NDA/BLA Multi-Disciplinary Review and Evaluation

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Reviewer Name(s)	**Clinical:** Roma Rajput, MD (Reviewer) Julie Weisman, MD (Team Leader) Tanya Wroblewski, MD (Division Director and Signatory) **Statistical:** Xiaoxia Champon, PhD (Reviewer) Lola Luo, PhD (Team Leader) Yeh-Fong Chen, PhD (Supervisor) **Clinical Pharmacology:** Yaning Sun (Reviewer) Sudharshan Hariharan (Team Leader)
Review Completion Date	12/2/2025
Established/Proper Name	Ferric Maltol
(Proposed) Trade Name	Accrufer
Applicant	Shield Therapeutics
Dosage Form(s)	Capsule
Applicant Proposed Dosing Regimen(s)	Oral
Applicant Proposed Indication(s)/Population(s)	For the treatment of iron deficiency in adults and children 10 years of age and above
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of iron deficiency in adults and children 10 years of age and above

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Glossary

This glossary should include all acronyms used in your review. The sample list below includes commonly used acronyms and may be used as a starting point.

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
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
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice

ICH	International Council for Harmonization
ID	Iron deficiency
IDA	Iron deficiency anemia
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
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
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
sNDA	supplemental new drug application
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TSAT	transferrin saturation

1. Executive Summary

1.0. 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 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.

Ferric maltol was FDA approved in 2019 as an iron replacement product indicated for the treatment of iron deficiency in adults. The recommended dosage of ferric maltol is 30 mg twice daily. Treatment duration will depend on severity of iron deficiency but generally at least 12 weeks of treatment is required and should be continued as long as necessary until ferritin levels are within normal range.

The Applicant's proposed indication is to expand the indication for the approved 30 mg capsules presentation to pediatric patients 10 years of age and older.

The Applicant intends to submit a new drug application once the oral suspension is ready for commercial use with the intent to further expand the indication to children under 10 years of age for treatment of iron deficiency.

1.1. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) of ferric maltol (30mg orally twice daily capsules) for the treatment of iron deficiency in pediatric patients 10 years of age and older is based on a randomized, open-label, active-controlled, multicenter, study (ST-10-01-305). Additional evidence comes from the partial extrapolation of efficacy demonstrated in the adult population.

The efficacy of ferric maltol for the treatment of iron deficiency in pediatric patients 10 years and older was evaluated in 24 patients ages 10 to less than 18 years (age range 10-17 years; 4 males and 20 females; with iron deficiency who received aged-based dosing of ferric maltol twice daily in Study ST-10-01-305. Patients aged 10-11 years received 15 mg twice daily while patients 12 to less than 18 years received 30 mg twice daily. Although Study ST-10-01-305 was a randomized trial (ferric maltol versus ferrous sulfate), the statistical methodology of the trial was designed to assess efficacy based on evaluation of the mean change in hemoglobin at Week 12 from baseline in the ferric maltol arm only.

Efficacy was assessed by evaluation of the mean change in hemoglobin from baseline at Week 12. In pediatric patients aged 10 to less than 18 years (n=24), the baseline Hb concentration (g/dL) was 10.73 (SD 0.89) and the mean change from baseline to Week 12 was 1.10 (SD 1.06). The mean change in Hb at Week 12 in the subgroup (N=21) who received the 30mg orally twice daily was 1.23 g/dL (SD 1.00). In participants aged 10 to less than 18 years of age, there was a higher mean change in hemoglobin from baseline at Week 12 in participants who received ferric maltol 30 mg twice daily (n=21) compared to those that received ferric maltol 15 mg twice daily (n=3) (1.23 vs. -0.15 g/dL) supporting the use of 30 mg twice daily (capsule formulation) dose for children aged 10 years and older.

The dose selection is supported by PK data obtained from both adult and pediatric populations, which provided a clear scientific rationale for the age-stratified dosing approach based on physiological iron requirements across different developmental stages. The oral suspension was utilized in the pediatric study ST10-01-305, making the bridge between suspension and capsule formulations critical for approval of capsules for pediatric subjects in the current submission. Given that the capsule formulation demonstrates higher exposure levels, efficacy was adequately bridged for using the capsules in pediatric subjects greater than 10 years of age.

The course of the disease (iron deficiency) and the effect of ferric maltol are sufficiently similar in the pediatric and adult populations to permit partial extrapolation from the adult population to pediatric patients.

1.2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Efficacy: Study ST-10-01-305 evaluated the efficacy of ferric maltol oral suspension from baseline to Week 12 in 65 children and adolescents ages 1 month to less than 18 years with iron deficiency anemia. Although Study ST-10-01-305 evaluated pediatric patients from 1 month of age to less than 18 years of age, the Applicant intends to submit a new drug application once the oral suspension is ready for commercial use with the intent to expand the indication to children under 10 years of age. The Sponsor also provided PK from Study ST-10-01-103 and also provided data to demonstrate that an appropriate bridge was demonstrated between the oral suspension and capsule formulation was.

The efficacy of ferric maltol for the treatment of iron deficiency was evaluated in Study ST-10-01-305, 24 patients 10 to less than 18 years of age (age range 10-less than 18 years; 4 males and 20 females; with iron deficiency who received aged-based dosing of ferric maltol twice daily in Study ST-10-01-305. Patients aged 10-11 years received 15 mg twice daily while patients 12 to <18 years received 30 mg twice daily. Efficacy was assessed based on mean change from baseline to Week 12 in Hb (g/dL) (descriptive statistics). The baseline Hb concentration (g/dL) was 10.73 (SD 0.89) in the 10 to < 18 years (n=24) and the mean change from baseline to week 12 was 1.10 (SD 1.06). In addition, the mean ferritin levels in subjects aged 10 to <18 years (N=24) at baseline were 11.4 mcg/L [SD 10.06] and the mean ferritin levels at Week 12 were 20 mcg/L [SD 13.51] with a mean overall improvement of 8.6 mcg/L [SD 10.29]. In participants aged 10 to less than 18 years of age, there was a higher mean change in hemoglobin from baseline at Week 12 in participants who received ferric maltol 30 mg twice daily (n=21) compared to those that received ferric maltol 15 mg twice daily (n=3) (1.23 vs. -0.15 g/dL) supporting the use of 30 mg twice daily (capsule formulation) dose for pediatric patients age 10 years and older.

Additional data was also derived from ST-10-01-103, an open label study to evaluate the pharmacokinetics (PK) and iron uptake of ferric maltol. The dose selection is supported by PK data obtained from both adult and pediatric populations, providing a clear scientific rationale for the age-stratified dosing approach based on physiological iron requirements across different developmental stages. The oral suspension was utilized in the pediatric study ST10-01-305, making the bridge between suspension and capsule formulations critical for approval of capsules for pediatric subjects in the current submission. Given that the capsule formulation demonstrates higher exposure levels, efficacy is

adequately bridged for using the capsules in pediatric subjects greater than 10 years of age.

