-301/302 and ST10-01-303 in patients receiving ferric maltol with or without concomitant proton pump inhibitor use. The Applicant stated that PPIs did not have an impact on the efficacy of ferric maltol.

Additional FDA analyses were conducted through the end of the double-blind period comparing patients with reported continuous use of a proton pump inhibitor throughout the double-blind period with patients who had no reported use of any potentially interacting medications (antacids, calcium supplements, or proton pump inhibitors). Due to differences in baseline lab values, responses, and the proportion of patients taking proton pump inhibitors in the different trials, evaluation of each trial separately was considered more informative than a pooled analysis. **Table 8** summarizes the change from baseline to end of the double-blind period in Hb, ferritin, and TSAT for patients in studies ST10-01-301, ST10-01-302, and ST10-01-303.

Table 8: Change from Baseline to End of Double-Blind Period in Efficacy and PD Endpoints

Endpoint	Study		Ferric Maltol		Placebo	
			Concomitant PPI			
			Yes	No	Yes	No
Hb (g/dL)	-301	n	4	22	3	20
		Mean (SD)	2.55 (0.98)	2.44 (1.20)	-0.13 (0.55)	0.22 (0.95)
	-302	n	8	18	9	16
		Mean (SD)	1.59 (0.70)	2.18 (1.38)	-0.10 (0.88)	0.01 (0.84)
	-303	n	28	44	15	16
		Mean (SD)	0.63 (0.84)	0.64 (1.57)	0.27 (0.72)	0.09 (0.71)
Ferritin (µg/L)	-301	n	4	22	3	20
		Mean (SD)	6.25 (8.06)	12.9 (11.2)	5.33 (12.7)	5.55 (11.8)

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Transferrin Saturation (%)	-302	n	8	19	9	16
		Mean (SD)	25.6 (12.9)	12.6 (7.60)	2.67 (8.87)	-1.06 (3.19)
	-303	n	30	44	15	16
		Mean (SD)	16.5 (59.4)	36.8 (46.3)	-13.8 (45.4)	0.19 (24.8)
	-301	n	4	22	2	20
		Mean (SD)	15.0 (18.2)	18.1 (13.2)	-1, -3 ^a	1.05 (9.38)
	-302	n	8	19	9	16
		Mean (SD)	19.5 (23.9)	17.8 (22.6)	-1.89 (4.14)	-0.81 (8.86)
	-303	n	30	44	15	16
		Mean (SD)	4.53 (7.37)	4.07 (7.91)	0.33 (6.81)	-0.94 (5.16)

Source: FDA Analysis

a: Individual values

In each individual study, the number of patients who received ferric maltol plus a proton pump inhibitor was small and the response was variable and inconsistent. However, changes in Hb, ferritin, and TSAT were observed in patients taking ferric maltol with a concomitant proton pump inhibitor across all three studies. Due to limitations of these analyses including their *post hoc* nature, small sample size, and reliance on patient reported concomitant medication use, there is insufficient evidence to conclude a lack of interaction between ferric maltol and proton pump inhibitors.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Three randomized, double-blind, placebo-controlled, multicenter Phase III pivotal studies investigated ferric maltol treatment in patients with IDA (ST10-01-301/302 and ST10-01-303). For the purposes of this review, studies ST10-01-301 and 302 were identical protocols and efficacy and safety data pooled for both efficacy and safety reviews. Details for each pivotal study are provided in the table below.

Table 9: Listing of Clinical Trials Relevant to NDA 212320

Trial and Status	Trial Design	Regimen/Schedule/Route	Primary Endpoint	Treatment Duration and Follow Up	No. of Patients Enrolled	Study Population	Countries and no. of sites
Controlled Studies to Support Efficacy and Safety							
ST10-01-301/302 (Pooled)	Pivotal Phase III Prospective, multi-center, randomized, double-blind, placebo controlled	12-week double-blind treatment phase with an open-label follow-up period for 52 weeks Double-blind: Oral ferric maltol 30 mg BID or matching placebo BID Open-label: Oral ferric maltol 30 mg BID	Change in Hb concentration from Baseline to Week 12	Double-blind phase: 12 weeks; Open label: 52 weeks	N=128 Double-blind: Ferric maltol 30 mg: 64 Placebo: 64 Open-label: 97 (50 ferric maltol - ferric maltol), 47 (placebo - ferric maltol)	Subjects with UC (301) or CD (302) and IDA where OFPs have failed or cannot be used	Germany (18), Hungary (8), Austria (7), UK (16)
ST10-01-303	Pivotal Phase III Prospective, multi-center, randomized, double-blind, placebo controlled	16-week double-blind treatment phase with an open-label follow-up period for 36 weeks Double-blind: Oral ferric maltol 30 mg BID or matching placebo BID Open-label: Oral ferric maltol 30 mg BID	Change in Hb concentration from Baseline to Week 16	Double-blind phase: 16 weeks; Open label: 36 weeks	N=167 Double-blind: Ferric maltol: 111 Placebo: 56	Subjects with non-dialysis CKD and IDA	United States (30)

APPEARS THIS WAY ON ORIGINAL

7.2. Review Strategy

The key materials used for the review of efficacy and safety included:

- NDA datasets (raw and derived), clinical study reports, and responses to the review team's information requests
- Relevant published literature
- Relevant information in the public domain

Clinical data was provided in the Clinical Data Interchange Standards Consortium (CDISC) Foundational Standards SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model Implementation). Also submitted were the define files for the variables and the corresponding SAS programs for the primary ADaM data derivation to document the analysis results. The reviewers were able to duplicate the analysis results based on the applicant's submitted datasets.

Sections 7 and 8 of this Review were performed jointly by Dr. Laurel Menapace, MD and Dr. Lola Luo, PhD. Analyses by Dr. Luo were performed using SAS 9.4 (SAS Institute, Inc.).

Analyses by Dr. Menapace were performed utilizing JMP 13.0 (SAS Institute, Inc.) and JMP Clinical 6.1. MedDRA Adverse Events Diagnostic (MAED) 1.3 (Clinical Trials and Surveys Corporation & FDA) was used to assess safety signals. Unless specifically referenced, all analyses and presentation of findings are the work of FDA reviewers.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study ST10-01-301 and ST10-01-302

Overview and Objective

The primary objective of the study was to evaluate the efficacy of oral ferric maltol compared with placebo in the treatment of IDA in subjects with IBD at 12 weeks. The study also included an open label extension phase which evaluated safety and efficacy up to 52 weeks.

Trial Design

Studies ST10-01-301 (AEGIS 1) and ST10-01-302 (AEGIS 2) were Phase III, multicenter, randomized, double-blind, placebo-controlled studies which investigated oral ferric maltol administration for the treatment of IDA in subjects with IBD who had failed other oral iron replacement products or could not be used. This study was conducted via two separate protocols:

- ST10-01-301 (AEGIS 1) in patients with quiescent ulcerative colitis (UC)
- ST10-01-302 (AEGIS 2) in patients with quiescent Crohn's disease (CD)

The study designs for these protocols were essentially identical except for the enrolled patient populations. The primary objective of each study was to demonstrate the efficacy of oral ferric maltol over placebo in the treatment of IDA (as measured by a change in Hb from Baseline to Week 12) in subjects with IBD where OFP had failed or could not be used. Secondary objectives of each study were to evaluate the safety and tolerability of ferric maltol in this patient population over a treatment duration of up to 12 weeks and up to 64 weeks (long-term safety and tolerability).

A total of 128 subjects at 32 sites in Austria, Germany, Hungary and the UK were randomized on a 1:1 basis to receive oral ferric maltol 30 mg capsules BID or matching oral BID placebo during the double-blind phase. At the end of the double-blind phase, any placebo subjects who remained in the study were transferred to active treatment (with the exception of subjects in Austria where the open-label treatment period was not approved). All continuing subjects received ferric maltol 30 mg BID during the open-label treatment phase.

Eligible subjects were adults (aged ≥ 18 years) with a current diagnosis of IBD and IDA as defined by the following inclusion criteria:

- Quiescent UC (Simple Clinical Colitis Activity Index [SCCAI] score <4) or quiescent CD (Crohn's Disease Activity Index [CDAI] score <220)
- Anemia (Hb ≥9.5 to <12.0 g/dL for females, ≥9.5 to <13.0 g/dL for males),
- Iron deficiency (ferritin <30 µg/L)

Enrolled patients were required to have OFP failure or were otherwise intolerant to OFP treatment as defined by the following criteria:

- Adverse drug effects that led to withdrawal from OFP (at least one of the following nausea, diarrhea, constipation, abdominal pain, flatulence) and/or,
- Deterioration of the primary disease caused by OFP and/or,
- Lack of efficacy and/or,
- Other signs of failure to OFP or reasons why OFP could not be used as documented by the Investigator.

The remainder of the study eligibility criteria are listed below.

Inclusion Criteria

- Patients receiving protocol-allowed immunosuppressants at screening must have been on a stable dose for at least 4 weeks prior to randomization. Permitted immunosuppressants included azathioprine, 6-mercaptopurine, tumor necrosis factor (TNF)-alpha antagonists and corticosteroid doses less than or equal to the equivalent of 25 mg/day prednisolone.
- Female patients of childbearing potential age (including perimenopausal females who had had a menstrual period within 1 year prior to screening) must agree to use a reliable method of contraception until study completion and for at least 4 weeks following their final study visit.

Exclusion Criteria

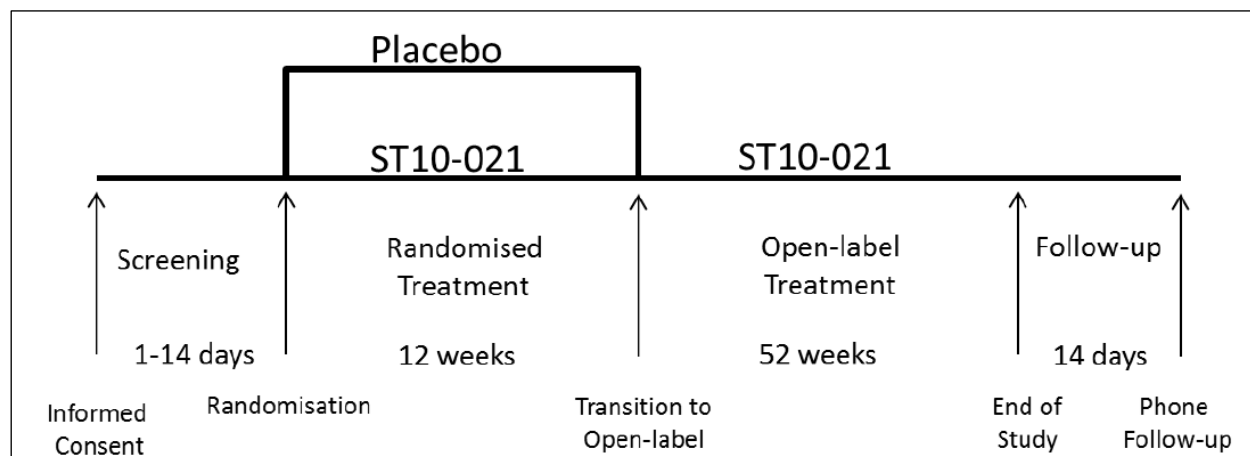
- Anemia due to any cause other than iron deficiency, including, but not limited to: severe malabsorption, immunosuppressant use
- Receipt of blood transfusion(s), intramuscular (IM) or intravenous (IV) administration of iron replacement products, or erythropoietin/ESAs within the 12 weeks prior to randomization

- Oral iron replacement products or an immunosuppressant known to induce anemia within the 4 weeks prior to randomization
- Patient who had received folic acid and/or vitamin B12 injections/infusions within 4 weeks prior to randomization
- Vitamin B12 concentration below the lower limit of normal (LLN) as measured at the Screening Visit
- Folic acid deficiency as assessed at the Screening Visit
- Contraindications for treatment with iron preparations (e.g., haemochromatosis, chronic hemolytic disease, sideroblastic anemia, thalassemia, or lead intoxication induced anemia)
- Serum creatinine >2.0 mg/dL (176 µmol/L) as measured at the Screening Visit
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥5 times the upper limit of normal (ULN) at the Screening Visit
- History of malignancy within the past 5 years with the exception of in situ removal of basal cell carcinoma
- Female patients who were pregnant or lactating

The screening period for Study ST10-01-301 was up to 14 days (patients with UC) whereas it was only 7 days for Study ST10-01-302 (patients with CD). Enrolled patients were randomized in a 1:1 ratio to oral ferric maltol 30 mg BID or matching placebo BID for 12 weeks, followed by open-label treatment (ferric maltol 30 mg BID) for 52 weeks.

The following figure outlines the study schema for both protocols.

Figure 2: ST10-01-301 and ST10-01-302 Study Design



Note 1: Screening period for AEGIS 1 (UC protocol) was up to 14 days; screening period for AEGIS 2 (CD protocol) was 7 days.

Note 2: The 52-week open-label treatment phase was not approved by the IEC in Austria, therefore Austrian subjects participated only in the 12-week randomised treatment phase of the study. The study was conducted under a country-specific protocol for Austria.

Source: Applicant's Clinical Study Report, Module 5.3.5.1, Section 9

Patients had study site visits every 4 weeks during the double-blind phase and up to Week 24 of the study, and at Weeks 36, 48, and 64, with additional telephone contact at Weeks 2 and 14 as well as 2 weeks after the end of study visit (at Week 64 or premature discontinuation).

Patients who developed Hb concentrations ≤ 8.5 g/dL (5.3 mmol/L) and/or an IBD flare, either UC as defined by SCCAI ≥ 5 , or CD as defined by CDAI ≥ 320 , were withdrawn from the study to receive best standard medical care.

The following concomitant medications and therapies were not permitted on protocol:

- Oral or intravenous (IV) iron preparation besides the study drug
- Blood transfusions
- Erythropoietin stimulating agents (ESAs)
- Vitamin B12
 - Parenteral vitamin B12 (injections or infusions) was prohibited within the 4 weeks prior to randomization and within the 4 weeks prior to the Week 12 visit
 - Parenteral vitamin B12 was allowed between Day 0 and the Week 8 visit provided the regimen had been stable for 12 weeks prior to randomization. Parenteral

vitamin B12 was allowed after the Week 12 visit and treatment regimens could be adjusted as necessary

- o Oral vitamin B12 was allowed at any time during the study provided the treatment regimen had been stable for 12 weeks prior to randomization and remained stable through the Week 12 visit. Oral vitamin B12 was allowed after the Week 12 visit and treatment regimens could be adjusted as necessary
- Folic Acid
 - o Parenteral folic acid (injection or infusion) was prohibited within the 4 weeks prior to randomization and within the 4 weeks prior to the Week 12 visit
 - o Parenteral folic acid was allowed between Day 0 and the Week 8 visit provided the regimen had been stable for 12 weeks prior to randomization. Parenteral folic acid was allowed after the Week 12 visit and treatment regimens could be adjusted as necessary
 - o Oral folic acid was allowed at any time during the study provided the treatment regimen had been stable for 12 weeks prior to randomization and remained stable through the Week 12 visit. Oral folic acid was allowed after the Week 12 visit and treatment regimens could be adjusted as necessary.
- Initiation of immunosuppressant therapy or increases to existing dosing regimen
 - o For patients receiving allowed immunosuppressants at screening, the dose must have been stable for 4 weeks prior to randomization but could be adjusted down as necessary during the study. Dose increases and/or initiation of immunosuppressant therapy were prohibited during the first 12 weeks of the study.

The following tables outline the study schedule of assessments.

Table 10: Study ST10-01-301/302 Schedule of Assessments

PERIODS		SCREENING	RANDOMISED TREATMENT					OPEN-LABEL TREATMENT							FOLLOW-UP
	Duration	1 to 14 days	12 weeks (84 days)					52 weeks (364 days)							14 days after End of Study Visit
VISITS	Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Name	Screening	Randomisation	Week 2 ²	Week 4	Week 8	Week 12	Week 14 ²	Week 16	Week 20	Week 24	Week 36	Week 48	Week 64 End of Study Visit ⁸	Follow-up ²
	Day ¹	Between -14 and -1 for AEGIS 1; -8 to -7 for AEGIS 2	0	14	28	56	84	98	112	140	168	252	336	448	462
Informed Consent		X													
Demographics		X													
Medical History		X													
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination ³		X					X				X	X	X	X	
Vital Signs ⁴		X	X		X	X	X		X	X	X	X	X	X	
Pregnancy Test ⁵		X	X		X	X	X		X	X	X	X	X	X	
Clinical Laboratory Tests ⁶		X	X		X	X	X		X	X	X	X	X	X	

PERIODS		SCREENING	RANDOMISED TREATMENT					OPEN-LABEL TREATMENT							FOLLOW-UP
	Duration	1 to 14 days	12 weeks (84 days)					52 weeks (364 days)							14 days after End of Study Visit
VISITS	Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Name	Screening	Randomisation	Week 2 ²	Week 4	Week 8	Week 12	Week 14 ²	Week 16	Week 20	Week 24	Week 36	Week 48	Week 64 End of Study Visit ⁸	Follow-up ²
	Day ¹	Between -14 and -1 for AEGIS 1; -8 to -7 for AEGIS 2	0	14	28	56	84	98	112	140	168	252	336	448	462
SCCAI for AEGIS 1 or CDAI for AEGIS 2		X	X		X	X	X		X	X	X	X	X	X	
SF-36 Questionnaire			X				X				X	X	X	X	
IBDQ			X				X				X	X	X	X	
Randomisation			X												
Dispense Study Drug			X		X	X	X		X	X	X	X	X		
Return Study Drug					X	X	X		X	X	X	X	X	X	
Adverse Events ⁷			X	X	X	X	X	X	X	X	X	X	X	X	X

SCCAI, Simple Clinical Colitis Activity Index; CDAI, Crohn's Disease Activity Index; SF-36, Medical outcomes study 36-item short form; IBDQ, Inflammatory Bowel Disease Questionnaire.

1. Visit window for all visits was ± 2 days; screening could occur any time within 2 weeks prior to randomisation
2. By telephone
3. Including body weight, height at Screening Visit only

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4. Blood pressure and heart rate
5. For female subjects of childbearing potential
6. Including clinical chemistry, haematology (all visits) and retained samples (Randomisation Visit and Week 12 only). Note that the efficacy variables, haemoglobin and iron indices, were included in the haematology laboratory tests
7. SAE and AE documentation and reporting according to protocol-defined safety reporting requirements
8. Subjects who prematurely discontinued study drug during the first 12 weeks of the study returned to the clinic for all scheduled visits through Week 12. Subjects who prematurely discontinued study drug after Week 12 returned to the clinic for an End of Study Visit at the time of discontinuation. Procedures performed were the same as those for the End of Study Visit at Week 64 for subjects who completed the study.

Source: Applicant's Clinical Study Report, Module 5.3.5.1

Study Endpoints

The primary efficacy endpoint was change in Hb concentration from Baseline to Week 12.

Secondary efficacy endpoints were as follows:

- Change in Hb concentration from Baseline to Week 48, 64.
- Change in Ferritin from Baseline to Week 12, 64.

Statistical Analysis Plan

Randomization Scheme:

Approximately 60 patients in the combined study is randomized at a ratio of 1:1 to the following treatment:

- Oral ferric maltol: 30 mg capsule bid
- Oral matching placebo capsule bid.

Statistical Hypothesis:

Let Y be the Test group (ferric maltol), X be the Control group (placebo), μ be the mean of change in Hb concentration from baseline to Week 12.

$$H_0: \mu_X = \mu_Y$$

$$H_A: \mu_X < \mu_Y$$

Sample Size Consideration:

Sample size calculation is based on results from previous exploratory studies. Assuming no change ($\mu_X = 0$ g/dL) in the Control group and an increase of Hb of $\mu_Y = 1.3$ g/dL in the Test group and a common standard deviation of $\sigma = 1.65$, an effect size $\delta = (\mu_Y - \mu_X)/\sigma = 0.788$ can be expected. To derive the required sample size, the effect size δ is converted to the corresponding effect size $P(X < Y)$ for the Mann-Whitney statistic. $P(X < Y)$ is the probability that an observation, X, in the Control group will be less than an observation Y in the Test group when the alternative hypothesis of superiority of Test compared to Control is true. The expected δ corresponds to $P(X < Y)$ is 0.711.

A sample size of 49 subjects in each group provides 95% power to detect a probability $[P(X<Y)]$ of 0.711 that an observation in the Control group (placebo) shows a lower increase of Hb than in the Test group (ferric maltol) using the Wilcoxon (Mann-Whitney) rank-sum test with a 0.025 one sided significance level. To allow for non-evaluable subjects (e.g. drop-outs), a total of 60 subjects per treatment group, and 120 subjects across studies AEGIS 1 and AEGIS 2 are needed.

Sample size is calculated by nQuery Advisor 7.0 using a normal approximation formula.

Efficacy Analysis Population:

Intent-to-treat (ITT): all subjects who are randomized.

Full Analysis Set (FAS): all subjects who are randomized and have had at least one dose of study drug.

Modified Full Analysis Set (mFAS): all subjects who are randomized and have had at least one dose of study drug and had at least one post-baseline Hb measurement.

Statistical Analysis:

The primary efficacy endpoint is the change in Hb concentration from baseline to Week 12. Baseline is defined as the pre-dose Hb concentration measured at randomization visit. Missing randomization Hb values will be replaced by screening Hb values if the randomization has been within the protocol specified window.

Effectiveness will be analyzed by determining whether the ferric maltol arm shows a statistically significant superiority as compared to the placebo arm. An Analysis of Covariance (ANCOVA) is used to analyze the primary endpoint using the FAS analysis population.

Missing Hb concentration measurements at Week 4, 8 and 12 are imputed using a multiple imputation (MI) method through the SAS procedure PROC MI as described below:

1. Five datasets are generated containing imputed values for non-monotone missing measurements in the original dataset.
2. Then, the remaining monotone missing measurements are imputed.

Baseline Hb concentration, treatment, disease (UC or Crohn's disease) and gender are used in the imputation. For each imputed dataset, the change from baseline to Week 12 is analyzed using an ANCOVA model with treatment as the factor and gender, disease, baseline Hb as covariates. The SAS procedure PROC MIANALYSE is then used to combine the individual analysis result.

Sensitivity Analyses for the Primary Analysis:

Mixed Model Repeated Measures (MMRM):

The MMRM analysis includes the fixed, categorical effects of treatment, gender, disease, week, and treatment by week interaction, as well as the continuous, fixed covariate of baseline Hb concentration. An unstructured (co)variance structure is used to model the within-patient errors. Significance test is based a one-sided α of 0.025.

Last Observation Carried Forward (LOCF):

Missing Week 12 Hb concentration is imputed as the last observed Hb concentration prior to the discontinuation of study drug. An ANCOVA model is used to analyze the data. The analysis includes treatment, gender, disease as well as baseline Hb concentration.

Week 12:

This analysis is conducted to include only those subjects who have both baseline and Week 12 Hb concentrations. An ANCOVA model is used to analyze the data.

Complete Case:

This analysis is conducted to include only those subjects who have baseline, Week 4, 8, and 12 Hb concentrations. An ANCOVA model is used to analyze the data.

Multiplicity Adjustment:

There is no multiplicity adjustment planned. The results from endpoints other than the primary endpoint are considered exploratory.

Interim Analysis:

Not Applicable.

Protocol Amendments

Table 11: Protocol Amendments for ST10-01-301/302

Date	Amendment(s)
October 13, 2011	Protocol Amendment 1 Study modified to include a 52-week open-label extension to further evaluate the safety and efficacy of ferric maltol in all randomized subjects. Study visits and procedures during the first 12 weeks of the pivotal study were unchanged from the original

Date	Amendment(s)
	protocol. • Several changes to Inclusion and Exclusion Criteria were made, including definition of anemia; removal of mean corpuscular volume (MCV) criteria for study entry; exclusion of vitamin B12 or folic acid deficiency and associated treatments; and creatinine exclusion criterion • Secondary endpoint definitions were updated to indicate that the proportion rather than number of subjects was to be used and that the endpoint evaluation was to take place following the randomized phase of the study
December 11, 2011	Protocol Amendment 2 • The lower limit Hb level for inclusion was lowered from 10.0 g/dL to 9.5 g/dL following discussions with AEGIS Investigators • Duration patients must be stable on parenteral Vitamin B12 decreased from 6 months to 3 months • TSAT < 16% removed as inclusion criteria
January 30, 2012	Protocol Amendment 3 • Folate exclusion criteria amended from “below lower limit of normal” to “folate deficiency”
August 23, 2012	Protocol Amendment 4 • Change in Primary Analysis Methodology from Wilcoxon-Mann Whitney (WMW) to ANCOVA; missing data imputed using MI; sensitivity analysis using LOCF and complete case analysis (ANCOVA and MMRM) • Amendment to allow analysis of the study data from ST10-01-301 and ST10-01-302 as a single integrated data set of target size 120 (previously 120 patients were targeted per study)

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

The Applicant submitted financial disclosure information from all investigators for this trial. There were no clinical investigators with disclosable financial arrangements in relation to studies ST10-01-301 and ST1-01-302.

Patient Disposition

The first patient's first visit was on 03 October 2011 and the last patient's last visit for the double-blind treatment period was on 11 October 2013.

The double-blind (DB) treatment period was completed by 84.4% of subjects (85.9% in ferric maltol arm and 82.8% in the placebo arm). The most common reasons for withdrawal from the study were AEs (7.8%) and patient's decision to withdraw (6.3%).

Table 12: Patient Disposition for Study ST10-01-301 and ST10-01-302

	Placebo n (%)	Ferric Maltol n (%)	Total n (%)
Intent-to-treat (ITT)	64 (100)	64 (100)	128 (100)
Full Analysis Set (FAS)	64 (100)	64 (100)	128 (100)
Completed the DB phase	53 (82.8)	55 (85.9)	108 (84.4)
Early withdrawal from the DB phase	11 (17.2)	9 (14.1)	20 (15.6)
Reason for withdrawal from DB phase			
Adverse Event	4 (6.3)	6 (9.4)	10 (7.8)
Physician decision	1 (1.6)	0	1 (0.8)

	Placebo n (%)	Ferric Maltol n (%)	Total n (%)
Withdrawal by patient	5 (7.8)	3 (4.7)	8 (6.3)
Protocol violation	1 (1.6)	0	1 (0.8)

Source: FDA analysis

Protocol Violations/Deviations

The majority of protocol deviations that occurred on protocol were minor in nature. Nine ferric maltol and 7 placebo patients were excluded from the per protocol analysis (PPAS) due to major protocol violations; these are presented in the table below.

Table 13: Protocol Violations Leading to Exclusion from the Per Protocol Analysis Set

Double-blind Treatment	Subject Number	Reason for exclusion from the PPAS
ST10	(b) (6)	Variation in dose in immunosuppressant has an effect on anaemia
ST10		Immunosuppressant given for a long period of time to treat disease
ST10		Numerous changes in immunosuppressants
ST10		Subject was not on a stable dose of immunosuppressant during the 4 weeks prior to randomisation therefore did not meet inclusion criterion 6
ST10		IMP compliance 53.45%
ST10		IMP compliance 58.70%
ST10		Major violation of exclusion criterion 2a
ST10		IMP compliance 79.41%
ST10		Deviates (75 days) allowed time window between Visit 2 and Visit 6
Placebo		Window between Visit 2 and Visit 6 is too long (99 days)
Placebo		Subject received prohibited concomitant medication
Placebo		Subject met discontinuation criterion
Placebo		IMP compliance 75.88%
Placebo		Major changes in immunosuppressant treatment
Placebo		Exceeds (121 days) allowed time window between Visit 2 and Visit 6 compliance found to be 71.13%
Placebo		IMP compliance 77.78%

Source: Table reproduced from Applicant's Study Report for ST10-01-301/302, Section 10.1

Demographic Characteristics

Between the two treatment arms, subjects were balanced for age, sex, race, and ethnicity (refer to table below). The median age was 38 years with range between 18 and 76 years. 120 (93.8%) subjects were less than 60 years old. 83 subjects (64.8%) were female, a little higher than the number of male subjects. 95.3% of the subjects were Caucasian, and 96.9% were not Hispanic or Latino.

Table 14: Demographic Characteristics of Primary Efficacy Analysis

Demographic Characteristics	Placebo (n=64)	Ferric Maltol (n=64)	Total (n=128)
Age (years)			
N	64	64	128
Mean(SD)	38.5 (12.3)	40.1 (13.5)	39.3 (12.9)
Median	37.5	38.5	38
(Min, Max)	(19, 76)	(18, 75)	(18, 76)
Age Group (years), n (%)			
<60	60 (93.8%)	60 (93.8%)	120 (93.8)
≥60	4 (6.2%)	4 (6.2%)	8 (6.2)
Gender, n (%)			
Female	43 (67.2%)	40 (62.5%)	83 (64.8)
Male	21 (32.8%)	24 (37.5%)	45 (35.2)
Race, n (%)			
White	60 (93.8%)	62 (96.9%)	122 (95.3)
Black or African American	1 (1.6%)	0	1 (0.8)
Asian	2 (3.1%)	1 (1.6%)	3 (2.3)
Other	1 (1.6%)	1 (1.6%)	2 (1.6)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not-Hispanic or Latino	63 (98.4%)	61 (95.3%)	124 (96.9)
Unknown	1 (1.6%)	3 (4.7%)	4 (3.1)

Source: FDA Analysis

Other Baseline Characteristics

In total, 58 subjects (29 in each treatment arm) had ulcerative colitis (UC) and 70 subjects (35 in each treatment arm) had Crohn's disease (refer to table below). The median duration of UC was 6.5 years (range: 0.3 - 38.5) in the ferric maltol arm and 8.4 years (range: 1.3 - 50.6) in the placebo arm. The median duration of Crohn's disease was similar between the two treatment arms with 10.1 years (range: 0.5 – 40.3) in the ferric maltol arm and 10.9 years (range: 0 – 30.8) in the placebo arm. The median duration since last disease flare was 8.7 months (range: 0 - 450.4) in the ferric maltol arm and 6.5 months (range: 0 - 258.8) in the placebo arm.

The median length of prior OFP treatment was 53.3 days (range: 0 - 1095.8) in the ferric maltol arm and 45.7 days (range: 0 - 1826.3) in the placebo arm. The median duration of time since last OFP dose was 21.8 month (range: 0.2 - 175.4) in the ferric maltol arm and 17.4 months (range: 0 - 206.8) in the placebo arm.

Table 15: Summary of Baseline Disease Characteristics - FAS

Baseline Disease Characteristics	Placebo (n=64)	Ferric Maltol (n=64)	Total (n=128)
Disease Type, n (%)			
Ulcerative Colitis	29 (45.3)	29 (45.3)	58 (45.3)
Crohn's Disease	35 (54.7)	35 (54.7)	70 (54.7)
Duration of Ulcerative Colitis (years)			
N	29	29	58
Mean (SD)	11.0 (11.4)	9.0 (8.3)	10.0 (9.9)
Median (Range)	8.4	6.5	6.7
(Min, Max)	(1.3, 50.6)	(0.3, 38.5)	(0.3, 50.6)
Duration of Crohn's Disease (years)			
N	35	35	70
Mean (SD)	11.0 (8.1)	11.2 (9.3)	11.1 (8.7)
Median	10.9	10.1	10.2
(Min, Max)	(0.0, 30.8)	(0.5, 40.3)	(0, 40.3)
Duration since last disease flare (months)			
N	64	64	128
Mean (SD)	21.5 (38.5)	24.8 (59.2)	23.2 (49.7)
Median	6.5	8.7	7.4
(Min, Max)	(0, 258.8)	(0, 450.4)	(0, 450.4)
Length of prior OFP treatment (days)			
N	57	56	113
Mean (SD)	124.7 (270.4)	97.3 (176.4)	111.1 (228.1)
Median	45.7	53.3	45.7
(Min, Max)	(0, 1826.3)	(0, 1095.8)	(0, 1826.3)
Time since last OFP dose (months)			
N	59	59	118
Mean (SD)	33.3 (44.0)	36.2 (40.1)	34.8 (42.0)
Median	17.4	21.8	18.5
(Min, Max)	(0, 206.8)	(0.2, 175.4)	(0, 206.8)

Source: FDA Analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Subjects were considered non-compliant with the study medication if they were less than 80% or more than 120% compliant with the dosage schedule. Median compliance in the double-blind phase was 96.6% in the ferric maltol treatment arm and 96.7% in the placebo arm.

During the double-blind phase, the most common medications (taken by at least 10% of patients) in the ferric maltol treatment arm were mesalazine taken by 35 (54.7%) patients followed by azathioprine (17 [26.6%]); adalimumab (12 [18.8%]), infliximab (12 [18.8%]);

prednisolone (8 [12.5%]); and paracetamol (8 [12.5%]). The most common medications in the placebo treatment arm were mesalazine taken by 35 (54.7%) patients followed by azathioprine (21 [32.8%]); infliximab (14 [21.9%]); adalimumab (12 [18.8%]); and ibuprofen (8 [12.5%]). The most common medications were expected for the enrolled IBD patient population.

Efficacy Results – Primary Endpoint

Table below provides the summary statistics of the Hb concentration measurements at baseline and Week 4, 8 and 12 during the 12 weeks of the double-blind treatment period. The observed mean Hb at baseline were similar between the two treatment arms (11.0 g/dL [SD: 1.03] in the ferric maltol arm and 11.1 g/dL [SD: 0.85] in the placebo arm). At Week 12, the observed mean Hb was 13.2 g/dL (SD: 1.04) in the ferric maltol arm and was 11.2 g/dL (SD: 1.04) in the placebo arm.