Partial extrapolation from efficacy findings in adult population given similar pathophysiology, clinical signs and symptoms and treatment course. The partial extrapolation of efficacy from adults to pediatric patients is based on the following findings of clinical benefit from three randomized, double-blind, placebo-controlled, multi-center phase 3 pivotal studies in adult populations 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. 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 hemoglobin 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.

Safety: The total safety database consisted of 34 pediatric patients aged 1 month to less than 18 years in study ST-10-01-305 and 37 pediatric patients aged 10 to less than 18 years in study ST-10-01-103, In Study ST-10-01-305, subjects 1 month to less than 2 years received ferric maltol oral suspension at 0.6 mg/kg/dose twice daily, subjects 2 to 11 years received 15 mg twice daily, and subjects 12 to less than 18 years received 30 mg twice daily. Subjects randomized to receive oral ferrous sulfate received 3 mg/kg/dose of elemental iron twice daily. All subjects were treated for the duration of the study (12 weeks). No deaths, serious adverse reactions, or adverse reactions leading to permanent drug discontinuation were reported. The most frequently reported adverse reactions (>5%) in the ferric maltol arm were diarrhea and nausea. In study ST-10-01-103, subjects 10 to less than 18 years of age were randomized 1:1:1 to receive ferric maltol 7.8 mg capsule, 16.6 mg capsule, or 30 mg capsule twice daily oral on days 1 to 9 and a single dose on Day 10. No deaths or serious adverse events (SAEs) were reported. The most frequently reported adverse reactions (>10%) in the ferric maltol arm were discolored feces, headache, dizziness, diarrhea, and fatigue. Overall, the safety profile of ferric maltol in the pediatric population was consistent with the current prescribing information for adults. No new safety signals were observed.

Benefit-Risk

The treatment benefit of ferric maltol, as an iron replacement product, in pediatric patients aged 10 years and older with iron deficiency is demonstrated by an increase in hemoglobin after 12 weeks of treatment. The safety profile of ferric maltol in this population is tolerable and similar to that observed in the adult population. The benefit-risk assessment of ferric maltol in pediatric patients (10 to less than 18 years of age) for the treatment of iron deficiency is favorable and supports the expansion of the indication of ferric maltol for the treatment of iron deficiency in children 10 years of age and older.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Iron deficiency is the most common cause of anemia in children in the United States. • Causes of iron deficiency in children include inadequate dietary iron intake, poor absorption due to abnormalities in the gastrointestinal tract, and blood loss. • Clinical findings of iron deficiency anemia (IDA) in pediatric patients include pale skin, irritability, fatigue, tachycardia, cardiomegaly, pica in addition to mood and neurocognitive disorders.	Iron deficiency may cause serious complications.
Current Treatment Options	• Ferrous salts are the most common oral iron replacement products used in pediatric patients which include ferrous sulfate (most commonly used), ferrous fumarate, and ferrous gluconate. • Oral iron is the first-line and preferred treatment for iron deficiency, however, intravenous iron therapy (see section 2.2 for list of available intravenous therapy) is preferred when patients are	There is a need for alternative FDA approved oral iron replacement therapies for pediatric patients with iron deficiency.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	refractory to oral iron, in cases of severe anemia (Hb < 7 g/dL), chronic blood loss difficult to manage with oral iron, use of erythropoiesis-stimulating agents in chronic kidney disease, anatomic or physiologic conditions that interfere with oral iron absorption or coexisting inflammatory states that interfere with iron homeostasis. • Ferrous salts with sulfate, fumarate, or gluconate are widely available but may be poorly tolerated in certain individuals who may be able to better tolerate ferric complexes.	
Benefit	• In participants aged 10 to less than 18 years (n=24), the baseline Hb concentration (g/dL) was 10.73 (SD 0.89) and the mean change from baseline to Week 12 was 1.10 (SD 1.06).)In participants aged 10 to less than 18 years of age, there was a higher mean change in hemoglobin from baseline in participants who received ferric maltol 30 mg twice daily (n=21) compared to those that received ferric maltol 15 mg twice daily (n=3) (12.3 vs. -1.5 g/L) at Week 12. • ST-10-01-103 was an open label study to evaluate the pharmacokinetics (PK) and iron uptake of ferric maltol. The dose selection is supported by PK data obtained from both adult and pediatric populations, providing a clear scientific rationale for the age-stratified dosing approach based on physiological iron requirements across different developmental stages. • The oral suspension was utilized in the pediatric study ST10-01-305, making the bridge between suspension and capsule formulations critical for approval of capsules for pediatric subjects in the current	The Applicant's data supports the use of 30 mg twice daily dose with the 30 mg capsule formulation for children aged 10 and older.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	submission. Given that the capsule formulation demonstrates higher exposure levels, efficacy is adequately bridged for using the capsules in pediatric subjects greater than 10 years of age.	
Risk and Risk Management	• The most common adverse reactions observed in greater than 5% of patients included nausea and diarrhea. • No new safety signals were observed in the pediatric patients.	The overall safety profile of ferric maltol is acceptable for pediatric patients aged 10 years and older with iron deficiency with adequate recommendations in the label. The safety profile reported in pediatric patients aged 10 years and older is consistent with the safety profile reported in adult patients.

1.3. Patient Experience Data

Qualitative assessments of palatability, acceptability, and ease of use were conducted in Study ST-10-01-305 and will be summarized in Section 6.

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		Section 6.1.2.
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

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 prevalence of iron deficiency in the US during August 2021-August 2023 was 9.3%[(1)] Most iron is present in circulating red blood cells (RBCs), with additional iron stored in myoglobin and certain enzymes. Causes of iron deficiency in children include inadequate dietary iron intake, which is the most common cause, poor absorption due to abnormalities in the gastrointestinal tract, and blood loss[(2)].

Iron deficiency occurs in several stages defined by the extent of iron depletion. Eventually, if negative iron balance is sustained, production of iron-deficient red blood cells and ineffective hematopoiesis occurs 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 iron stores and decline in transferrin saturation precede decrease in hemoglobin levels) [(3)]. Thus, in early iron deficiency the complete blood count (CBC) may remain relatively normal.

Pediatric patients with mild iron deficiency anemia (IDA) can be asymptomatic. When anemia becomes more severe, patients develop usual signs of anemia such as pallor, fatigue, dyspnea on exertion, and headaches. [(4)] Non-hematological findings of iron deficiency anemia include neurological manifestations (decreased cognitive function, sleep disturbances), gastrointestinal disturbances (anorexia, glossitis, pica), integumentary system problems (spoon nails, hair loss, easy breakage of nails)[(5)]. IDA left untreated in infants and young children may cause permanent neurocognitive impairments, reduced learning capacity, and altered motor ability. [(4)]

Management of iron deficiency in the pediatric population includes investigation and elimination of the cause leading to iron deficiency, improvement of nutrition, education, and replacement with oral or intravenous iron therapy. There are certain conditions in which intravenous iron may be preferable, such as refractoriness to oral iron, severe anemia (Hb< 7 g/dL), chronic blood loss difficult to manage with oral iron, use of erythropoiesis-stimulating agents in chronic kidney disease, anatomic or physiologic conditions that interferes with oral iron absorption, or coexisting inflammatory states that interferes with iron homeostasis [(6, 7)]. However, for most patients, oral iron is the first line and preferred treatment. [(8)].