Table 16: Summary Statistics of the Hb Concentration during the 12 Weeks of Double-Blind Treatment Period - FAS

Hb Concentration (g/dL)	Placebo (n=64)	Ferric Maltol (n=64)	Total (n=128)
Baseline			
N	64	64	128
Mean (SD)	11.1 (0.85)	11.0 (1.03)	11.0 (0.94)
Median	11.1	11.1	11.1
(Min, Max)	(9.5, 13.5)	(9.2, 13.5)	(9.2, 13.5)
Week 4			
N	61	59	120
Mean (SD)	11.1 (0.97)	12.0 (0.80)	11.6 (1.01)
Median	11.1	12.1	11.6
(Min, Max)	(8.5, 14.3)	(10.5, 14.2)	(8.5, 14.3)
Week 8			
N	56	59	115
Mean (SD)	11.2 (0.98)	12.8 (0.97)	12.0 (1.25)
Median	11.1	12.6	12.1
(Min, Max)	(8.9, 13.7)	(10.5, 15)	(8.9, 15)
Week 12			
N	53	58	111
Mean (SD)	11.2 (1.04)	13.2 (1.04)	12.2 (1.46)
Median	11.1	13	12.1
(Min, Max)	(9.3, 13.8)	(11.3, 15.5)	(9.3, 15.5)

Source: FDA Analysis

Table below summarized the amount of missing values at baseline, Week 4, 8, and 12. At Week 12, 9.4% of subjects in the ferric maltol arm had missing values and 17.2% of subjects in the placebo arm had missing values.

Table 17: Missing Data Pattern during the 12 Weeks Double-Blind Treatment Period - FAS

Missing data assessment, n (%)	Placebo (n=64)	Ferric Maltol (n=64)	Total (n=128)
Baseline	0	0	0
Week 4	3 (4.7)	5 (7.8)	8 (6.3)
Week 8	8 (12.5)	5 (7.8)	13 (10.2)
Week 12	11 (17.2)	6 (9.4)	17 (13.3)

Source: FDA Analysis

The results of the inferential comparison of change in Hb concentration from baseline to Week 12 between the ferric maltol arm and the placebo arm is presented in the table below. These results were derived from an ANCOVA model with missing Hb measurements at Week 12 were replaced by an imputed value from a multiple imputation (MI) method. The least square (LS) mean change from baseline to Week 12 was 2.25 g/dL (SE: 0.12) in the ferric maltol arm and 0.06 g/dL (SE: 0.13) in the placebo arm. The difference in LS mean change from baseline to Week 12 between ferric maltol and placebo was 2.18 g/dL (SE: 0.19). This difference resulted a statistically significant P-value of less than 0.0001.

Table 18: Primary Analysis Result for Change in Hb Concentration from Baseline to Week 12 (Analysis using Multiple Imputation) - FAS

Hb Concentration (g/dL)	Placebo (n=64)	Ferric Maltol (n=64)
LS mean change from baseline to week 12 ^{ab} (SE)	0.06 (0.13)	2.25 (0.12)
Difference in LS mean change from baseline to week 12 (SE), 1-sided lower bound of the 97.5% CI	2.18 (0.19) (1.81)	
P-value	<0.0001	

^a missing value at Week 12 is replaced with an imputed value using a MI method

^b LS mean change from baseline to Week 12 is derived from an ANCOVA model with treatment as factor and gender, disease (UC or Crohn's disease), baseline Hb as covariates.

Source: FDA Analysis

Sensitivity Analyses of the Primary Endpoint:

Table below summarizes the number of subjects in each analysis population used in the sensitivity analyses. Full analysis set (FAS) population is consisted of all randomized subjects who had at least one dose of study drug. FAS is used for the primary analysis. Modified full analysis set (mFAS) includes all randomized subjects who had at least one dose of study drug and had at least one post-baseline Hb measurement. Week 12 population includes randomized subjects who had Hb measurement at Week 12. Complete Case population includes randomized subjects who had Hb measurements at Week 4, 8, and 12.

Table 19: Summary of the Analysis Population for the Sensitivity Analyses

	Placebo n (%)	Ferric Maltol n (%)	Total n (%)
Full analysis Set (FAS)	64 (100)	64 (100)	128 (100)
Modified Full Analysis Set (mFAS)	61 (95.3)	59 (92.2)	120 (93.8)
Week 12	53 (82.8)	58 (90.6)	111 (86.7)
Complete Case	52 (81.3)	58 (90.6)	110 (85.9)

Source: FDA Analysis

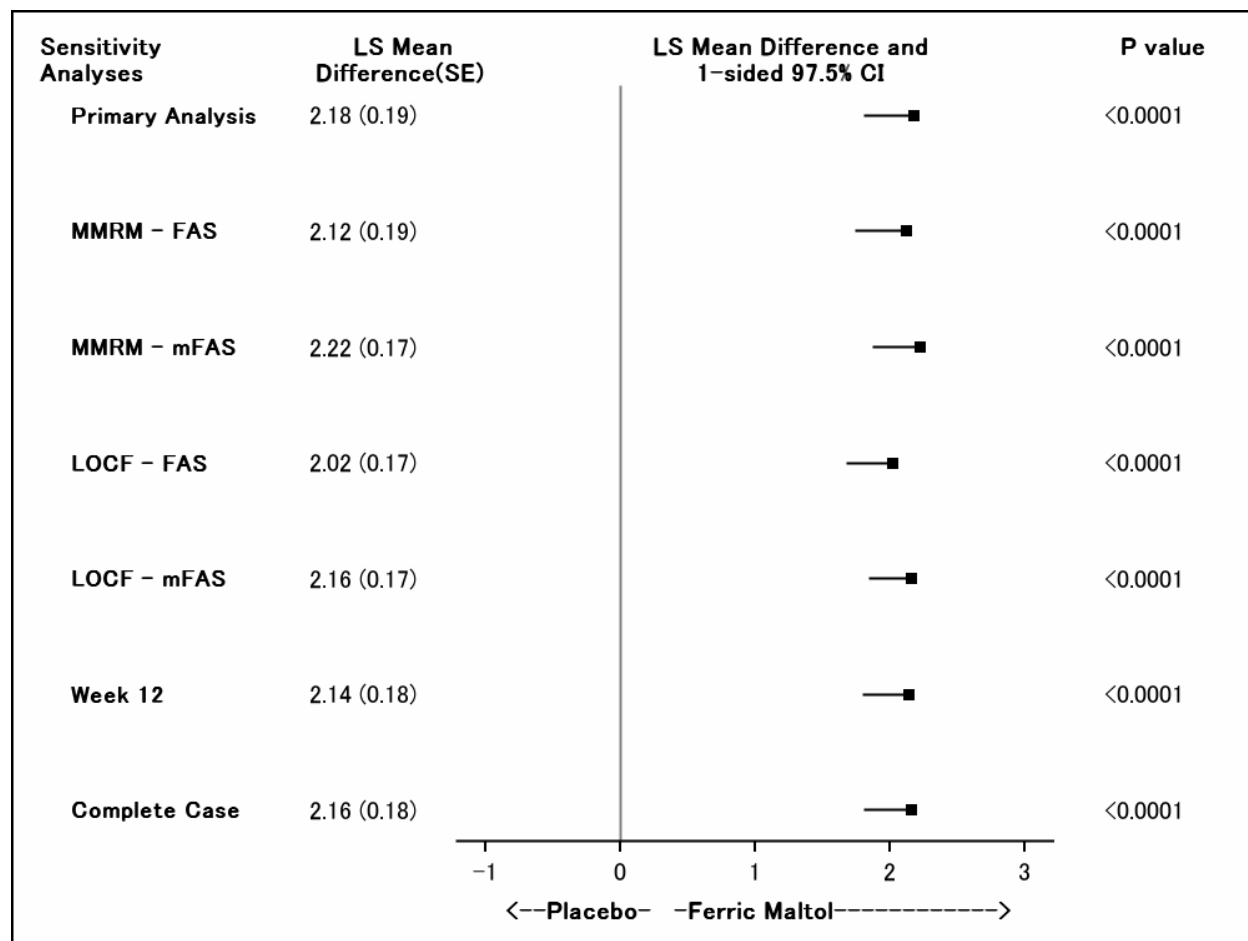
Table and Figure below show the results from the sensitivity analyses. These results support the primary analysis result. Therefore, the treatment effect of ferric maltol compared to placebo seems to be robust.

Table 20: Sensitivity Analyses for the Primary Endpoint

	LS Mean Difference (SE)	1-sided lower bound of the 97.5% CI	P-Value
Primary Analysis (MI) - FAS	2.18 (0.19)	(1.81)	<0.0001
MMRM - FAS	2.12 (0.19)	(1.74)	<0.0001
MMRM - mFAS	2.22 (0.17)	(1.87)	<0.0001
LOCF - FAS	2.02 (0.17)	(1.68)	<0.0001
LOCF - mFAS	2.16 (0.17)	(1.84)	<0.0001
Week 12	2.14 (0.18)	(1.80)	<0.0001
Complete Case	2.16 (0.18)	(1.81)	<0.0001

Source: FDA Analysis

Figure 3: Forest Plot of the Sensitivity Analyses



Source: FDA Analysis

Subgroup Analyses:

Since majority of subjects were less than 60 years old, Caucasian, and not Hispanic or Latino ethnically, only subgroups by gender and disease type (UC or Crohn's disease) are analyzed for the primary endpoint (refer to the table and figure below). The results from the subgroup analyses are, in general, support the findings from the primary analysis.

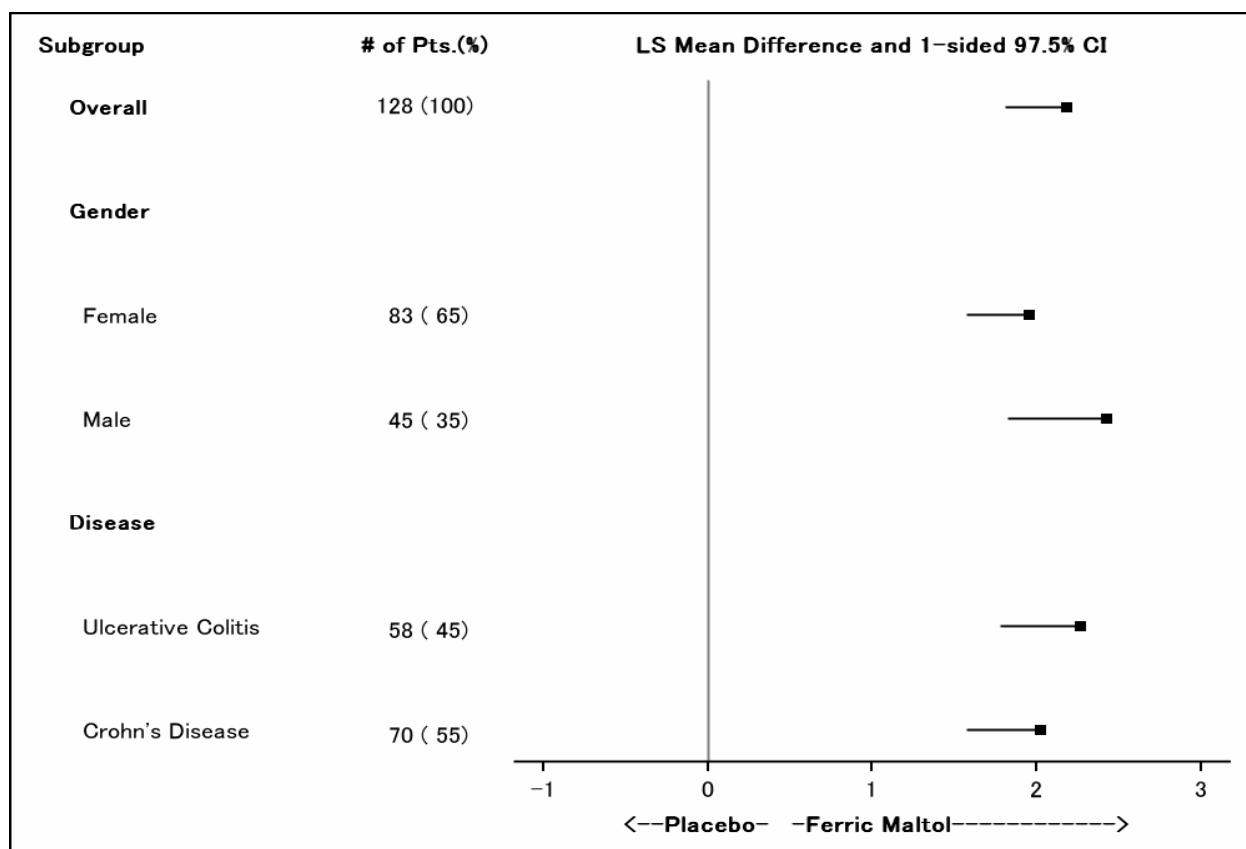
Table 21: Summary of Subgroup Analyses by Gender and Disease Type - FAS

	LS Mean Difference (SE)	1-sided 97.5% CI
Primary Analysis (n=128 [100%])	2.18 (0.19)	(1.81)
Gender		
Female (n=83 [64.8%])	1.95 (0.19)	(1.57)

Male (n=45 [35.2%])	2.42 (0.30)	(1.82)
Disease		
Ulcerative Colitis (n=58 [45.3%])	2.26 (0.24)	(1.78)
Crohn's Disease (n=70 [54.7%])	2.02 (0.23)	(1.57)

Source: FDA Analysis

Figure 4: Forest Plot for the Subgroup Analyses - FAS



Source: FDA Analysis

Data Quality and Integrity

The reviewer did not find any issues with the integrity and the quality of the data submitted for this study.

Efficacy Results – Secondary and other relevant endpoints

Hb Concentration during the Open Label Treatment:

Table below provides a descriptive summary of the Hb concentration during the open-label phase of the study. The observed mean changes from baseline to Week 64 (end of open-label phase) were 3.1 g/dL (SD: 1.46) in the ferric maltol arm and 2.2 g/dL (SD: 1.61) in the placebo arm.

Table 22: Summary Results of the Hb Concentration in the Open Label Phase - FAS

Hb Concentration (g/dL)	Placebo (n=64)	Ferric Maltol (n=64)	Total (n=128)
Baseline			
N	64	64	128
Mean (SD)	11.1 (0.85)	11 (1.03)	11.0 (0.94)
Median	11.1	11.1	11.1
(Min, Max)	(9.5, 13.5)	(9.2, 13.5)	(9.2, 13.5)
Week 48			
N	37	40	77
Mean (SD)	13.2 (1.07)	14.0 (1.00)	13.6 (1.10)
Median	13	13.9	13.5
(Min, Max)	(10.6, 15)	(11.9, 15.6)	(10.6, 15.6)
Change from Baseline to Week 48			
N	37	40	77
Mean (SD)	2 (1.19)	3.1 (1.34)	2.6 (1.37)
Median	2.1	2.8	2.6
(Min, Max)	(-0.8, 4.4)	(0.2, 6.3)	(-0.8, 6.3)
Week 64			
N	36	35	71
Mean (SD)	13.3 (1.46)	14.0 (1.26)	13.6 (1.39)
Median	13.5	13.8	13.7
(Min, Max)	(7.6, 15.6)	(10.1, 15.9)	(7.6, 15.9)
Change from Baseline to Week 64			
N	36	35	71
Mean (SD)	2.2 (1.61)	3.1 (1.46)	2.6 (1.59)
Median	2.4	3.1	2.8
(Min, Max)	(-3, 5.4)	(-0.2, 5.8)	(-3, 5.8)

Source: FDA Analysis

Ferritin:

A descriptive summary of ferritin measurements at baseline, Week 12, and Week 64 are presented in Table below. At Week 12, the observed mean change from baseline was 17.3 µg/L (SD: 28.30) in the ferric maltol arm and 1.2 µg/L (SD: 7.85) in the placebo arm. At Week 64, the

observed mean change from baseline was 60.4 µg/L (SD: 93.35) in the ferric maltol arm and 36.6 µg/L (SD: 46.80) in the placebo arm.

Table 23: Summary Results of Ferritin at Baseline, Week 12 (end of DB treatment period), and Week 64 (end of open-label phase) - FAS

Ferritin (µg/L)	Placebo (n=64)	Ferric Maltol (n=64)	Total (n=128)
Baseline			
N	64	64	128
Mean (SD)	8.2 (6.46)	8.6 (6.77)	8.4 (6.60)
Median	6.5	6.5	6.5
(Min, Max)	(2, 40)	(1, 46)	(1, 46)
Week 12			
N	53	59	112
Mean (SD)	9.8 (9.55)	26.0 (30.57)	18.3 (24.44)
Median	6	19	14
(Min, Max)	(1, 44)	(6, 240)	(1, 240)
Change from Baseline to Week 12			
N	53	59	112
Mean (SD)	1.2 (7.85)	17.3 (28.30)	9.7 (22.63)
Median	0	13	6.5
(Min, Max)	(-24, 27)	(-12, 215)	(-24, 215)
Week 64			
N	36	36	72
Mean (SD)	46 (51.15)	68.9 (96.24)	57.4 (77.38)
Median	32.5	42	40.5
(Min, Max)	(4, 288)	(10, 545)	(4, 545)
Change from Baseline to Week 64			
N	36	36	72
Mean (SD)	36.6 (46.80)	60.4 (93.35)	48.5 (74.3)
Median	25	34.5	28.5
(Min, Max)	(-1, 260)	(2, 520)	(-1, 520)

Source: FDA Analysis

Dose/Dose Response

Taken from the clinical pharmacology review, “the proposed dosing regimen is supported by the observed PK, safety, and efficacy data from studies ST10-01-301/302 (including PK sub-study ST10-01-102), ST10-01-303, and ST10-01-101.” Refer to the clinical pharmacology section of this review for additional details.