There are various types of oral iron supplements; the two major classes are ferrous (Fe^{2+}) salts and ferric (Fe^{3+}) complexes. Ferrous salts with sulfate, fumarate, or gluconate are widely

available but may be poorly tolerated in certain individuals who may be able to better tolerate ferric complexes [8]. There is a need for alternative easy-to-use oral iron replacement therapies for pediatric patients with iron deficiency.

2.2. Analysis of Current Treatment Options

Ferrous salts are the most common oral iron replacement products used in pediatric patients which include ferrous sulfate (most commonly used), ferrous fumarate, and ferrous gluconate. Some salts are available over the counter for general iron supplementation while other compounds are available as prescription medications, approved for treating diagnosed iron deficiency and IDA. Liquid formulations are commonly prescribed for infants and young children. Adolescents typically use the adult formulations (i.e. tablet or capsule). Dosing typically ranges from 1-2 mg/kg/day of elemental iron for supplementation with higher doses of 6 mg/kg/day to treat iron deficiency.

Current FDA approved iron products for pediatric patients are summarized in the table below.

Table 1 Available Iron Products in Pediatric Patients

Product (s) Name	Relevant Indication	Year of Approval	Dosage Form	Important Safety and Tolerability Issues
InFeD (iron dextran)	Documented iron deficiency in adult and pediatric patients > 4 months of age in whom oral iron administration is unsatisfactory or impossible	1974	Injection	Boxed warning for anaphylactic-type reactions.
Ferrlecit (sodium ferric gluconate complex)	Iron deficiency anemia in adult patients and in pediatric patients aged 6 years and older with chronic kidney disease receiving	1999	Injection	Warnings and precautions for hypersensitivity reactions, hypotension, iron overload, and benzyl alcohol toxicity in premature and low-birth weight infants.

Product (s) Name	Relevant Indication	Year of Approval	Dosage Form	Important Safety and Tolerability Issues
	hemodialysis who are receiving supplemental epoetin therapy			
Venofer (iron sucrose)	Iron deficiency anemia in adult and pediatric patients 2 years of age and older with chronic kidney disease	2000	Injection	Warnings and precautions for hypersensitivity reactions, hypotension, and iron overload.
Injectafer (ferric carboxymaltose)	Iron deficiency anemia (IDA) in: • adult and pediatric patients 1 year of age and older who have either intolerance or an unsatisfactory response to oral iron. • adult patients who have non-dialysis dependent chronic kidney disease.	2021	Injection	Warnings and precautions for hypersensitivity reactions, symptomatic hypophosphatemia, and hypertension.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ferric Maltol received initial United States (US) approval on July 30, 2019, as an iron replacement product indicated for the treatment of iron deficiency in adults. Ferric Maltol is not approved for pediatric patients. See Appendix 12.2 for list of the post-marketing requirements were issued at the time of the initial approval.

3.2. Summary of Presubmission/Submission Regulatory Activity

The key pre-submission regulatory activities for this supplement are outlined in the table below.

Table 2 NDA212320/S-019 Pre-Submission Regulatory History

Date	Meeting or Event
December 13, 2017	Agreed initial Pediatric Study Plan
July 17, 2019	Inadequate Proposed Pediatric Study Request Letter Issued
December 31, 2019	Inadequate Proposed Pediatric Study Request Letter Issued
November 30, 2021	Inadequate Proposed Pediatric Study Request Letter Issued
May 9, 2023	Type C Teleconference held to reach alignment on study design amendments for pediatric study ST-10-01-305 to ensure the study will fulfill PMR commitments
December 10, 2024	Inadequate Proposed Pediatric Study Request Letter Issued
April 1, 2025	Type B pre-sNDA meeting teleconference held to discuss package to support pediatric indication and addition of a pediatric

Date	Meeting or Event
	formulation. The Sponsor proposes to submit two (b) (4) sNDA applications: 1) Extension of indication granted for Accrufer 30 mg capsule to the treatment of iron deficiency in adults and children 10 years and above. 2) Addition of a new formulation (Accrufer oral suspension (b) (4) with an indication of the treatment of iron deficiency in adults and children (b) (4)

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

4.1. Office of Scientific Investigations (OSI)

The FDA Office of Scientific Investigations was not consulted for this submission.

4.2. Product Quality

Refer to CMC review for details.

4.3. Clinical Microbiology

Not Applicable.

4.4. Devices and Companion Diagnostic Issues

Not Applicable. There are no devices or companion diagnostics associated with this drug product.

5. Clinical Pharmacology

In the current submission, the Applicant submitted data from 3 clinical studies to support the application. ST10-01-103 was a Phase I, open-label, randomized study evaluating the pharmacokinetics (PK), safety and tolerability of ferric maltol in pediatric subjects aged 10 to less than 18 years with iron deficiency. Participants received one of three dosing levels (30 mg, 16.6 mg, or 7.8 mg twice daily) in repeated doses. This study served as a dose selection study for the Phase 3 program. ST10-01-104 evaluated the relative bioavailability of the oral suspension formulation compared to the oral capsule formulation in a healthy population, providing supportive data for the use of oral suspension in the Phase 3 study. ST10-01-305 was the pivotal Phase 3, active-controlled study comparing the safety and tolerability of ferric maltol oral suspension versus ferrous sulfate in children and adolescents (2 to <18 years) for iron deficiency anemia treatment. Clinical pharmacology review of this submission is focused on reviewing PK/PD results and verifying the appropriateness of the proposed dosing in pediatric subjects.

5.1. Dose selection for Phase 3 Study ST10-01-305

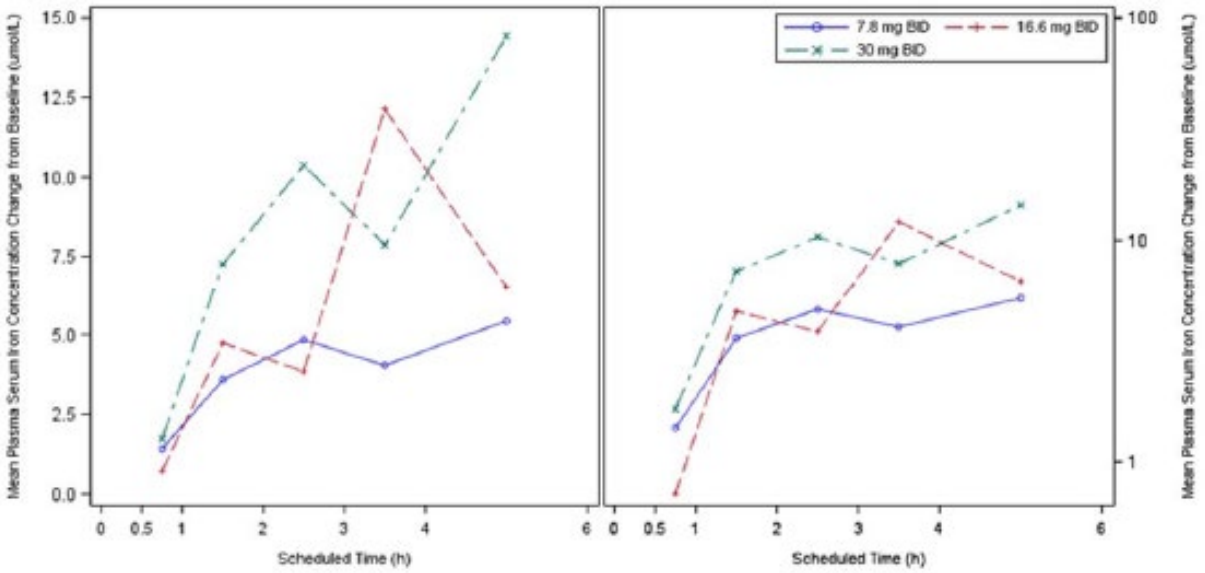
5.1.1. Adult Clinical Experience

The pediatric dose selection was grounded on extensive adult clinical data with ferric maltol. The approved adult dose of 30 mg twice daily (BID) was established through Phase 3 studies demonstrating efficacy and safety in adults with iron deficiency anemia (IDA) associated with inflammatory bowel disease (IBD) and chronic kidney disease (CKD). Additional dose-ranging studies revealed increased absorption at 60 mg dosing but no further benefit at 90 mg, confirming a saturable absorption mechanism.

5.1.2. Pediatric Pharmacokinetic study

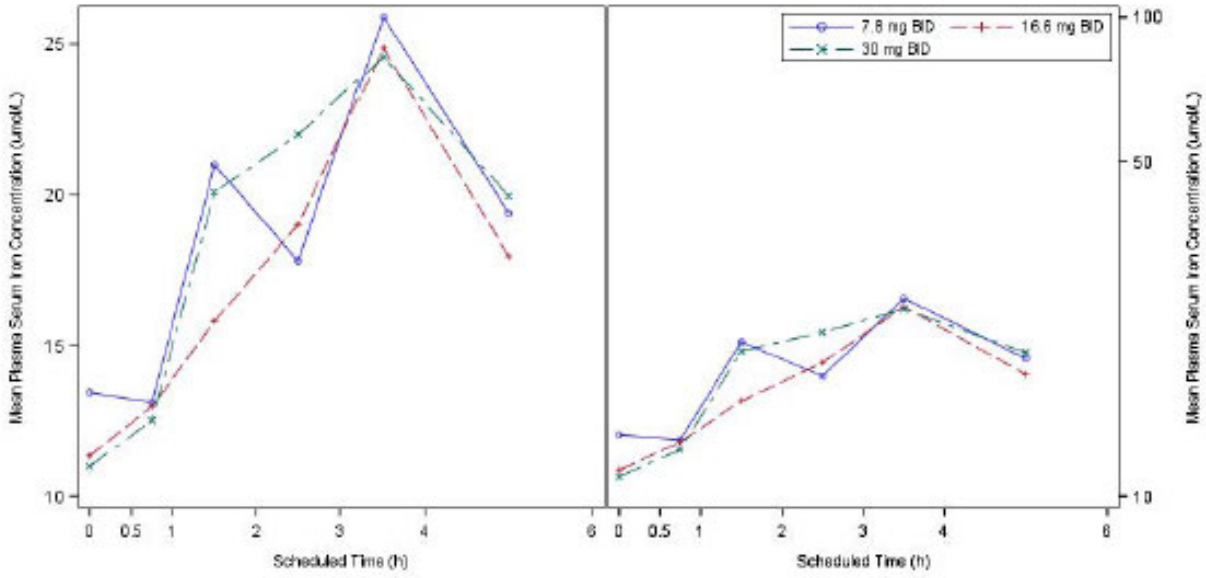
Phase I pediatric study (ST10-01-103) in children and adolescents aged 10 to less than 18 years provided relevant PK and PD information. This study evaluated repeated doses of ferric maltol at three dose levels (7.8 mg, 16.6 mg, and 30 mg twice daily) over 9 days and confirmed that serum iron exhibited a saturable PK pattern with less than proportional increases in uptake at higher doses (Figure 1, Figure 2). From a pharmacodynamic perspective, all three doses demonstrated increased iron uptake as measured by serum iron and transferrin saturation (TSAT) levels (Figure 3), while maintaining favorable safety profiles with good tolerability across all dose levels.

Figure 1 Serum Iron Concentration Change from Baseline by Dose Group on Day 1



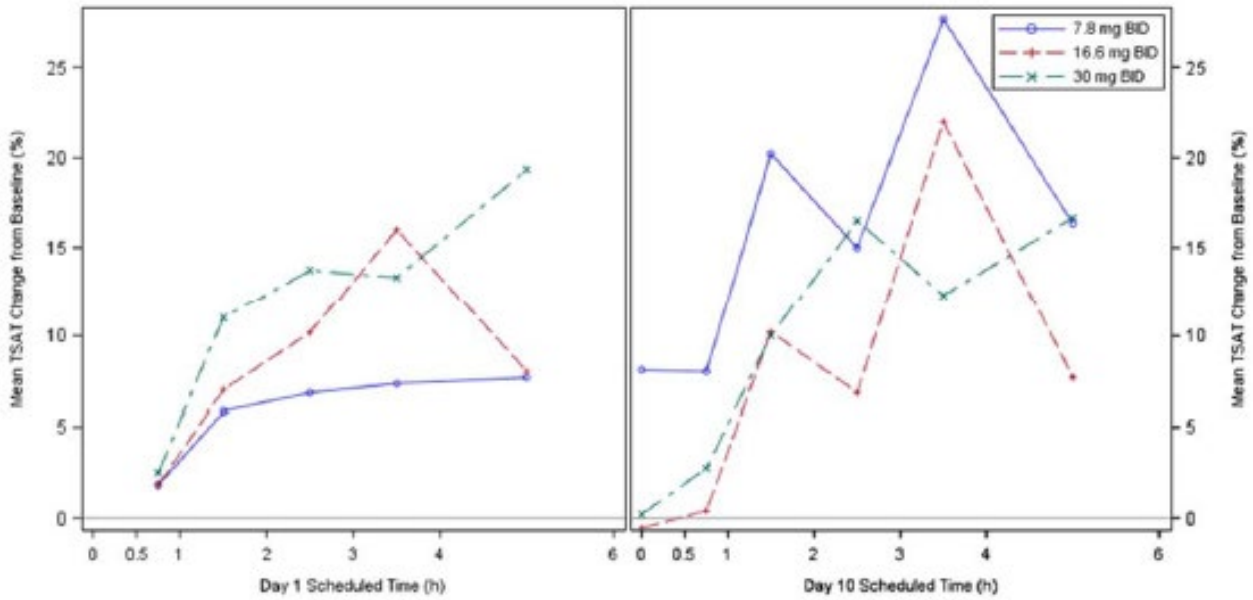
Source: CSR of ST10-01-103, Figure 9. Left panel- Linear scale, and right panel-Semi-Logarithmic Scales