Durability of Response

The study met the primary efficacy endpoint of change in hemoglobin concentration after 12 weeks of treatment with ferric maltol compared to placebo. Data from the open-label phase showed that over the long-term, mean hemoglobin continued to rise with ferric maltol treatment and no evidence of a reduction in efficacy. In addition, ferritin also continued to rise over longer-term treatment (up to 64 weeks) with ferric maltol.

Persistence of Effect

Since the primary endpoint, change from baseline in Hb concentration to Week 12, was not measured once the treatment was stopped, no data were available to investigate the persistence of the treatment effect following the termination of the treatment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

This section is not applicable. There were no PRO endpoints in the study.

8.2. Study ST10-01-303

8.2.1. Study Design

Overview and Objective

The primary objective of the study was to evaluate the efficacy of oral ferric maltol compared with placebo in the treatment of IDA in subjects with non-dialysis dependent CKD at 16 weeks. The study also included an open label extension phase which evaluated safety and efficacy up to 52 weeks.

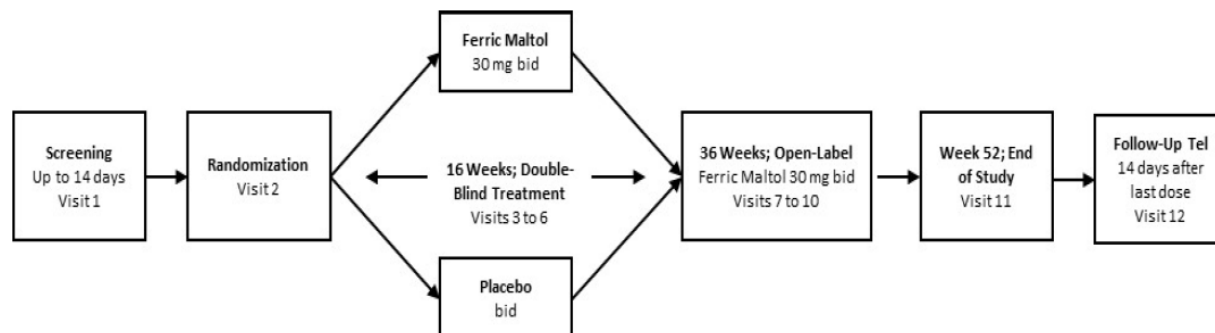
Trial Design

ST10-01-303 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of ferric maltol treatment versus placebo in patients with non-dialysis dependent CKD and concomitant IDA.

A total of 167 patients were randomized in a 2:1 ratio ferric maltol or matching placebo. All study sites were in the U.S. Randomization was stratified according to screening Hb (<9.5 g/dL or ≥9.5 g/dL) and eGFR (≤30 mL/min/1.73m² or >30 mL/min/1.73m²). Patients received oral ferric maltol 30 mg capsules BID or oral matching placebo bid for 16 weeks. Patients were permitted to continue ferric maltol or switch from placebo after 16 weeks for a total of 36 weeks in the open-label phase of the study.

The following figure outlines the study schema for ST10-01-303.

Figure 5: Study ST10-01-303 Schema



Source: Applicant's Clinical Study Report, Module 5.3.5.1

Adult patients with CKD and an eGFR of ≥ 15 mL/min/1.73m² and < 60 mL/min/1.73m² were enrolled in this study. It was anticipated that this population had less significant renal disease and comorbidities and would be able to tolerate the placebo phase of the study. Patients had concomitant IDA as defined by Hb, ferritin, and TSAT levels. Patients were not severely anemic and had Hb ≥ 8.0 g/dL. Patients who had recently received IV iron, blood transfusions, or renal transplant were not permitted to enter the study.

All subjects entering this study were anemic (Hb < 11.0 g/dL) below the lower limit of normal Hb (13.5 g/dL for males and 12.0 g/dL for females per KDOQI 2006), for investigational purposes, since the benefits to subjects who were treated with ferric maltol with Hb between 11.0 g/dL and the lower limit of normal could be marginal.

The eligibility criteria for the study are summarized below.

Inclusion Criteria

- Age ≥ 18 years
- CKD with an eGFR of ≥ 15 mL/min/1.73m² and < 60 mL/min/1.73m², as calculated using the abbreviated version of the modified diet in renal disease (MDRD) equation
- Iron deficiency anemia as defined by ferritin < 250 ng/mL with a TSAT $< 25\%$ OR ferritin < 500 ng/mL with a TSAT of $< 15\%$
- Female patients of childbearing potential age (including perimenopausal females who had had a menstrual period within 1 year prior to screening) must agree to use a reliable method of contraception until study completion and for at least 4 weeks following their final study visit.

Exclusion Criteria

- Anemia due to any cause other than iron deficiency, including, but not limited to: severe malabsorption, immunosuppressant use
- Administration with any of the following prior to randomization:
 - Intravenous iron injection within the previous 4 weeks or administration of intramuscular or depot iron preparation within the previous 12 weeks
 - Single agent oral iron supplementation, taken specifically to treat anemia (e.g., ferrous sulfate, fumarate, or gluconate) within the previous 2 weeks. multivitamins were permitted
 - Use of ferric citrate or sucroferric oxyhydroxide within the previous 1 week (at screening)
 - Erythropoiesis-stimulating agents within the previous 4 weeks (at screening)
 - Blood transfusion or donation within the previous 12 weeks (at screening)
 - Dimercaprol or chloramphenicol within the previous 7 days (at screening)
 - Use of methyldopa at the time of screening
- Received dialysis at the time of screening or initiation of dialysis was considered likely during the study
- Renal transplant within 12 months prior to randomization or was considered likely during the study
- Contraindication for treatment with iron preparations (e.g. hemochromatosis, chronic hemolytic disease, sideroblastic anemia, thalassemia, or lead intoxication induced anemia)
- ALT or AST >3 times the upper limit of normal as assessed via screening laboratory results
- Clinically significant vitamin B12 or folic acid deficiency as determined by the screening laboratory results (retest following at least 2 weeks of starting treatment with vitamin B12 or folate replacement was permitted)
- Concomitant medical conditions with significant active bleeding
- Scheduled or expected major surgery during the course of the study

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The following tables outline the study schedule of assessments.

Table 24: ST10-01-303 Schedule of Assessments

PERIODS	SCREENING	RANDOMIZED TREATMENT					OPEN-LABEL TREATMENT					FOLLOW-UP
Visit Duration	1-14 days	16 weeks					36 weeks					14 days after last dose
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Visit Name	Screening Period ¹	Randomization	Week 4	Week 8	Week 12 (Phone)	Week 16 ²	Week 20 (Phone)	Week 24	Week 32	Week 42	Week 52 End of Study ²	Phone Follow-up ³
Visit Window		14 days from Screening ¹	±3 days				±7 days					14-21 days after last dose of study drug
Informed Consent	X											
Demographics	X											
Medical History	X											
Concomitant Medications and Procedures	X	X ⁴	X	X	X	X	X	X	X	X	X	X
Physical Examination		X				X					X	
Vital Signs		X ⁴				X					X	
12-Lead ECG		X ⁴									X	
Urine Pregnancy Test	X	X ⁴	X	X		X		X	X	X	X	
Hematology, Chemistry, and Iron Markers	X	X ⁴	X	X		X		X	X	X	X	

Source: Applicant's Clinical Study Report, Module 9.5.1

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PERIODS	SCREENING	RANDOMIZED TREATMENT					OPEN-LABEL TREATMENT					FOLLOW-UP
Visit Duration	1-14 days	16 weeks					36 weeks					14 days after last dose
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Visit Name	Screening Period ¹	Randomization	Week 4	Week 8	Week 12 (Phone)	Week 16 ²	Week 20 (Phone)	Week 24	Week 32	Week 42	Week 52 End of Study ²	Phone Follow-up ³
Visit Window		14 days from Screening ⁴	±3 days				±7 days					14-21 days after last dose of study drug
Population PK Sampling ⁵		X ⁴	X			X					X ⁵	
eGFR	X					X					X ⁵	
Retention Samples ⁵		X ⁴				X					X	
Eligibility Confirmation and Randomization		X ⁴										
Dispense Study Drug		X	X	X		X		X	X	X		
Return Study Drug			X	X		X		X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X

Note: unscheduled visits may have been required (eg. repeat laboratory sampling or safety assessments).

1. A subject may have been retested once for laboratory criteria that did not meet protocol criteria so long as randomization occurred no more than 14 days from the initial test result (if eligible).
2. Subjects who withdrew from the study before Week 16 had assessments conducted per Week 16/End of Randomized Treatment Period or per Week 52/End of Study if withdrawn after Week 16. Subjects who discontinued from study drug prior to Week 16 were encouraged to continue with study visits and assessments up to and including assessments at Week 16.
3. Follow-up call was not required if the subject prematurely discontinued treatment and the End of Study Visit occurred 14 days after the last dose taken.
4. Laboratory sampling and assessments were completed prior to the first dose of study drug.

Source: Applicant's Clinical Study Report, Module 9.5.1

Study Endpoints

The primary efficacy endpoint was to evaluate change in Hb concentration from baseline to Week 16.

The secondary efficacy endpoints were as follows:

- Change in Hb concentration from baseline to Week 4
- Change in Hb concentration from baseline to Week 8
- Changes in iron parameters (ferritin) at Weeks 16

Statistical Analysis Plan

Randomization Scheme:

Subjects is randomized at a 2:1 ratio to one of the following two treatment arms:

- Oral ferric maltol, 30 mg capsule bid
- Oral matching placebo capsule bid

The randomization is stratified according to screening Hb (< 9.5 g/dL or ≥ 9.5 g/dL) and eGFR values (≤ 30 or > 30 mL/min/1.73m²).

Statistical Hypothesis:

Let Y be the ferric maltol group, X be the placebo group, μ be the mean of change in Hb concentration from baseline to Week 16.

$$H_0: \mu_X = \mu_Y$$

$$H_A: \mu_X < \mu_Y$$

Sample Size Consideration:

The sample size calculation is based on the primary endpoint, change in Hb concentration from baseline to Week 16.

A sample size of 135 subjects (randomized 2:1, ferric maltol: placebo, 90 in ferric maltol group and 45 placebo) provides 95% power to detect a statistically significant treatment difference of 1.0 g/dL between ferric maltol and placebo, using a two-sided 0.05 significance level. This calculation assumes a common standard deviation of 1.5 g/dL for the endpoint. Assuming a drop-out rate of 20%, approximately 168 subjects total is accrued.

Efficacy Analysis Population:

Intent-to-treat (ITT): all randomized subjects. It is used for the primary efficacy analysis.

Statistical Reviewer's Comment: The efficacy measurements for some patients in the ITT analysis population are removed from the primary analysis and replaced with missing values if these measurements are obtained after patients had one of the following protocol violations:

- SAE of hemorrhage
- Received a blood transfusion
- Received in IV iron or erythropoiesis stimulating agent
- Received oral iron medication

Statistical Analysis:

The primary endpoint analysis is performed using an Analysis of Covariance (ANCOVA) on the ITT analysis population. Missing values are imputed using a multiple imputation (MI) method in two steps. Hb measurements excluded after the protocol prohibited events occurred in the SAP amendment and statistical memorandum are treated as missing values and are imputed along with all other missing values.

- Step 1: ten datasets are generated containing imputed values for non-monotone missing values in the original dataset. In this step it is assumed that any intermediate missing data points (e.g. missing at week 4 but not missing at week 8 or later) are missing at random (MAR).

- Step 2: the remaining monotone missing values are imputed. Hb concentrations at baseline, Week 4, Week 8 and gender are included as variables helpful in guiding this imputation for Hb at Week 16.

For each imputation dataset, the change from baseline to Week 16 is analyzed using ACOVA with treatment as a factor and baseline Hb and eGFR as covariates.

By combining the results from these ten analyses, the treatment estimates are constructed using the parameter estimates and associated standard errors. Similarly, the difference of the adjusted treatment means (ferric maltol – placebo) are constructed with the associated standard error and 2-sided 95% CI.

Sensitivity Analyses for the Primary Analysis:

Mixed Model Repeated Measures (MMRM):

A mixed model for repeated measures (MMRM) including all available assessments of change in Hb from baseline to Week 4, Week 8 and Week 16 is fitted. This model assumes that:

- Any missing data are missing at random (MAR)
- An unstructured variance-covariance structure (UN) should be used first. If the model fails to converge using an UN matrix, then a compound symmetry variance-covariance structure will be used instead

If any data are missing, the statistical model will use all information from all other time points to determine the mean treatment difference at each time point as well as for the primary endpoint (Week 16). Covariates in the MMRM will be the fixed effects of treatment, baseline Hb, baseline eGFR, week, and treatment-by week interaction; the random effect will be patient.

Last Observation Carried Forward (LOCF):

Missing week 16 Hb concentration is imputed as the last observed Hb concentration prior to the discontinuation of study drug. An ANCOVA model is used to analyze the data.

Week 16:

This analysis will be conducted including only those subjects who have both baseline and Week 16 Hb concentrations. An ANCOVA model is used to analyze the data.

Complete Case:

This analysis will be conducted including only those subjects who have baseline, Week 4, 8, and 16 Hb concentrations. An ANCOVA model is used to analyze the data.

Multiplicity Adjustment:

There are no planned adjustments for multiple comparisons. The results from other endpoints are considered exploratory.

Interim Analysis:

This section is not applicable.

Protocol Amendments

Table 25: Protocol Amendments for ST10-01-303

Date	Amendment(s)
September 12, 2016	Protocol Amendment 1 • Analysis of PK samples revised to occur more frequently based on available sample stability data. Both placebo and ferric maltol samples will be analyzed throughout the double-blind treatment period but results will not be made available to the Sponsor or CRO until post database lock. • Revision of discontinuation criteria by stating “subjects who discontinue from study treatment prior to Week 16 will be encouraged to continue with study visits and assessments up to and including assessments at week 16.”

Data Quality and Integrity: Sponsor's Assurance

The data submitted in this NDA were of high quality and facilitated an adequate efficacy review. The Sponsor asserts they complied with good clinical practice and financial disclosures and the Agency agrees with this assertion. There were no concerns regarding the integrity of the data in this submission.

8.2.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

The applicant submitted financial disclosure information from all investigators for this trial. There were no clinical investigators with disclosable financial arrangements in relation to study ST10-01-303.

Patient Disposition

The following table outlines patient disposition for the double-blind portion of the ST10-01-303 study. The initiation date of the study was on 01 December 2016 and the last visit of DB treatment phase was on 18 January 2018.

Of the 167 subjects who were randomized, 111 subjects were assigned to the ferric maltol arm and 56 subjects were assigned to the placebo arm (Table 1). In total, 129 subjects (77.2%) completed the DB 16-week treatment period: 90 subjects (81.1%) in the ferric maltol arm and 39 subjects (69.6%) in the placebo arm.

Thirty-eight subjects (22.8%) withdrew from the DB treatment period: 9 subjects (5.4%) due to withdrawal by subjects, 8 subjects (4.8%) due to an adverse event, 8 subjects (4.8%) due to use of prohibited concomitant medication, 6 subjects (3.6%) were unable to comply with study requirements, 4 subjects (2.4%) were lost to follow-up, 2 subjects (1.2%) due to death, and 1 patient (0.6%) due to lack of efficacy.

Table 26: Disposition for the Double-Blind Portion of ST10-01-303

	Placebo n (%)	Ferric Maltol n (%)	Total n (%)
Randomized / ITT	56 (100)	111 (100)	167 (100)
Completed the double-blind phase	39 (69.6)	90 (81.1)	129 (77.2)
Early withdrawal from the double-blind phase	17 (30.4)	21 (18.9)	38 (22.8)
Reason for withdrawal from double-blind phase			
Adverse Event	3 (5.4)	5 (4.5)	8 (4.8)
Death	1 (1.8)	1 (0.9)	2 (1.2)
Lost to follow-up	2 (3.6)	2 (1.8)	4 (2.4)
Lack of Efficacy	1 (1.8)	0 (0.0)	1 (0.6)
Withdrawal by patient	3 (5.4)	6 (5.4)	9 (5.4)
Use of prohibited concomitant medication	4 (7.1)	4 (3.6)	8 (4.8)
Unable to comply with study requirements	3 (5.4)	3 (2.7)	6 (3.6)

Source: FDA Analysis

Protocol Violations/Deviations

Protocol Prohibited Events:

In total, 23 subjects (13.8%) from the ITT population (14 [12.6%] in the ferric maltol arm and 9 [16.1%] in the placebo arm) had their Hb concentration measurements removed from the primary efficacy analysis after the protocol prohibited events occurred during the 16-week DB treatment period (refer to table below). These subjects were balanced between the two treatment arms. The most common events were ferrous sulfate with 5 subjects (3.0%) and epoetin alfa with 4 subjects (2.4%).