Figure 2 Serum Iron Concentration Change from Baseline by Dose Group on Day 10



Source: CSR of ST10-01-103, Figure 10. Left panel- Linear scale, and right panel-Semi-Logarithmic Scales

Figure 3 Transferrin Saturation (TSAT %) Change from Baseline by Dose Group on Linear Scale on Days 1 and 10



Source: CSR of ST10-01-103, Figure 13. Left panel- day 1, and right panel-Semi-day 10

5.1.3. **Age-Stratified Dosing Strategy**

The final dosing regimen for Study ST10-01-305 employed a weight and age-based approach that considered age-specific iron requirements throughout development. Adolescents aged 12-less than 18 years received 30 mg twice daily (equivalent to the adult dose), justified by elevated iron requirements during growth spurts and physiological similarities to adults. Children aged 2-11 years received 15 mg twice daily, providing approximately 7.2 mg of potentially available iron (based on 24% bioavailability) to meet basal requirements plus disease-related needs. Infants aged 1 month to <2 years received weight-based dosing at 0.6 mg/kg twice daily, reflecting their unique physiological needs.

5.1.4. **Safety**

The proposed doses remain within the established range of approved oral ferrous products for children, which can provide up to 200 mg elemental iron daily, ensuring the dosing strategy aligns with existing pediatric iron supplementation standards.

Reviewer assessment:

The dose selection is supported by PK data obtained from both adult and pediatric populations, providing a clear scientific rationale for the age-stratified dosing approach based on

physiological iron requirements across different developmental stages. The proposed dosing regimen received regulatory agreement through the Pediatric Study Plan (PSP) process with FDA under IND 114832.

From a Clinical Pharmacology perspective, the dose selection for this study is acceptable.

5.2. Evaluation of food effect and formulation effect

5.2.1. Development of Pediatric-Specific Formulation

While ferric maltol capsules received regulatory approval for adult patients, the existing capsule formulation presented significant limitations for pediatric use. Children often experience difficulty swallowing capsules and require more flexible dosing options. The Applicant has developed an oral suspension formulation for pediatrics to fulfill Post-Marketing Requirements (PMR 3667-4 and PMR 3667-5). The oral suspension formulation was used in the subsequent Phase 3 study (ST10-01-305) where pediatric patients ranging from 1 month to less than 18 years old were enrolled.

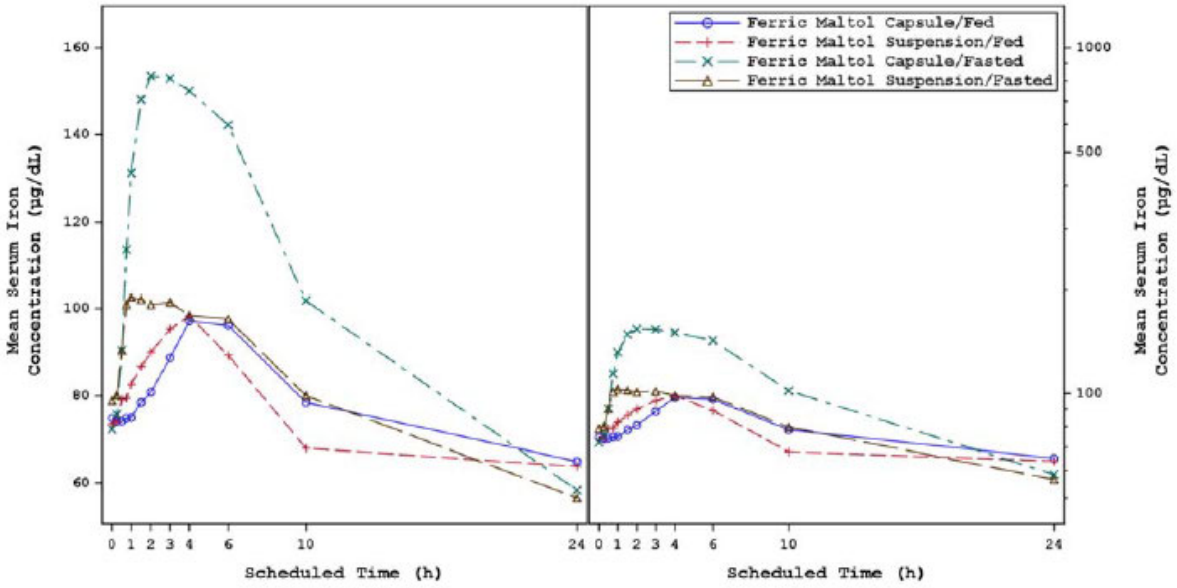
5.2.2. Evaluation of food effect and formulation effect in Study ST10-01-104

Study 104 was a Phase 1, randomized, open-label, single-dose, 4-way crossover study comparing the bioavailability of the newly developed oral suspension formulation to the approved capsule formulation under fasted and fed conditions. A single 30 mg dose of ferric maltol was administered as either capsule or oral suspension to healthy adult subjects.

Formulation comparison

Under fasted conditions, the ferric maltol suspension showed reduced serum iron exposure compared to the capsule formulation (Cmax: 107.8 ng/mL vs 154.1 ng/mL, AUC_{last}: 1775.0 h*ng/mL vs 2289.2 h*ng/mL). Under fed conditions, the capsule and suspension formulations demonstrated comparable Cmax (103.7 ng/mL vs 104.6 ng/mL) and AUC_{last} values (1653.9 h*ng/mL vs 1705.2 h*ng/mL) (Figure 4, Table 4 and Table 5).

Figure 4 Serum Iron Concentration with Oral Suspension and Capsule Formulation Under Fasted and Fed Conditions.



Source: CSR of ST10-01-104, Figure 2.

Table 3 PK Parameters for Serum Iron in Fasted Condition

Parameter Statistic	Ferric Maltol Capsule/Fasted (N=32)	Ferric Maltol Suspension/Fasted (N=32)
C_{max} (ng/mL)		
n	32	32
Geometric LS mean	154.09	107.78
Treatment comparison ferric maltol suspension/fasted vs capsule/fasted		
Ratio of geometric LS mean (%)		69.94
90% CI for ratio (%)		(61.75, 79.23)
AUC_{last} (h*ng/mL)		
n	32	32
Geometric LS mean	2289.24	1774.97
Treatment comparison ferric maltol suspension/fasted vs capsule/fasted		
Ratio of geometric LS mean (%)		77.54
90% CI for ratio (%)		(70.38, 85.42)
AUC_{inf} (h*ng/mL) [1]		
n	19	13
Geometric LS mean	3854.96	3013.01
Treatment comparison ferric maltol suspension/fasted vs capsule/fasted		
Ratio of geometric LS mean (%)		78.16
90% CI for ratio (%)		(65.64, 93.06)

Source: CSR of ST10-01-104, Table 9.

Table 4 PK Parameters for Serum Iron in Fed Condition

Parameter Statistic	Ferric Maltol Capsule/Fed (N=32)	Ferric Maltol Suspension/Fed (N=32)
C_{max} (ng/mL)		
n	32	32
Geometric LS mean	104.63	103.71
Treatment comparison ferric maltol suspension/fed vs capsule fed		
Ratio of geometric LS mean (%)		99.11
90% CI for ratio (%)		(87.50, 112.27)
AUC_{last} (h*ng/mL)		
n	32	32
Geometric LS mean	1705.15	1653.90
Treatment comparison ferric maltol suspension/fed vs capsule/fed		
Ratio of geometric LS mean (%)		96.99
90% CI for ratio (%)		(88.04, 106.86)

Source: CSR of ST10-01-104, table 10.

Food effect

For the suspension formulation, food intake did not significantly impact the exposure of serum iron, including Cmax (103.7 ng/mL vs 107.8 ng/mL) and AUC_{last} (1653.9 h*ng/mL vs 1775.0 h*ng/mL), but did cause a delay in the time to reach peak serum iron concentration (median Tmax: 3.5 h vs 2.0 h). Administration of ferric maltol capsules following a test meal resulted in decreased serum iron exposure compared to fasted conditions (Cmax: 104.6 ng/mL vs 154.1 ng/mL, AUC: 1705.2 h*ng/mL vs 2289.2 h*ng/mL).

Food effects varied significantly between formulations: the capsule showed a notable food effect with 47% higher Cmax and 34% higher AUC_{last} in fasted versus fed conditions, while the suspension formulation demonstrated minimal food effect with similar PK parameters regardless of food intake. These findings suggest that the suspension formulation may offer more consistent absorption regardless of food intake, while the capsule formulation provides optimal bioavailability when administered in the fasted state.

Reviewer comments: In Study ST10-01-104, the Applicant used serum iron instead of baseline-corrected serum iron as the primary PK endpoint for food effect and formulation comparison. When comparing the exposure differences, the magnitude of change was much larger when using baseline corrected serum iron compared to when using absolute serum iron. This observation was communicated to the Applicant in an Information Request dated October 21, 2025.

In the IR response dated on Oct 30, 2025, the Applicant argues that absolute serum iron levels are more relevant for potential systemic toxicity than baseline-corrected serum iron levels and notes that the safety of 30 mg twice daily capsule dosing is demonstrated in Study ST10-01-103.

Additionally, the Applicant emphasizes that total exposure of 30 mg twice daily capsule is significantly lower than that of Injectafer 15 mg twice daily, which achieves serum iron levels "3 orders of magnitude higher" than ferric maltol capsules.

While the reviewer does not fully agree with the argument for using serum iron for bioavailability and food effect assessments, study results of serum iron and baseline corrected serum iron both demonstrated that 1) food is expected to have no significant impact on exposure of the suspension formulation; and 2) suspension formulation is expected to have a significant lower bioavailability compared to capsule under fasting condition.

The oral suspension was utilized in the pivotal pediatric study ST10-01-305, making the bridge between suspension and capsule formulations critical for approval of capsules for pediatric subjects in the current submission. Given that the capsule formulation demonstrates higher exposure levels, efficacy is adequately bridged for using the capsules in pediatric subjects >10 years of age.

The safety profile of the 30 mg twice daily capsule dosing has been established in Study ST10-01-103 albeit following a shorter duration of treatment. Based on this consideration, the reviewer considers the results from Study ST10-01-104 to be supportive.

5.3. Pharmacokinetic results and conclusion of Study ST10-01-305

A total of 20 patients receiving ferric maltol were included in the PK analysis. All subjects 2 to 9 years of age were dosed with 15 mg twice daily of ferric maltol, all subjects 10 to 11 years of age received 15 mg twice daily of ferric maltol, and all subjects 12 to <18 years of age were dosed with 30 mg twice daily of ferric maltol. The PK results were further stratified by age, into two groups: 2 to 9 years of age and 10 to <18 years of age sub-groups. Therefore, the 10 to <18 years of age sub-group consisted of 2 dosing groups (15 mg twice daily and 30 mg twice daily).

Blood sampling for maltol and maltol glucuronide assessment was carried out pre-dose, and then at two additional time points between 0.5 to 10 hours post-dose in subjects 2 to <18 years of age.

5.3.1. PK of maltol glucuronide

PK results for maltol glucuronide demonstrated that younger children (2-9 years) had lower systemic exposure than older children (10 to less than 18 years), with decreased AUC_{0-t} and Cmax values observed on both Day 1 and Days 7-10.

In the older age group (10 to <18 years), dose-proportional exposure was observed by Days 7-10, where the 15 mg twice daily dose produced approximately half the AUC_{0-t} compared to the 30 mg twice daily dose, while Cmax showed less than dose-proportional increases. Notably, on Day 1, patients aged 10-17 years showed comparable AUC and Cmax values between the 15 mg twice daily and 30 mg twice daily doses (Table 6).

Pre-dose maltol glucuronide concentrations on Days 7-10 remained predominantly undetectable or near the limit of quantification across all age groups, confirming minimal drug accumulation with repeated administration.

Table 5 Summary of PK Parameters for Plasma Maltol Glucuronide

Visit Treatment Group Age Group	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (h×ng/mL)
Day 1			
Ferric maltol 15 mg			
2-9 years (N'=9)	4350	1.00	4670
10-17 years (N'=8)	6810	2.13	12000
Ferric maltol 30 mg			
10-17 years (N'=16)	6420	0.52	14600
Day 7-10			
Ferric maltol 15 mg			
2-9 years (N'=10)	4250	0.98	5900
10-17 years (N'=9)	5940	2.78	8070
Ferric maltol 30 mg			
10-17 years (N'=20)	8160	3.63	16700

15 mg 10 to 17 years age group only contained 10- and 11-year-olds.
30 mg 10 to 17 years age group only contained 12- to 17-year-olds.
Certara Phoenix WinNonlin Version 8.3 was used to validate PK parameters.
AUC_{0-t} = area under the plasma concentration-time curve from pre-dose (time 0) to the time of last quantifiable plasma concentration; C_{max} = maximum plasma concentration; N' = number of measurable concentrations used in pharmacokinetic parameter calculation; PK = pharmacokinetic(s); T_{max} = time to maximum plasma concentration.
Source: Post-text Table 14.2.4.2.2

Source: CSR of ST10-01-305, table 20.

5.3.2. PK of serum iron

The PK results of baseline-corrected serum iron demonstrated a dose-response relationship on Day 1, with the 30 mg twice daily group showing higher Cmax and AUC_{0-t} values compared to the 15 mg twice daily group in both age groups. Age-related differences were also observed, as younger children (2-9 years) receiving 15 mg twice daily exhibited higher Cmax and AUC_{0-t} for baseline-corrected serum iron compared to older children (10-11 years) at the same dose of 15 mg twice daily (Table 7).