Table 27: Summary of Subjects with Data Removed from ITT Analyses because of the Protocol Prohibited Events

	Placebo (n=56)	Ferric Maltol (n=111)	Total (n=167)
Protocol Prohibited Events, n (%)			
Blood and Related Products	2 (3.6)	0	2 (1.2)
Red Blood Cells/ RBC Concentrated	0	3 (2.7)	3 (1.8)
Darbepoetin Alfa	0	1 (0.9)	1 (0.6)
Epoetin Alfa	1 (1.8)	3 (2.7)	4 (2.4)
Ferrous Sulfate	2 (3.6)	3 (2.7)	5 (3.0)
Ferumoxytol	1 (1.8)	0	1 (0.6)
Gastrointestinal Hemorrhage	0	1 (0.9)	1 (0.6)
Hematochezia	0	1 (0.9)	1 (0.6)
Hemorrhoidal Hemorrhage	0	1 (0.9)	1 (0.6)
Hemorrhagic Anemia	1 (1.8)	0	1 (0.6)
Methyldopa	0	1 (0.9)	1 (0.6)
Saccharated Iron Oxide	2 (3.6)	0	2 (1.2)
Overall, n (%)	9 (16.1)	14 (12.6)	23 (13.8)

Source: FDA Analysis

Demographic Characteristics

Table below summarizes baseline demographic characteristics for the ITT population. The median age of all the subjects was 70 years with range between 30 and 90 years. 114 subjects (68.3%) were greater than or equal to 65 years old. 117 subjects (70.1%) were female, more than twice the number of male subjects. Majority of the subjects were Caucasian (73.7%), not-Hispanic or Latino (75.4%). The two treatment arms were comparable with respect to demographic characteristics.

Table 28: Summary of Baseline Demographic Characteristics - ITT

Demographic Characteristics	Placebo (n=56)	Ferric Maltol (n=111)	Total (n=167)
Age (years)			
N	56	111	167
Mean (SD)	65.2 (12.79)	68.5 (12.43)	67.4 (12.61)
Median	68	71	70
(Min, Max)	(30, 83)	(33, 90)	(30, 90)
Age Group (years), n (%)			
<65	19 (33.9)	34 (30.6)	53 (31.7)
≥65	37 (66.1)	77 (69.4)	114 (68.3)
Gender, n (%)			
Female	39 (69.9)	78 (70.3)	117 (70.1)
Male	17 (30.4)	33 (29.7)	50 (29.9)
Race, n (%)			
White	42 (75.0)	81 (73.0)	123 (73.7)
Black or African American	12 (21.4)	23 (20.7)	35 (21.0)
Asian	0	2 (1.8)	2 (1.2)
Other	2 (3.6)	5 (4.5)	7 (4.1)
Ethnicity, n (%)			
Hispanic or Latino	14 (25.0)	26 (23.4)	40 (24.0)
Not-Hispanic or Latino	42 (75.0)	84 (75.7)	126 (75.4)
Unknown	0	1 (0.9)	1 (0.6)

Source: FDA Analysis

Other Baseline Characteristics

Baseline Disease Characteristics:

Table below summarizes baseline disease characteristics for the ITT population. The mean Hb was 10.1 g/dL (SD: 0.77) in the ferric maltol arm and 10.0 g/dL (SD: 0.82) in the placebo arm. The mean eGFR was 31.9 mL/min/1.73m² (SD: 11.53) in the ferric maltol arm and 29.7 mL/min/1.73m² (SD: 10.56) in the placebo arm.

Table 29: Summary of Baseline Disease Characteristics - ITT

Baseline Disease Characteristics	Placebo (n=56)	Ferric Maltol (n=111)	Total (n=167)
Baseline Hb (g/dL)			
N	56	111	167
Mean (SD)	10.0 (0.82)	10.1 (0.77)	10.1 (0.78)
Median	10.2	10	10
(Min, Max)	(7.7, 11.4)	(7.7, 11.6)	(7.7, 11.6)

Baseline eGFR (mL/min/1.73m ²)			
N	56	111	167
Mean (SD)	29.7 (10.56)	31.9 (11.53)	31.1 (11.23)
Median	29.5	30	30
(Min, Max)	(15, 58)	(15, 57)	(15, 58)

Source: FDA Analysis

Randomization Stratification Factors:

Table below describes the distribution of the two randomization stratification factors. 135 subjects (80.8%) had Hb greater than or equal to 9.5 g/dL at screening and 89 subjects (53.3%) had eGFR measurement less than or equal to 30 mL/min/1.73m².

Table 30: Summary of Randomization Stratification Factors - ITT

Randomization Stratification Factors	Placebo (n=56)	Ferric Maltol (n=111)	Total (n=167)
Screening Hb Concentration (g/dL)			
Hb < 9.5	11 (19.6)	21 (18.9)	32 (19.2)
Hb ≥ 9.5	45 (80.4)	90 (81.1)	135 (80.8)
Screening eGFR Measurement (mL/min/1.73m ²)			
Screen eGFR ≤ 30	30 (53.6)	59 (53.2)	89 (53.3)
Screen eGFR > 30	26 (46.4)	52 (46.8)	78 (46.7)

Source: FDA Analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The most commonly used concomitant medication classes were 3-hydroxy 3-methylglutaryl-coenzyme A reductase inhibitors (121 [72.5%]), vitamin D and analogues (120 [71.9%]), platelet aggregation inhibitors excluding heparin (102 [61.1%]), and sulfonamides, (102 [61.1%]).

Efficacy Results - Primary Endpoint

Descriptive summarizes of the Hb concentration at baseline, Week 4, 8, and 16 are presented in table below. The observed mean Hb at baseline were similar between the two treatment arms (10.1 g/dL [SD: 0.77] in the ferric maltol arm and 10.0 g/dL [SD: 0.82] in the placebo arm). At Week 16, the observed mean Hb was 10.7 g/dL (SD: 1.18) in the ferric maltol arm and was 10.2 g/dL (SD: 1.07) in the placebo arm.

Table 31: Summary Statistics of the Hb Concentration during the 16 Weeks Double-Blind Treatment Period - ITT

Hb Concentration (g/dL)	Placebo (n=56)	Ferric Maltol (n=111)	Total (n=167)
-------------------------	-------------------	--------------------------	------------------

Baseline			
N	56	111	167
Mean (SD)	10.0 (0.82)	10.1 (0.77)	10.1 (0.78)
Median	10.2	10	10
(Min, Max)	(7.7, 11.4)	(7.7, 11.6)	(7.7, 11.6)
Week 4			
N	52	103	155
Mean (SD)	10.1 (0.98)	10.3 (0.98)	10.2 (0.98)
Median	10.1	10.4	10.4
(Min, Max)	(7.4, 12.3)	(6.5, 12.2)	(6.5, 12.3)
Week 8			
N	46	94	140
Mean (SD)	10.2 (0.92)	10.7 (0.82)	10.5 (0.88)
Median	10.3	10.7	10.5
(Min, Max)	(7.7, 12.1)	(8.9, 13)	(7.7, 13)
Week 16			
N	40	88	128
Mean (SD)	10.2 (1.07)	10.7 (1.18)	10.5 (1.16)
Median	10.4	10.5	10.5
(Min, Max)	(7.3, 12.9)	(7.6, 15.7)	(7.3, 15.7)

Source: FDA Analysis

The missing data pattern at each visit during the DB period is described in table below. By Week 16, 23.4% of Hb values were missing (20.7% in the ferric maltol arm and 28.6% in the placebo arm).

Table 32: Missing Data Pattern during the 16 Weeks Double-Blind Treatment Period - ITT

Missing data assessment, n (%)	Placebo (n=56)	Ferric Maltol (n=111)	Total (n=167)
Baseline	0	0	0
Week 4	4 (7.1)	8 (7.2)	12 (7.2)
Week 8	10 (17.9)	17 (15.3)	27 (16.2)
Week 16	16 (28.6)	23 (20.7)	39 (23.4)

Source: FDA Analysis

The results of the inferential comparison of change in Hb concentration from baseline to Week 16 between the ferric maltol arm and the placebo arm is summarized in table below. These results were derived from an ANCOVA model with missing Hb measurements at Week 16 were replaced by an imputed value from a multiple imputation (MI) method. The least square (LS) mean change from baseline to Week 16 was 0.5 g/dL (SE: 0.12) in the ferric maltol arm and

-0.02 g/dL (SE: 0.16) in the placebo arm. The difference in LS mean change from baseline to Week 16 was 0.52 g/dL (SE: 0.21). This difference resulted a statistically significant P-value of 0.0149.

Table 33: Primary Analysis Result for Change in Hb Concentration from Baseline to Week 16 (Analysis using Multiple Imputation) - ITT

Hemoglobin Concentration (g/dL)	Placebo (n=56)	Ferric Maltol (n=111)
Least square (LS) mean change from baseline to Week 16 (SE)	-0.02 (0.16)	0.5 (0.12)
Difference between LS mean change from baseline to Week 16 (SE), 95% CI	0.52 (0.21) (0.10, 0.93)	
P-value	0.0149	

^a missing value at week 16 is replaced with an imputed value through a MI method

^b LS mean change from baseline is derived from an ACOVA model with factors for treatment, baseline eGFR and baseline Hb.

Source: FDA Analysis

Sensitivity Analyses of the Primary Endpoint:

Table below summarizes the number of subjects in each analysis population used in the sensitivity analyses. Intent-to-treat population is consisted of all randomized subjects. Modified intend-to-treat population includes all randomized subjects who had at least one post-baseline Hb measurement. Week 16 population includes randomized subjects who had Hb measurement at Week 16. Complete Case population includes randomized subjects who had Hb measurements at Week 4, 8, and 16.

Table 34: Summary of the Analysis Population for the Sensitivity Analyses

	Placebo n (%)	Ferric Maltol n (%)	Total n (%)
Intent-to-treat (ITT)	56 (100)	111 (100)	167 (100)
Modified intent-to-treat (mITT)	52 (92.9)	105 (94.6)	157 (94.0)
Week 16	40 (71.4)	88 (79.3)	128 (76.6)
Complete Case	38 (67.9)	82 (73.9)	120 (71.9)

Source: FDA Analysis

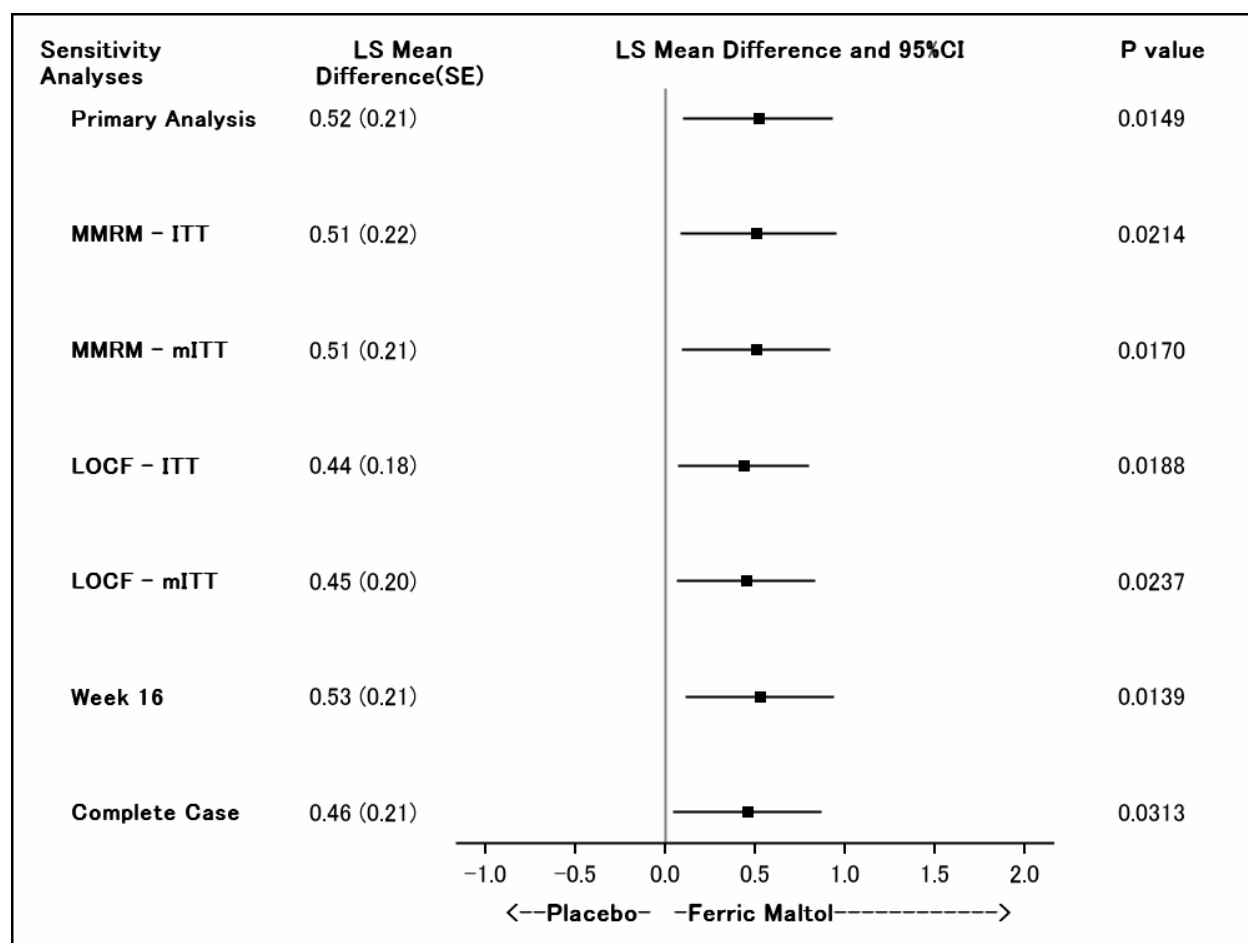
Table and Figure below show the results from the sensitivity analyses performed. All the results support the primary analysis result. Therefore, the treatment effect of ferric maltol compared to placebo seems to be robust.

Table 35: Sensitivity Analyses for the Primary Endpoint

	LS Mean Difference (SE)	95% CI	P-Value
Primary Analysis (MI) - ITT	0.52 (0.21)	(0.10, 0.93)	0.0149
MMRM - ITT	0.51 (0.22)	(0.08, 0.95)	0.0214
MMRM - mITT	0.51 (0.21)	(0.09, 0.92)	0.0170
LOCF - ITT	0.44 (0.18)	(0.07, 0.80)	0.0188
LOCF - mITT	0.45 (0.20)	(0.06, 0.83)	0.0237
Week 16	0.53 (0.21)	(0.11, 0.94)	0.0139
Complete Case	0.46 (0.21)	(0.04, 0.87)	0.0313

Source: FDA Analysis

Figure 6: Forest Plot for the Sensitivity Analyses



Source: FDA Analysis

Subgroup Analyses:

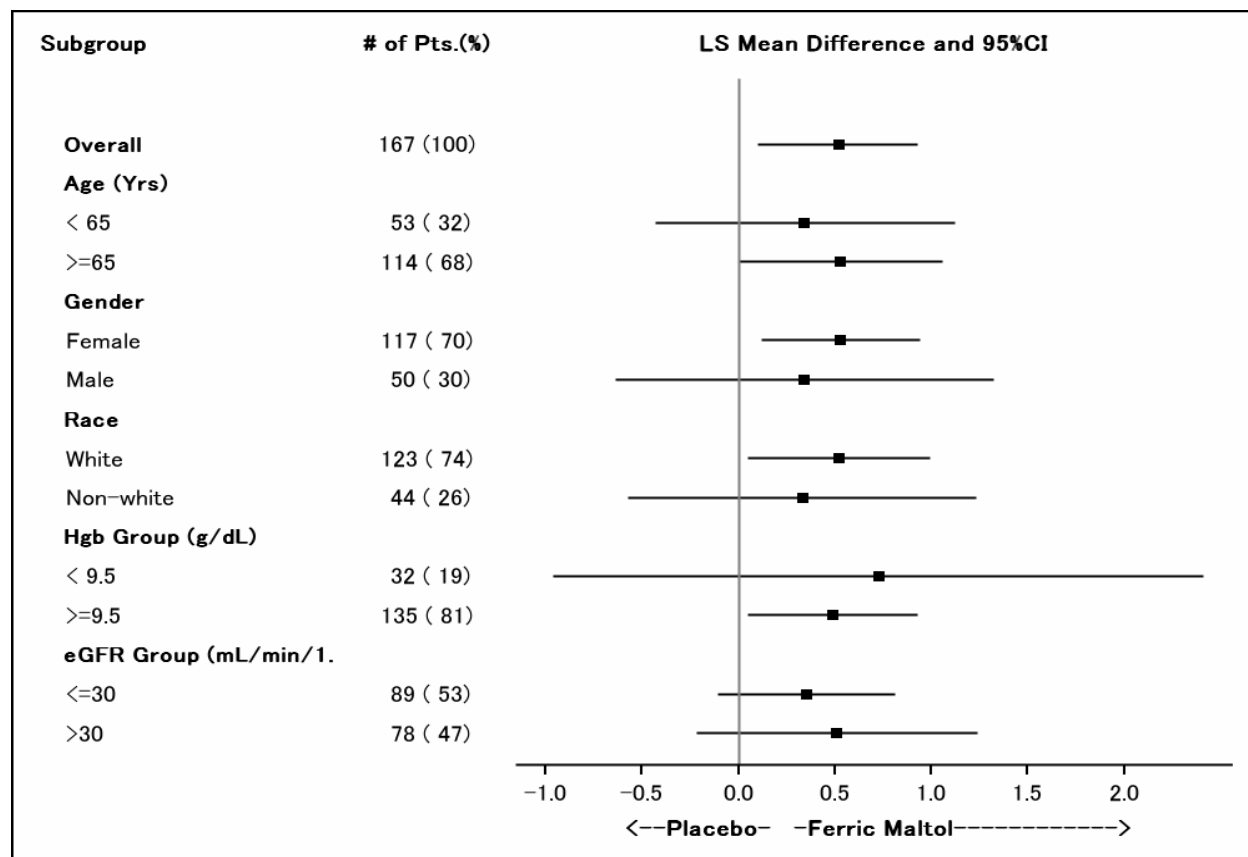
Table and figure below present the results from subgroup analyses by age, gender, race, Hb group at Screening and eGFR group at Screening for the primary endpoint. The results are, in general, support the findings from the primary analysis.

Table 36: Summary of Subgroup Analyses by Demographic and Stratification Factors - ITT

	LS Mean Difference (SE)	95% CI
Primary Analysis (n=167 [100%])	0.52 (0.21)	(0.10, 0.93)
Age group (years)		
<65 (n=53 [31.7%])	0.34 (0.40)	(-0.43, 1.12)
≥65 (n=114 [68.3%])	0.53 (0.27)	(0, 1.06)
Gender		
Female (n=117 [70.1%])	0.53 (0.21)	(0.12, 0.94)
Male (n=50 [29.9%])	0.34 (0.50)	(-0.64, 1.32)
Race		
White (n=123 [73.7%])	0.52 (0.24)	(0.05, 0.99)
Non-white (n=44 [26.3%])	0.33 (0.45)	(-0.57, 1.23)
Hb Group at Screening (g/dL)		
< 9.5 (n=32 [19.2%])	0.73 (0.83)	(-0.96, 2.41)
≥ 9.5 (n=135 [80.8%])	0.49 (0.22)	(0.05, 0.93)
eGFR Group at Screening (mL/min/1.73m ²)		
≤ 30 (n=89 [53.3%])	0.35 (0.23)	(-0.11, 0.81)
>30 (n=78 [46.7%])	0.51 (0.37)	(-0.22, 1.24)

Source: FDA Analysis

Figure 7: Forest Plot of the Subgroup Analyses - ITT



Source: FDA Analysis

Data Quality and Integrity – Statistical Reviewers' Assessment

The sponsor has made modifications to the SAP twice. First time was through a SAP amendment (version 1.1), which was finalized on 8 February 2018. Secondary time was through a statistical memorandum, which was finalized on 7 March 2018. After the DB phase ended on 18 January 2018, sponsor conducted an unplanned analysis on the primary endpoint after data cleaning and prior to the full database lock. According to the sponsor, this was done to “fulfill a corporate need for early top-line data”. The comparison of ferric maltol to placebo from this analysis failed to show a statistically significant difference in the primary endpoint (change in Hb concentration from baseline to week 16). Sponsor’s review of the specified protocol deviations found some of the participants who had protocol prohibited events (i.e. hemorrhage, a blood transfusion, and/or rescue medication such as IV iron or ESAs) were kept in the study and had their Hb concentration measurements continuously recorded instead of been removed from the study due to protocol violations. These Hb measurements recorded after these events caused an increase in the mean change in Hb values from baseline to Week 16 in the placebo arm, which resulted a statistically nonsignificant difference from the ferric maltol arm.

Sponsor claimed that the treatment effect of ferric maltol vs placebo estimated with these Hb concentration measurements recorded after protocol prohibited events in the analysis was not an accurate estimation of the true treatment effect of ferric maltol because the estimated effect was confounded by the protocol prohibited events. Therefore, sponsor amended the SAP with version 1.1 on 8 February 2018, before the database lock and un-blinding the data. In this version, for patients who had protocol prohibited events, their Hb measurements after these events would be removed from the primary analysis and considered as missing data. After unbinding the data, sponsor performed full final analyses on 02 March 2018 based on SAP v1.1 and discovered that some participants who received oral iron medication, which was also a protocol prohibited medication, did not have their Hb measurements removed after it happened. This would also bias the estimation of the treatment effect because oral iron is also a confounder. Sponsor then added oral iron medication to the list of the confounders and the measurements were removed after the iron were taken for those participants. Sponsor decided to only add a statistical memo on 07 March 2018 to document this change because the modification was considered minor. Based on the sponsor's response on 04 March 2019 to FDA's clinical information request dated 25 February 2019, there were 23 participants (14 in the ferric maltol arm and 9 in the placebo arm) who had a confounding event but continued to have efficacy data recorded up to and including Week 16 (refer to Table 19).

In general, making changes to SAP based on a nonsignificant result of a previous analysis of the whole study data would raise major concerns about the validity of the subsequent analyses. (i.e. Is the integrity of the trial jeopardized by the changes? Is sponsor discarding unwanted measurements to get statistically significant results after previous analysis showed nonsignificant results?) However, in this case, this reviewer believes that the changes were warranted and will not undermine the integrity of the trial. The intent of the modifications was to remove the confounding effect caused by the protocol prohibited events and provide a more accurate estimate of the true treatment effect of ferric maltol compared to placebo. Further, the ITT analysis population remained the same cohort of participants with the same treatment assignment for each participant. The removed measurements are results of protocol misconduct by some investigators and should not be in the study if it were conducted properly. In conclusion, this reviewer believes the primary analysis based on the amendments is acceptable.

Efficacy Results - Secondary and other relevant endpoints

Change from Baseline in Hb Concentration to Week 4 and Week 8:

The LS mean difference of change from baseline in Hb concentration to Week 4 was 0.13 g/dL (SE: 0.14). This difference increased to 0.46 g/dL (SE: 0.16) at Week 8 (refer to table below).

Table 37: Change in Hb Concentration from Baseline to Week 4 and 8 (Analysis using Multiple Imputation) - ITT

Hemoglobin Concentration (g/dL)	Placebo (n=56)	Ferric Maltol (n=111)
LS mean change from baseline to Week ^{ab} 4 (SE)	0.03 (0.11)	0.16 (0.08)
Difference between LS mean change from baseline to Week 16 (SE), 95% CI	0.13 (0.14) (-0.13, 0.40)	
LS mean change from baseline to Week ^{ab} 8 (SE)	0.03 (0.12)	0.49 (0.10)
Difference between LS mean change from baseline to Week 16 (SE), 95% CI	0.46 (0.16) (0.14, 0.78)	

^a missing value at week 4 and 8 is replaced with an imputed value through a MI method

^b LS mean change from baseline is derived from an ACOVA model with factors for treatment, baseline eGFR and baseline Hb.

Source: FDA Analysis

Ferritin:

A descriptive summary of ferritin measurements at baseline, Week 16, and change from baseline to Week 16 are presented in table below. At Week 16, the observed mean change from baseline was 49.3 µg/L (SD: 150.10) in the ferric maltol arm and 6.6 µg/L (SD: 57.34) in the placebo arm.

Table 38: Summary Results of Ferritin at Baseline and Week 16 - ITT

Ferritin (µg/L)	Placebo (n=56)	Ferric Maltol (n=111)	Total (n=167)
Baseline			
N	55	111	166
Mean (SD)	105.9 (79.75)	97.0 (88.50)	100.0 (85.56)
Median	93	70	73.5
(Min, Max)	(9, 312)	(5, 408)	(5, 408)
Week 16			
N	50	102	152
Mean (SD)	107.9 (82.63)	147.5 (180.09)	134.5 (155.75)
Median	93.5	96.5	95
(Min, Max)	(7, 344)	(10, 1423)	(7, 1423)
Change from Baseline to Week 16			
N	49	102	151
Mean (SD)	6.6 (57.34)	49.3 (150.10)	35.4 (128.94)
Median	-4	19.5	7
(Min, Max)	(-122, 193)	(-117, 1310)	(-122, 1310)

Source: FDA Analysis

Dose/Dose Response

Please refer to the clinical pharmacology section of this review for discussion of dose-response.

Durability of Response

In Study ST10-01-303 patients were continued on treatment for up to 16 weeks. The increase in hemoglobin was demonstrated from baseline to week 16 demonstrating durable effect of treatment.

Persistence of Effect

Since the primary endpoint, change from baseline in Hb concentration to Week 16, was not measured once the treatment was stopped, no data were available to investigate the persistence of the treatment effect following the termination of the treatment.

Additional Analyses Conducted on the Individual Trial

No additional analyses were conducted. **Additional Analyses Conducted on the Individual Trial**

Not Applicable

Integrated Review of Effectiveness

8.2.3. Assessment of Efficacy Across Trials

The efficacy of ferric maltol in treatment of anemia is assessed in two different studies, study ST-10-101-301/302 and study ST-10-101-303. Both studies were prospective, multicenter, randomized, double-blind, placebo-controlled, phase 3 studies with ferric maltol for the treatment of iron deficient anemia. Study ST-10-101-301/302 enrolled subjects with ulcerative colitis and Crohn's disease and study ST-10-101-303 enrolled subjects with CKD.

Primary Endpoints

The primary endpoint in both studies is change from baseline in Hb concentration to end of double-blind treatment period (Week 12 for Study ST-10-101-301/302 and Week 16 for Study ST-10-101-303). The results of the primary endpoint from both studies demonstrated a statistically significant superior efficacy effect of oral ferric maltol over placebo in the treatment of IDA.

Secondary and Other Endpoints

Since all other endpoints are considered exploratory in both studies and are defined differently, they are not assessed here. Descriptive summaries of relevant endpoints can be viewed in the

early section under each study.

Subpopulations

The subpopulations of pooled populations were not conducted since the patient populations are different in these two studies.

Additional Efficacy Considerations

Not applicable.

8.2.4. Integrated Assessment of Effectiveness

To support this application, the Applicant submitted results from two phase 3, randomized, double-blind, placebo-controlled studies (ST-10-01-301/302 and ST-10-01-303) as the primary evidence of the efficacy of oral ferric maltol compared with placebo in the treatment of IDA in subjects with UC, Crohn's disease, and CKD. Both studies successfully demonstrated substantial evidence of efficacy as determined primarily based on statistically significant improvements in treatment IDA in the primary endpoints, change from baseline in Hb concentration to end of double-blind treatment.

8.3. Review of Safety

The following sections describe the overall approach to safety analyses in the pivotal clinical studies ST01-10-301, ST01-10-302, and ST01-10-303 as well as pertinent safety findings.

8.3.1. Safety Review Approach

The clinical review of safety for this NDA was based on safety data from studies ST10-01-301/302 and ST10-01-303. Further details regarding respective study design and protocols are provided in section 5.1 of this review. The Applicant presented safety data in a pooled fashion comparing patients who had received ferric maltol to patients who had received placebo. All enrolled patients had a history of IDA. There were no key safety issues identified a priori.

8.3.2. Review of the Safety Database

Overall Exposure

During the double-blind phase, the mean (standard deviation [SD]) duration of treatment was 13.05 (4.07) weeks, 11.16 (2.89) weeks, and 13.53 (4.79) weeks for the ferric maltol, 301/302 placebo, and 303 placebo groups, respectively. The majority of patients in the ferric maltol and placebo treatment arms had ≥ 12 weeks of exposure. The median (range) ferric maltol dose received was 5580.0 mg (300 to 8400 mg).

Table 39: Duration of Exposure

	Pooled Ferric Maltol 30 mg BID (n=175)	ST10-01-301/302 Placebo (n=64)	ST10-01-303 Placebo (n=56)
Exposure (Weeks)			
Mean (SD)	13.1 (4.1)	11.2 (2.9)	13.5 (4.8)
Median	13.7	11.9	16.1
Range	0.1-21	0.6-17	0.1-20
Exposure (Weeks) (n[%])			
0 - <4	11 (6.3)	3 (4.7)	4 (7.1)
4 - <8	11 (6.3)	4 (6.3)	4 (7.1)
8 - <12	21 (12)	13 (20.3)	6 (10.7)
12 - <16	69 (39.4)	42 (65.6)	8 (14.3)
16 - <20	62 (35.4)	2 (3.1)	33 (58.9)
20 - <24	1 (0.6)	0	1 (1.8)

Source: FDA Clinical Reviewer Analysis, JMP Clinical 6.1

Relevant characteristics of the safety population:

Safety population demographic characteristics for the pooled Phase III studies (ST10-01-301/302 and ST10-01-303) are summarized by treatment in the table below. The majority of patients were female and white. Subjects in the pooled ferric maltol group were generally older than those in the combined placebo group (median [range] 61.0 years [18 to 90] versus 49.0 years [19 to 83]), which was also reflected in the proportions of subjects who were <60 years and ≥60 years in each group.

Table 40: Demographic Characteristics of Pooled Safety Population

	Pooled Ferric Maltol 30 mg BID (n=175)	ST10-01-301/302 Placebo (n=64)	ST10-01-303 Placebo (n=56)	Pooled Placebo (n=120)
Sex				
Female	118 (67.4)	43 (67.2)	39 (69.6)	82 (68.3)
Male	57 (32.6)	21 (32.8)	17 (30.4)	38 (31.7)
Age				
Mean	58.1 (18.8)	38.5 (12.3)	65.2 (12.8)	51 (18.3)
Median	61	37.5	68	49
Range (Min-Max)	18-90	19-76	30-83	19-83
Age Group				
< 60 years of age	85 (48.6)	60 (93.8)	14 (25)	74 (61.7)
≥ 60 years of age	90 (51.4)	4 (6.3)	42 (75.0)	46 (38.3)
Race				

	Pooled Ferric Maltol 30 mg BID (n=175)	ST10-01-301/302 Placebo (n=64)	ST10-01-303 Placebo (n=56)	Pooled Placebo (n=120)
White	143 (81.7)	60 (93.8)	42 (75)	102 (85)
Black or African American	23 (13.1)	1 (1.6)	12 (21.4)	13 (10.8)
Asian	3 (1.7)	2 (3.1)	0 (0.0)	2 (1.7)
Other	5 (2.9)	1 (1.6)	2 (3.6)	3 (2.5)
Ethnicity				
Hispanic or Latino	26 (14.9)	0 (0.0)	14 (25.0)	14 (11.7)
Not Hispanic or Latino	145 (82.9)	63 (98.4)	42 (75.0)	105 (87.5)
Not Reported	4 (2.3)	1 (1.6)	0 (0.0)	1 (0.8)
Country				
Germany	34 (19.4)	33 (51.6)	0 (0.0)	33 (25.0)
Hungary	11 (6.3)	15 (23.4)	0 (0.0)	15 (12.5)
Austria	4 (2.3)	6 (9.4)	0 (0.0)	6 (5.0)
UK	15 (8.6)	10 (15.6)	0 (0.0)	10 (8.3)
US	111 (63.4)	0 (0.0)	56 (100.0)	56 (46.7)

Source: FDA Clinical Reviewer Analysis, JMP Clinical 6.1

Adequacy of the safety database:

The demographics of the safety population are consistent with those of the intended patient population. The safety database enrolled a heterogeneous population so that pooled safety results are generalizable to the intended patient population.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of safety data submitted was adequate to permit substantial primary review. The Applicant provided analysis-ready datasets for all pivotal studies. Narrative for patient deaths and patients who experienced SAEs and discontinued the study were provided at the time of the NDA submission. No issues regarding data integrity were identified during this review, or in the course of clinical investigational site inspections. Responses to Agency information requests were rapid and complete.

Categorization of Adverse Events

All AEs from ST10-01-303 were coded from verbatim text to preferred terms (PTs) and grouped by system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1. For AEs in protocols ST10-01-301 and ST10-01-302, which were coded using an

earlier version of MedDRA (Version 15.1), each PT was compared against Version 18.1 and any outdated PTs were amended to the appropriate PT active in Version 18.1 prior to data pooling.