Following repeated dosing, changes in serum iron exposure from Day 1 to Days 7-10 varied by age and dose group. Patients aged 12 to less than 18 years receiving 30 mg twice daily showed significant increases in both Cmax and AUC, while children aged 2-9 years on 15 mg twice daily demonstrated more modest increases in exposure. Notably, patients aged 10-11 years treated with 15 mg twice daily actually exhibited lower AUC and Cmax levels on Days 7-10 compared to Day 1, suggesting a potential for under dosing in this specific age and dose subgroup.

Table 6 Summary of PK Parameters for Baseline Corrected Serum Iron

Visit Treatment Group Age Group	C_{max} (µg/dL)	T_{max} (h)	AUC_{0-t} (h×µg/dL)
Day 1			
Ferric maltol 15 mg			
2-9 years (N'=18)	87.0	2.37	64.4
10-17 years (N'=12)	40.0	2.13	60.1
Ferric maltol 30 mg			
10-17 years (N'=30)	119	2.00	374
Day 7-10			
Ferric maltol 15 mg			
2-9 years (N'=18)	96.5	2.10	100
10-17 years (N'=12)	21.0	2.78	1.93
Ferric maltol 30 mg			
10-17 years (N'=30)	364	6.63	1180

15 mg 10 to 17 years age group only contained 10- and 11-year-olds.
30 mg 10 to 17 years age group only contained 12- to 17-year-olds.
Certara Phoenix WinNonlin Version 8.3 was used to validate PK parameters.
AUC_{0-t} = area under the plasma concentration-time curve from pre-dose (time 0) to the time of last quantifiable plasma concentration; C_{max} = maximum plasma concentration; N' = number of measurable concentrations used in pharmacokinetic parameter calculation; PK = pharmacokinetic(s); T_{max} = time to maximum plasma concentration.
Source: Post-text Table 14.2.4.2.4

Source: CSR of ST10-01-305, Table 21.

Reviewer assessment:

The PK profiles of maltol glucuronide and serum iron exhibited distinct patterns that do not align with each other. The Applicant explained that iron absorption is subject to physiological regulation and does not follow dose-proportional kinetics, whereas maltol absorption appears to occur through passive diffusion and demonstrates dose-proportional behavior. The Applicant emphasized that these differences are attributable to the distinct absorption, storage, and excretion mechanisms governing iron versus maltol, and do not impact the safety or efficacy of ferric maltol in pediatric populations. The Applicant's response appears reasonable.

The PK findings revealed that patients aged 10-11 years receiving 15 mg twice daily generated significantly lower exposure compared to both the 2-9 years group on 15 mg twice daily and the 12 to less than 18 years group on 30 mg twice daily. This reduced exposure was accompanied by a correspondingly smaller increase in mean hemoglobin at Week 12 for the 10-11 years subgroup (15 mg ferric maltol) relative to the other two subgroups (2-9 years [15 mg ferric maltol] and 12 to less than 18 years [30 mg ferric maltol]). These combined PK and efficacy observations suggest that a higher dose may be more appropriate for the 10-11 years age group, which will be further discussed in Section 4.

5.4. Evaluation of the proposed dosing regimen

5.4.1. Need for a higher dose in pediatric subjects aged 10 and 11 years

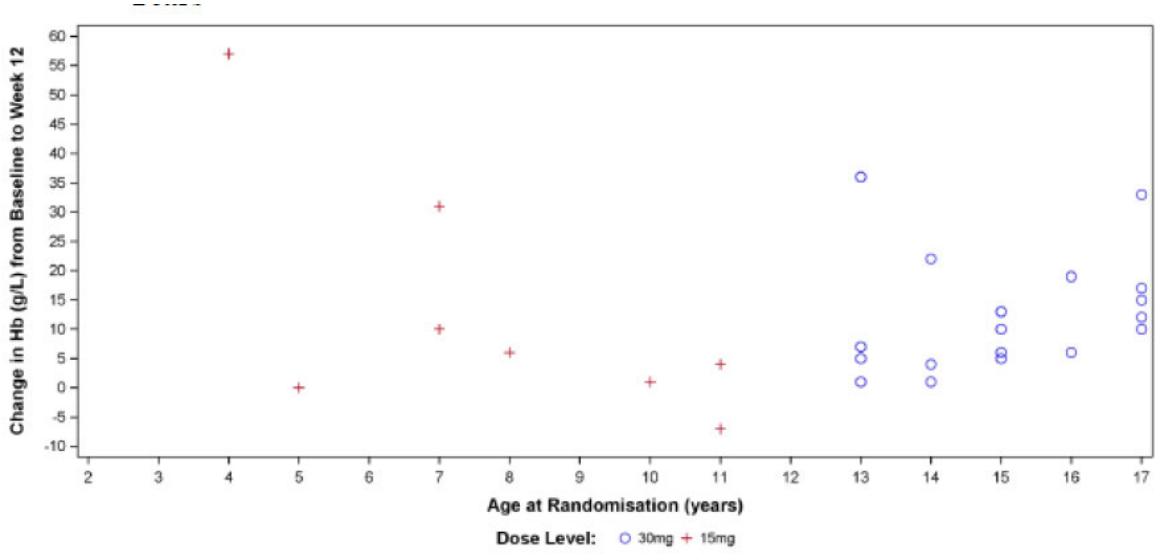
The Applicant proposes to administer a higher dose of 30 mg twice daily to patients aged 10 and 11 years, whereas these patients received 15 mg twice daily in Study ST10-01-305. The Applicant indicated that the poor hemoglobin response observed in patients aged 10 and 11 years provides the rationale for increasing the dose to 30 mg twice daily (Table 8).

The mean change from baseline hemoglobin rise at Week 12 was comparable between patients aged 2-9 years (17.5 g/L) receiving 15 mg twice daily and patients aged 12 to less than 18years (12.3 g/L) receiving 30 mg twice daily. However, patients aged 10-11 years receiving 15 mg twice daily did not demonstrate a hemoglobin rise (-1.5 g/L) (Table 7). Individual patient changes in hemoglobin at Week 12 are illustrated in Figure 5, and individual patient changes transferrin saturation are shown in Figure 6.