The adverse events of special interest (including hepatic, cardiac, hematology and gastroenterology events) were developed utilizing the MedDRA Standardized MedDRA Queries (SMQs) and assimilation of data from all currently available enteral iron preparations.

Routine Clinical Tests

The schedule of safety evaluations and clinical assessments for the ST10-01-301/302 and ST10-01-303 studies were described in Sections 8.1.1 and 8.2.1 respectively. The frequency of monitoring and laboratory assessments was considered adequate and appropriate for the enrolled patient population. Refer to the respective study schedule of assessments for further detail.

8.3.4. Safety Results

Deaths

No patient deaths were reported in the double-blind or open-label phases of studies ST10-01-301/302. There were two deaths reported during the double-blind phase of Study ST10-01-303: one case of sudden death (Subject (b) (6) ferric maltol group) and one case of myocardial infarction resulting in death (Subject (b) (6) placebo group). Neither death was considered related to study drug by the investigator. A narrative for Subject (b) (6) is provided below.

Subject (b) (6) Patient Narrative

Subject (b) (6) was a 74-year old white male patient who died suddenly on (b) (6). On (b) (6) the patient commenced treatment with oral blinded study medication (ferric maltol) capsules, 30 mg twice daily for iron deficiency anemia. The patient's past medical history included: prostate cancer status post radiotherapy, coronary artery disease (CAD), non-ST-segment elevation myocardial infarction (2012), coronary artery bypass grafting (three vessels, 2013), pacemaker insertion (2016), abdominal aortic aneurysm, congestive heart failure, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), chronic respiratory failure, hyperlipidemia, diabetes mellitus Type II, and chronic kidney disease.

On (b) (6), during a visit for pacemaker check, the patient was found to be hypoxic. Later that day, the patient was unresponsive at home and was pronounced dead when brought to the emergency room. No autopsy was performed.

Reviewer Comment: Given the patient's advanced age and multiple cardiac and pulmonary comorbidities, it is highly unlikely that the event of sudden death was related to study treatment.

Serious Adverse Events

During the double-blind phase of studies ST10-01-301 and 302, there were 3 treatment emergent SAEs reported for 1 patient (1.6%) in the ferric maltol treatment arm and 2 SAEs occurred in 2 (3.1%) patients in the placebo group; all were considered unrelated to study drug. There was 1 SAE of exacerbation of pre-existing Crohn's disease in the ferric maltol arm. There was 1 SAE of exacerbation of pre-existing Crohn's disease as well as 1 event of rectal abscess in the placebo group which is a known complication of IBD.

Table 41: Serious Adverse Events in the Double-Blind Phase of ST10-01-301 and ST10-01-302

SAE by SOC and PT	Ferric Maltol (N=64) n (%)	Placebo (N=64) n (%)	Total (N=128) n (%)
Gastrointestinal Disorders			
Abdominal Pain	1 (1.6)	0 (0.0)	1 (0.8)
Crohn's Disease*	1 (1.6)	1 (1.6)	2 (1.5)
Diarrhea	1 (1.6)	0 (0.0)	1 (0.8)
Infections and Infestations			
Rectal Abscess	0 (0.0)	1 (1.6)	1 (0.8)

Source: FDA Clinical Reviewer Analysis, JMP Clinical 6.1

*Refers to an exacerbation of the pre-existing condition.

During the open-label phase of studies ST10-01-301 and 302, there were a total of 8 SAEs in patients previously treated with ferric maltol in the double-blind phase and 3 SAEs in 2 patients previously treated with placebo. Only 1 event (severe abdominal pain in a patient previously treated with ferric maltol) was reported as related to treatment.

Table 42: Serious Adverse Events in the Open-Label Phase of ST10-01-301 and ST10-01-302

SAE by SOC and PT	Ferric Maltol → Ferric Maltol (N=50*) n (%)	Placebo → Ferric Maltol (N=47*) n (%)	Total (N=97*) n (%)
Cardiac Disorders			
Angina Pectoris	0 (0.0)	1 (2.1)	1 (1.0)
Gastrointestinal Disorders			
Abdominal Pain	2 (4.0)	0 (0.0)	2 (2.1)
Ulcerative Colitis**	1 (2.0)	0 (0.0)	1 (1.0)
Rectal Hemorrhage	1 (2.0)	0 (0.0)	1 (1.0)
General Disorders and Site Administration Conditions			
Hernia	1 (2.0)	0 (0.0)	1 (1.0)
Cholesteatoma removal	1 (2.0)	0 (0.0)	0 (0.0)
Infections and Infestations			
Pneumonia	0 (0.0)	1 (2.1)	1 (1.0)
Peritonitis	1 (2.0)	0 (0.0)	1 (1.0)

SAE by SOC and PT	Ferric Maltol → Ferric Maltol (N=50*) n (%)	Placebo → Ferric Maltol (N=47*) n (%)	Total (N=97*) n (%)
Herpes Zoster	1 (2.0)	0 (0.0)	1 (1.0)
Respiratory, Thoracic and Mediastinal Disorders			
Pulmonary Embolism	0 (0.0)	1 (2.1)	1 (1.0)

Source: FDA Clinical Reviewer Analysis, JMP Clinical 6.1

* Number of patients who entered open-label phase of study.

**Refers to an exacerbation of the pre-existing condition.

Reviewer Comment: While the overall incidence of SAEs in the open-label phase of ST10-01-301 and 302 was relatively low, a slightly higher frequency of gastrointestinal SAEs was noted in patients previously treated with ferric maltol in the double-blind portion of the study.

During the double-blind phase of study ST10-01-303, a total of 23 patients (20.7%) in the ferric maltol treatment arm and 12 (21.4%) patients in the placebo treatment cohort experienced treatment emergent SAEs. None of the SAEs were considered related to study treatment.

Table 43: Serious Adverse Events in the Double-Blind Phase of ST10-01-303

SAE by SOC and PT	Ferric Maltol (N=111) n (%)	Placebo (N=56) n (%)	Total (N=167) n (%)
Blood and lymphatic system disorders	3(2.7%)	4(7.1%)	7(4.2%)
Coagulopathy	1 (0.9)	0 (0.0)	1 (0.6)
Anemia	1 (0.9)	3 (5.4)	4 (2.4)
Hemorrhagic anemia	1 (0.9)	1 (1.8)	2 (1.2)
Cardiac disorders	9(8.1%)	4(7.1%)	13(7.8%)
Angina unstable	1 (0.9)	0 (0.0)	1 (0.6)
Atrioventricular block complete	1 (0.9)	0 (0.0)	1 (0.6)
Bradycardia	1 (0.9)	0 (0.0)	1 (0.6)
Acute myocardial infarction	0 (0.0)	1 (1.8)	1 (0.6)
Angina pectoris	1 (0.9)	1 (1.8)	2 (1.2)
Cardiac failure congestive	5 (4.5)	1 (1.8)	6 (3.6)
Coronary artery disease	0 (0.0)	1 (1.8)	1 (0.6)
Myocardial infarction	0 (0.0)	2 (3.6)	2 (1.2)

SAE by SOC and PT	Ferric Maltol (N=111) n (%)	Placebo (N=56) n (%)	Total (N=167) n (%)
Gastrointestinal disorders	8(7.2%)	2(3.6%)	10(6%)
Duodenal polyp	1 (0.9)	0 (0.0)	1 (0.6)
Enteritis	1 (0.9)	0 (0.0)	1 (0.6)
Gastritis erosive	1 (0.9)	0 (0.0)	1 (0.6)
Gastrointestinal hemorrhage	2 (1.8)	0 (0.0)	2 (1.2)
Gastrointestinal wall thickening	1 (0.9)	0 (0.0)	1 (0.6)
Hematochezia	1 (0.9)	0 (0.0)	1 (0.6)
Hemorrhoidal hemorrhage	1 (0.9)	0 (0.0)	1 (0.6)
Melena	1 (0.9)	0 (0.0)	1 (0.6)
Small intestinal obstruction	1 (0.9)	0 (0.0)	1 (0.6)
Gastroesophageal reflux disease	0 (0.0)	1 (1.8)	1 (0.6)
Pancreatitis acute	0 (0.0)	1 (1.8)	1 (0.6)
General disorders and administration site conditions	2(1.8%)		2(1.2%)
Asthenia	1 (0.9)	0 (0.0)	1 (0.6)
Sudden death	1 (0.9)	0 (0.0)	1 (0.6)
Infections and infestations	8(7.2%)	6(10.7%)	14(8.4%)
Abscess limb	1 (0.9)	0 (0.0)	1 (0.6)
Cellulitis	1 (0.9)	0 (0.0)	1 (0.6)
Sepsis	1 (0.9)	0 (0.0)	1 (0.6)
Septic shock	1 (0.9)	0 (0.0)	1 (0.6)
Streptococcal bacteremia	1 (0.9)	0 (0.0)	1 (0.6)
Clostridium difficile infection	0 (0.0)	1 (1.8)	1 (0.6)
Diverticulitis	0 (0.0)	1 (1.8)	1 (0.6)
Osteomyelitis	0 (0.0)	1 (1.8)	1 (0.6)
Pneumonia	4 (3.6)	2 (3.6)	6 (3.6)

SAE by SOC and PT	Ferric Maltol (N=111) n (%)	Placebo (N=56) n (%)	Total (N=167) n (%)
Pyelonephritis	1 (0.9)	1 (1.8)	2 (1.2)
Urinary tract infection	1 (0.9)	1 (1.8)	2 (1.2)
Injury, poisoning and procedural complications	5(4.5%)	2(3.6%)	7(4.2%)
Hip fracture	1 (0.9)	0 (0.0)	1 (0.6)
Rib fracture	2 (1.8)	0 (0.0)	2 (1.2)
Toxicity to various agents	2 (1.8)	0 (0.0)	2 (1.2)
Traumatic renal injury	1 (0.9)	0 (0.0)	1 (0.6)
Accidental overdose	0 (0.0)	1 (1.8)	1 (0.6)
Postoperative fever	0 (0.0)	1 (1.8)	1 (0.6)
Metabolism and nutrition disorders	6(5.4%)	1(1.8%)	7(4.2%)
Diabetic ketoacidosis	1 (0.9)	0 (0.0)	1 (0.6)
Fluid overload	1 (0.9)	0 (0.0)	1 (0.6)
Hypercalcemia	1 (0.9)	0 (0.0)	1 (0.6)
Hyperkalemia	1 (0.9)	0 (0.0)	1 (0.6)
Hypoglycemia	1 (0.9)	0 (0.0)	1 (0.6)
Hyperglycemia	1 (0.9)	1 (1.8)	2 (1.2)
Musculoskeletal and connective tissue disorders	1(0.9%)	0 (0.0)	1(0.6%)
Pathological fracture	1 (0.9)	0 (0.0)	1 (0.6)
Neoplasms benign, malignant and unspecified (cysts and polyps)	3(2.7%)	0 (0.0)	3(1.8%)
Lung adenocarcinoma	1 (0.9)	0 (0.0)	1 (0.6)
Metastatic squamous cell carcinoma	1 (0.9)	0 (0.0)	1 (0.6)
Rectosigmoid cancer	1 (0.9)	0 (0.0)	1 (0.6)
Nervous system disorders	4(3.6%)	0 (0.0)	4(2.4%)
Cerebellar infarction	1 (0.9)	0 (0.0)	1 (0.6)

SAE by SOC and PT	Ferric Maltol (N=111) n (%)	Placebo (N=56) n (%)	Total (N=167) n (%)
Cerebrovascular accident	1 (0.9)	0 (0.0)	1 (0.6)
Lacunar stroke	1 (0.9)	0 (0.0)	1 (0.6)
Syncope	2 (1.8)	0 (0.0)	2 (1.2)
Psychiatric disorders	0 (0.0)	1(1.8%)	1(0.6%)
Mental status changes	0 (0.0)	1 (1.8)	1 (0.6)
Renal and urinary disorders	3(2.7%)	3(5.4%)	6(3.6%)
Renal impairment	1 (0.9)	0 (0.0)	1 (0.6)
Renal tubular necrosis	1 (0.9)	0 (0.0)	1 (0.6)
Acute kidney injury	3 (2.7)	2 (3.6)	5 (3)
Chronic kidney disease	0 (0.0)	1 (1.8)	1 (0.6)
Reproductive system and breast disorders	0 (0.0)	1(1.8%)	1(0.6%)
Vaginal hemorrhage	0 (0.0)	1 (1.8)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	7(6.3%)	0 (0.0)	7(4.2%)
Acute pulmonary edema	1 (0.9)	0 (0.0)	1 (0.6)
Acute respiratory failure	3 (2.7)	0 (0.0)	3 (1.8)
Cough	1 (0.9)	0 (0.0)	1 (0.6)
Dyspnea	1 (0.9)	0 (0.0)	1 (0.6)
Pneumothorax	1 (0.9)	0 (0.0)	1 (0.6)
Pulmonary embolism	1 (0.9)	0 (0.0)	1 (0.6)
Vascular disorders	4(3.6%)	2(3.6%)	6(3.6%)
Deep vein thrombosis	1 (0.9)	0 (0.0)	1 (0.6)
Hypovolemic shock	1 (0.9)	0 (0.0)	1 (0.6)
Malignant hypertension	1 (0.9)	0 (0.0)	1 (0.6)
Hypertensive emergency	1 (0.9)	1 (1.8)	2 (1.2)
Hypotension	0 (0.0)	1 (1.8)	1 (0.6)

Source: FDA Clinical Reviewer Analysis, JMP Clinical 6.1

Reviewer Comment: There was a higher frequency of observed SAEs in the ST10-01-303 study as compared to ST10-01-301/302. None of the SAEs reported for ST10-01-3-3 were attributed to study drug. ST10-01-303 enrolled a patient population with CKD.

Dropouts and/or Discontinuations Due to Adverse Effects

In studies ST10-01-301 and ST10-01-302, adverse events that led to discontinuation were recorded for 6 patients (9.3%) in the ferric maltol group and 4 patients (6.3%) in the placebo arm during the double-blind phase. A total of 12 patients discontinued ferric maltol during the open label phase. Discontinuations secondary to treatment-related adverse events occurred in 3 (4.7%) patients in the ferric maltol arm and 2 (3.1%) patients in the placebo group during the double-blind phase and 5 patients in the open-label phase.

In the double-blind portion of study ST10-01-303, 5 patients (4.5%) in the ferric maltol treatment arm and 3 patients (5.4%) discontinued study drug due to adverse events.

Significant Adverse Events

Most patients experienced TEAEs that were mild or moderate in intensity. Overall, 10 (20.0%) patients treated with ferric maltol and 4 (8.5%) patients treated with placebo experienced one or more events that were reported as being severe. Many of these events were of the Gastrointestinal Disorders SOC.

Treatment Emergent Adverse Events and Adverse Reactions

The following table outlines common treatment emergent AEs reported in at least 10% of the safety population for the double-blind phase of studies ST10-01-301 and ST10-01-302. These included abdominal pain and nasopharyngitis.

Table 44: Common TEAEs in the Double-Blind Safety Population Studies ST10-01-301 and ST10-01-302

PT	Ferric Maltol (N=64) n (%)	Placebo (N=64) n (%)	Total (N=128) n(%)
Abdominal Pain	8 (12.5)	5 (7.8)	13 (20.3)
Nasopharyngitis	4 (6.3)	8 (12.5)	12 (18.8)

Source: FDA Clinical Reviewer Analysis, JMP Clinical 6.1

In the open label phase of studies ST10-01-301 and ST10-01-302, the most common TEAEs reported in at least 10% of patients included abdominal pain, diarrhea, exacerbation or flare of pre-existing IBD, and nasopharyngitis.

Table 45: Common TEAEs in the Open Label Phase Safety Population Studies ST10-01-301 and ST10-01-302

TEAE by SOC and PT	Ferric Maltol → Ferric Maltol (N=50*) n (%)	Placebo → Ferric Maltol (N=47*) n (%)	Total (N=97*) n (%)
Gastrointestinal Disorders	15 (30.0%)	26 (55.3%)	41 (42.3%)
Abdominal Pain	4 (8.0)	7 (14.9)	11 (11.3)
Ulcerative Colitis**	5 (10)	8 (17)	13 (13.4)
Crohn's Disease**	2 (4.0)	5 (10.6)	7 (7.2)
Diarrhea	4 (8.0)	6 (12.8)	10 (10.3)
Infections and Infestations	12 (24.0%)	8 (17.0%)	20 (20.6%)
Nasopharyngitis	12 (24.0))	8 (17.0)	20 (20.6)

Source: FDA Clinical Reviewer Analysis, JMP Clinical 6.1

*Number of patients who entered open-label phase.

**Refers to an exacerbation of the pre-existing condition.

The following table outlines common treatment emergent AEs reported in at least 10% of the safety population for the double-blind phase of study ST10-01-303.

TEAE by SOC and PT	Ferric Maltol (N=111) n (%)	Placebo (N=56) n (%)	Total (N=167) n (%)
Blood and lymphatic system disorders	5(4.5%)	7(12.5%)	12(7.2%)
Anemia	5 (4.5)	7 (12.5)	12 (7.2)
Gastrointestinal disorders	35(31.5%)	14(25%)	49(29.3%)
Constipation	11 (9.9)	5 (8.9)	16 (9.6)
Diarrhea	10 (9)	7 (12.5)	17 (10.2)
Feces discolored	8 (7.2)	1 (1.8)	9 (5.4)
Nausea	12 (10.8)	7 (12.5)	19 (11.4)
Vomiting	11 (9.9)	2 (3.6)	13 (7.8)
Infections and infestations	20(18%)	11(19.6%)	31(18.6%)
Nasopharyngitis	7 (6.3)	2 (3.6)	9 (5.4)
Upper respiratory tract infection	6 (5.4)	5 (8.9)	11 (6.6)
Urinary tract infection	9 (8.1)	6 (10.7)	15 (9)

	Ferric Maltol (N=111) n (%)	Placebo (N=56) n (%)	Total (N=167) n (%)
TEAE by SOC and PT			
Injury, poisoning and procedural complications	7(6.3%)	2(3.6%)	9(5.4%)
Fall	7 (6.3)	2 (3.6)	9 (5.4)
Metabolism and nutrition disorders	6(5.4%)	8(14.3%)	14(8.4%)
Hyperkalemia	6 (5.4)	8 (14.3)	14 (8.4)
Renal and urinary disorders	8(7.2%)	4(7.1%)	12(7.2%)
Acute kidney injury	8 (7.2)	4 (7.1)	12 (7.2)
Vascular disorders	7(6.3%)	3(5.4%)	10(6%)
Hypertension	7 (6.3)	3 (5.4)	10 (6)

Source: FDA Clinical Reviewer Analysis, JMP Clinical 6.1

Laboratory Findings

An independent analysis utilizing JMP Clinical 6.1 did not reveal any safety signals or significant derangements in laboratory findings other than anticipated changes in hemoglobin, hematocrit and iron studies.

Vital Signs

No clinically significant observations during physical examinations were recorded at the end of the double-blind treatment period in the pivotal Phase III studies.

Electrocardiograms (ECGs)

ECG results and corresponding changes from baseline were summarized by treatment arm and visit for QT, RR, HR, QTcB, QTcF, PR, and QRS and T- and U-wave morphology. There were no significant changes from baseline ECG in any parameter QT.

Immunogenicity

There are no immunogenicity concerns with the drug product, ferric maltol or its components.

8.3.5. Analysis of Submission-Specific Safety Issues

The safety profile of maltol was reviewed. Maltol occurs naturally in a variety of foods and synthetic maltol is widely used as a food additive and is used as an excipient in pharmaceutical formulations and in food products. The non-clinical and clinical pharmacology data support the safety of maltol in the formulation of ferric maltol. Refer to the non-clinical and clinical pharmacology sections of this review for additional details on the maltol component.

8.3.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no COA analyses conducted in the pivotal studies to inform safety and/or tolerability of the ferric maltol drug product. There was no COA or PRO data submitted with this application.

8.3.7. Safety Analyses by Demographic Subgroups

The overall incidence of TEAEs in the ferric maltol group was similar in subjects aged <60 years and those aged ≥60 years (65.9% versus 64.4%). In subjects aged ≥60 years, there was a higher incidence of serious TEAEs (20.0% versus 7.1%) and TEAEs of special interest (41.1% versus 31.8%) than in subjects aged <60 years. A greater proportion of subjects aged <60 years discontinued from the study due to a TEAE than subjects aged ≥60 years (12.9% versus 5.6%).

During the double-blind phase, there were no notable differences in the incidences of TEAEs between Caucasian and non-Caucasian patients in the ferric maltol treatment arm (overall incidence 65.0% versus 65.6%). However, given that the majority of enrolled patients were Caucasian, meaningful comparisons with non-Caucasian patients are not possible.

The overall incidence of TEAEs in the ferric maltol treatment arm during the double-blind phase was lower in males than in females (61.4% versus 66.9%); however, the incidence of serious TEAEs, TEAEs leading to discontinuations and severe TEAEs was higher in males than in females (19.3% versus 11.0%; 14.0% versus 6.8% and 19.3% versus 11.9%, respectively). In addition, a greater proportion of males experienced TEAEs of special interest (40.4% versus 34.7%).

8.3.8. Specific Safety Studies/Clinical Trials

This section is not applicable for this NDA.

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Formal human carcinogenicity studies were not carried out in the ferric maltol clinical development program. Tumor development is not expected based on the mechanism of action of ferric maltol.

Human Reproduction and Pregnancy

A single pregnancy was reported during the open-label phase of study ST10-01-302. This case concerned a 28-year-old patient with CD receiving ferric maltol. Relevant concomitant medications were azathioprine and mesalazine. A negative pregnancy test was recorded at the patient's first open-label visit. Four days later, the patient performed a pregnancy test which was positive. The following day, a urine pregnancy test was conducted at the study site, which

was also positive. The patient was withdrawn from the study and subsequently gave birth to a healthy infant; the date of conception was approximately 12 weeks after the start of treatment with ferric maltol. Drug-drug interaction was not suspected in this pregnancy.

There was also a report of pregnancy in PK Study ST10-01-101. The case involved a 26-year old patient receiving ferric maltol. Concomitant medications included azathioprine, cyclosporine, and the contraceptive belara (chlormadinone acetate/ethinylestradiol). Urine pregnancy tests conducted during the study were all negative. The patient was confirmed pregnant by ultrasound and it was estimated that she had become pregnant prior to administration of study drug. Follow-up verified that the patient had been taking oral contraceptives throughout the study. The outcome of the pregnancy was a normal, live birth.

Cumulatively, from February 18, 2016 to February 18, 2018, 1 postmarketing case of drug exposure during pregnancy was reported. The case involved a 29-year-old patient with CD who was receiving ferric maltol for IDA. Relevant concomitant medications included mesalazine. The patient continued ferric maltol during her pregnancy. No AEs were reported and the case was reported as non-serious. The outcome of the pregnancy is unknown.

Pediatrics and Assessment of Effects on Growth

No pediatric patients were enrolled on the pivotal studies to support NDA 212320. Therefore, no pediatric assessments were conducted.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no events of overdose reported during the pivotal Phase III studies following treatment with ferric maltol. There is no known abuse potential with ferric maltol, or the individual components, iron and maltol. There are no known withdrawal or rebound issues with ferric maltol, or the individual components, iron and maltol.

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Ferric maltol 30 mg capsules are commercially available in 12 countries under the trade name Ferracru®: United Kingdom (launched on June 6, 2016), Germany (launched September 2016), Austria (launched December 2016), Sweden (available August 2017), Denmark, Finland, Iceland, Norway, Poland, Bulgaria, Romania (available November 2017) and Hungary (available March 2018). Ferracru was granted a Marketing Authorization in Switzerland on September 22, 2017, but it has not yet been launched in that country. Cumulatively, from February 18, 2016 to February 18, 2018, patient exposure to ferric maltol from marketing experience was estimated to be 11,382 patient-months for the oral route. Cumulatively to February 18, 2018, a total of 41 adverse drug reactions (ADRs) were received in 22 reports (19 medically confirmed) from spontaneous sources, and all of these ADRs were non-serious in nature.

Over half of the ADRs were in the Gastrointestinal disorders SOC (14 cases, 21 ADRs), including the PTs of diarrhea (5 ADRs), abdominal pain (4), nausea (4), constipation (3), abdominal pain upper (2), flatulence (1), gastrointestinal disorder (1) and rectal hemorrhage (1). A total of 12 ADRs (10 cases) were reported in the Injury, poisoning and procedural complications SOC, including 4 reports each of intentional product use issue and off label use. The remaining ADRs were all single reports across SOCs, including one case of exposure during pregnancy which has been previously discussed in this review.

Expectations on Safety in the Postmarket Setting

There are no specific concerns regarding drug product safety in the postmarket setting.

8.3.11. Integrated Assessment of Safety

Pooled safety data from Studies ST10-01-301, ST10-01-302 and ST10-01-303 have demonstrated the safety and tolerability of oral ferric maltol (30 mg BID) in patients with IDA, irrespective of disease background and associated comorbidities.

SUMMARY AND CONCLUSIONS

8.4. Statistical Issues

For study ST10-01-301/302 and study ST10-01-303, the missing data of Hb measurements during the double-blind treatment period and their impact to the treatment effect size of ferric maltol were assessed through multiple sensitivity analyses. The findings of these analyses supported the results from the primary analysis.

In addition, for study ST10-01-303, the statistical reviewer evaluated sponsor's claims to modify the definition of the ITT analysis population and found the changes were warranted and will neither undermine the integrity of data nor change the efficacy conclusion. The detailed explanation can be viewed under *Data Quality and Integrity* section of Section 8.2.2.

8.5. Conclusions and Recommendations

In this NDA, the Applicant submitted results from two phase 3, randomized, double-blind, placebo-controlled studies (ST10-01-301/302 and ST10-01-303) to demonstrate the efficacy of oral ferric maltol compared with placebo in the treatment of IDA. Both studies showed statistically and clinically significant superior efficacy effect in ferric maltol over placebo in the primary endpoint, the change in Hb concentration from baseline to end of double-blind treatment period.

In conclusion, ferric maltol treatment resulted in substantial improvement in Hb from baseline levels at study entry as well as increased ferritin in the pivotal studies. Although there may be different underlying etiologies for iron deficiency anemia, the treatment of IDA is similar and thus supports the approval for iron deficiency anemia irrespective of the background disease. Oral ferric maltol represents an effective therapeutic option for the treatment of iron deficiency and resultant iron deficiency anemia.

Primary Statistical Reviewer
Lola Luo, PhD

Statistical Team Leader
Lei Nie, PhD

Primary Clinical Reviewer
Laurel Menapace, MD

Clinical Team Leader
Tanya Wroblewski, MD

9 Advisory Committee Meeting and Other External Consultations

This application was not presented to an Advisory Committee or any other external consultants.

10 Pediatrics

Pediatric data were not submitted as part of this application. The safety and efficacy of ferric maltol in children has not yet been established.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring the submission of the pediatric studies, because this product is ready for approval for use in adults and the pediatric studies have not been completed. The following postmarketing studies are required:

3667-1 Conduct and submit study report and datasets from a study (PK sub-study of ST10-01-305) in pediatric patients with iron deficiency age 1 month to < 10 years for pharmacokinetics (PK) and pharmacodynamics (PD) to confirm the dosing used in the efficacy and safety study.

The timetable you submitted on July 24, 2019, states that you will conduct this study according to the following schedule

Final Protocol: 10/ 2019
Study/Trial Completion: 10/2021
Final Clinical Study Report: 01/2022

3667-2 Conduct and submit study report and datasets from a study (ST10-01-103) in pediatric patients with iron deficiency age 10 to 17 years for pharmacokinetics and pharmacodynamics to determine the dosing to be used in an efficacy and safety study.

The timetable you submitted on July 24, 2019, states that you will conduct this study according to the following schedule

Final Protocol: N/A
Study/Trial Completion: 03/2018
Final Clinical Study Report: 10/2018
Submission of Clinical Study Report: August 2019

3667-3 Conduct and submit the study report and datasets from an open-label comparative efficacy and safety study of ST10 and oral ferrous sulfate in infants and children aged 1 month to 17 years with iron deficiency anemia (Study ST10-01-305). Data

from PK and PD studies should be utilized to select the doses of ferric maltol for Study ST10-01-305.

The timetable you submitted on July 24, 2019, states that you will conduct this study according to the following schedule

Final Protocol: 10/2019
Initiation: 09/2020
Study/Trial Completion: 10/2021
Final Study Report: 01/2022

3667-4: Develop a pediatric age appropriate oral formulation and conduct a study to evaluate the bioavailability relative to the capsule formulation in the fasted condition. Subjects should undergo serial blood sampling for serum iron concentration at scheduled intervals during each treatment period. Submit the protocol for review and concurrence prior to commencing.

Final Protocol: 12/2019
Study/Trial Completion: 07/ 2020
Final Report Submission: 10/2020

3667-6: Evaluate the effect of food on the bioavailability of the pediatric age appropriate oral formulation in healthy adults. Subjects should undergo serial blood sampling for serum iron concentration at scheduled intervals during each treatment period. Submit the protocol for review and concurrence prior to commencing.

Final Protocol: 12/ 2019
Study/Trial Completion: 12/2020
Final Report Submission: 03/2021

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
1. Indication and Usage	Treatment of iron deficiency anemia	Treatment of iron deficiency anemia in adults
(b) (4)		
7.1 Drug Interactions		Updated drug interaction language
8.1 Pregnancy		Included additional animal data
14. Clinical Efficacy	(b) (4)	Removed (b) (4) of efficacy data and presented in tabular format.

12 Risk Evaluation and Mitigation Strategies (REMS)

There are no additional risk management strategies beyond recommended labeling.

13 Postmarketing Requirements and Commitments

PMR #1:

PMR Description: Conduct in vitro binding studies to evaluate the potential for ferric maltol to bind commonly used concomitant oral medications. The studies should be performed under conditions that mimic the physicochemical conditions of the gastrointestinal tract. The list of drugs to be evaluated should be inclusive of alendronate, atorvastatin, calcium carbonate, ciprofloxacin, doxycycline, levothyroxine, lisinopril, metoprolol, mycophenolate, and warfarin. Submit the protocol and the list of drugs to be evaluated for review and concurrence prior to starting the study. The results of this study will identify drugs with significant or potentially clinically meaningful binding that require further in vivo evaluation.

PMR Milestones:

- Study Initiation: July 2019
- Study Completion: July 2020

PMC #1

PMR Description

1. Collect and submit multipoint dissolution profiles (5, 10, 15, 20 and 30 minutes) using the FDA's approved dissolution method (*USP II (paddle) with sinker, 75 rpm, Tier 1: KCl/HCl Buffer, pH 1.2; Tier 2: KCl/HCl buffer with addition of Pepsin (700,000 to 750,000 unit/L, 900 mL)* from newly manufactured commercial batches (minimum of six) and current stability-registration batches.
2. Include your proposal for the final acceptance criterion of the dissolution test of ACCRUFER capsules, 30 mg, which setting should be based on the newly collected data.
3. If Tier 1 dissolution fails due to crosslinking, you may proceed to use Tier 2 dissolution testing with Pepsin as per USP. Provide evidence of cross-linking in gelatin capsules. Include photographic documentation or capsule switching test might be used to confirm crosslinking.

PMC Schedule Milestones: Submission of PMC Report under a Prior Approval Supplement (PAS) to the NDA, including the requested dissolution data and proposed final dissolution acceptance criterion, within 12 months from the NDA's action date.

14 Division Director (DHOT)

John Leighton, PhD
Division Director, DHOT

15 Division Director (OCP)

Nam Atiqur Rahman, PhD
Division Director, OCP

16 Division Director (OB)

Thomas Gwise, PhD
Deputy Director, OB

17 Division Director (Clinical)

I concur with the recommendation to approve this oral iron formulation (capsules) for the treatment of iron deficiency based on the submitted package. This product has been approved in multiple countries in Europe for the past several years. Clinical pharmacology has agreement with the Applicant for a PMR for drug-drug interaction study and chemistry has agreement on a PMC for requested dissolution data and proposed final dissolution acceptance criterion. Several PREA PMRS were agreed to with the Applicant. Please see the letter for details.

Ann T. Farrell, MD

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Richard Pazdur, MD

19 Appendices

19.1. References

Campbell NR and Hasinoff BB. Iron supplements: a common cause of drug interactions. Br J Clin Pharmacol. 1991 Mar; 31(3): 251–255. PMID: 2054263.

19.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Protocol ST10-01-301 AEGIS 1 and Protocol ST10-01-302(AEGIS 2) and ST10-01-303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>27 In Aegis 1 and 35 in Aegis 2 and 30 in Study ST-01-303</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant) N/A
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		

Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation N/A from Applicant)
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19.3. Nonclinical Pharmacology/Toxicology

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

Not Applicable.

19.5. Additional Clinical Outcome Assessment Analyses

Not Applicable.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RACHEL S MCMULLEN
07/25/2019 11:47:45 AM

LAUREL A MENAPACE
07/25/2019 11:55:07 AM

SIMON WILLIAMS
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CHRISTOPHER M SHETH
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JOHN K LEIGHTON
07/25/2019 12:28:56 PM

LAUREN S PRICE
07/25/2019 12:31:49 PM

OLANREWAJU OKUSANYA
07/25/2019 01:16:51 PM

NAM ATIQUUR RAHMAN
07/25/2019 01:17:57 PM

LOLA LUO
07/25/2019 01:19:21 PM

THOMAS E GWISE on behalf of LEI NIE
07/25/2019 01:25:11 PM

THOMAS E GWISE
07/25/2019 01:25:52 PM

ANN T FARRELL on behalf of TANYA M WROBLEWSKI
07/25/2019 02:55:22 PM
Signing on behalf of Dr. Wroblewski

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07/25/2019 02:56:26 PM

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