Table 7 Summary of Hb (g/L) change from baseline at week 12

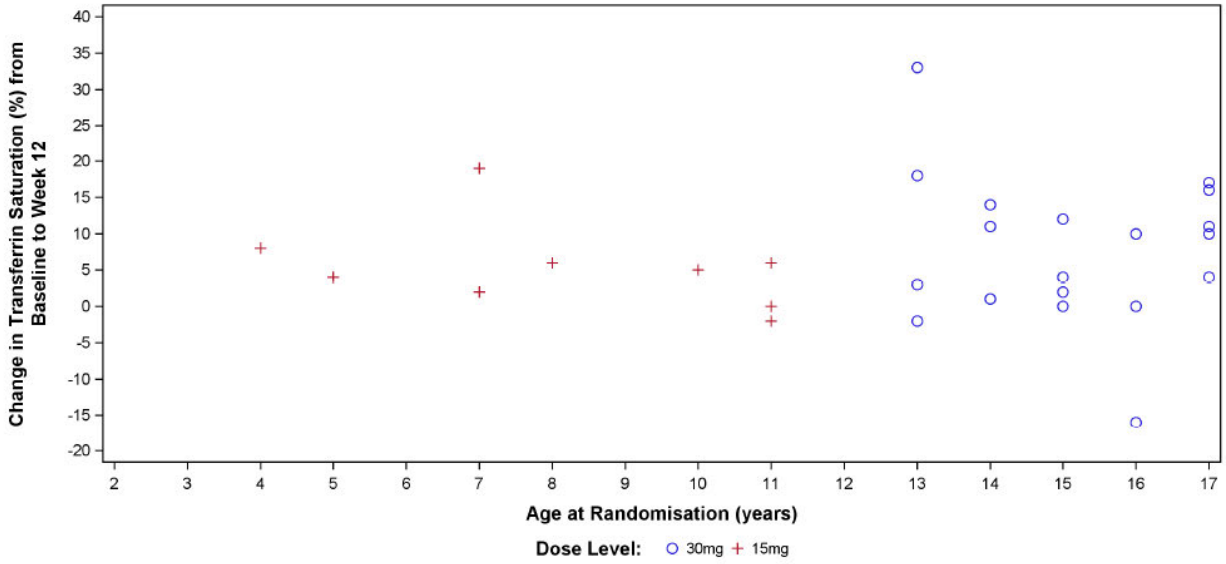
Visit Statistic	2-9 years 15mg BID	10-11 years 15mg BID	12-17 years 30mg BID
Hb			
Baseline			
n	7	3	21
Mean	98.9	110.0	106.9
Standard deviation	15.26	6.93	9.22
Median	104.0	114.0	110.0
Minimum	69	102	86
Maximum	113	114	118
Day 84			
n	6	2	18
Mean	114.2	112.5	119.3
Standard deviation	9.00	7.78	7.47
Median	114.0	112.5	119.5
Minimum	100	107	100
Maximum	126	118	136
Change from Baseline to Day 84			
n	6	2	18
Mean	17.5	-1.5	12.3
Standard deviation	22.40	7.78	10.02
Median	8.0	-1.5	10.0
Minimum	0	-7	1
Maximum	57	4	36
Source:ST10-01-305 CSR Post-text Table 14.2.1.1.7 and 14.2.1.1.8 and CSR Tables 15 and 16			

Figure 5 Scatterplot of Change in Hb (g/L) From Baseline to Week 12 Versus Age



Source: ST10-01-305 CSR Post-text Figure 14.2.3.2a

Figure 6 Scatterplot of Change in Transferrin Saturation (%) From Baseline to Week 12 Versus Age



Source: ST10-01-305 CSR Post-text Figure 14.2.4.2a

Reviewer comments:

The reviewer noted lower efficacy in 10–11-year-olds at the 15 mg twice daily dose of ferric maltol but emphasized that no firm conclusion can be drawn due to the extremely small sample size (only 3 patients). Despite this limitation, the review team assessed the Applicant proposed higher dose of 30 mg twice daily using the totality of available evidence from multiple studies. The primary rationale centers on exposure and efficacy: Study 305 showed markedly lower drug exposure in 10–11-year-olds at 15 mg twice daily, which correlated with the reduced hemoglobin response. Increasing the dose to 30 mg twice daily is expected to achieve exposure levels closer to those observed in older adolescents (12 to less than 18 years), where the observed efficacy was satisfactory, thereby improving treatment outcomes in the younger cohort.

From a safety perspective, the 30 mg twice daily dose has an established, favorable profile. Study ST10-01-103 tested doses up to 30 mg twice daily in patients aged 10 to less than 18 years with no meaningful safety differences across dose levels. Additional reassurance comes

from extensive pediatric experience with intravenous iron products which produce far higher systemic iron concentrations yet are approved and well-tolerated in children as young as 1 year. Given ferric maltol's substantially lower iron exposure compared with these IV formulations, the safety data supports the proposed 30 mg twice daily regimen to pediatric subjects aged 10 and 11 years.

5.4.2. Use of ferric maltol capsules in pediatric subjects >10 years

The Applicant is seeking approval for the use of the adult-approved capsule formulation to be administered on an empty stomach to pediatric patients 10 years and older as per the proposed product insert. However, only the oral suspension formulation was used to dose all pediatric patients in Study ST10-01-305. As noted in the results of Study ST10-01-104, the capsule formulation demonstrated higher absolute serum iron levels compared to the oral suspension formulation. Furthermore, the magnitude of increase was even greater in baseline-corrected serum iron than that observed with absolute serum iron measurements. Therefore, the reviewer sent an IR to the Applicant to justify the safety of using ferric maltol capsules in pediatric subjects.

In the IR response dated October 30, 2025, the Applicant provided justification that iron is a micronutrient that does not rely on drug/receptor interactions for efficacy or side effects. In this regard, Cmax is less relevant to exposure and potential systemic side effects than AUC. Since the body cannot differentiate between iron derived from ferric maltol and iron from other dietary sources, and because iron absorption is under physiological control, absolute serum iron levels rather than baseline-corrected serum iron levels are more relevant to potential systemic toxicity.

Although serum iron Cmax from capsule formulation taken fasted may be higher compared to a similar dose in suspension form, evidence from PK study ST10-01-103 demonstrated comparable adverse events among three doses (7.8 mg, 16.6 mg, and 30 mg twice daily). No dose-related increase in systemic adverse events was observed in subjects treated under fasted conditions for 9 days.

Furthermore, approved IV iron products achieve iron concentrations three orders of magnitude higher than oral ferric maltol (124-418.1 µg/mL) yet maintain established safety profiles in pediatric patients as young as 1 year old. Since these IV products are well-tolerated despite much higher systemic iron exposure, the exposure from oral ferric maltol capsules in pediatric subjects is adequately justified from a safety perspective.

Reviewer comment: The reviewer agrees with the Applicant's rationale and concludes that the proposed dose regimen using the capsule formulation is acceptable for pediatric patients aged 10 years and older. Refer to the reviewer's comments in Section 5.2.2 for additional details.

6. Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Table 8 Clinical Studies Included in sNDA212320/S-019

Trial	Trial Design	Regimen	Study Objectives	Study Population	# of patients enrolled	Treatment Duration
ST10-01-305	Phase 3 randomized open-label, active controlled, multicenter comparative study	**Treatment** Ferric maltol, Oral Suspension, twice daily <u>1 month to < 2 years:</u> 0.6 mg/kg/dose <u>2-11 years:</u> 15 mg/dose <u>12-less than 18 years:</u> 30 mg/dose **Comparator** Ferrous sulfate (125 mg/ml), oral liquid 3 mg/kg/dose, twice daily	**Primary:** • To assess the effect on hemoglobin in children and adolescents (1 month to <18 years) • To compare the safety and gastrointestinal tolerability of ferric maltol oral Suspension and ferrous sulfate oral liquid in children and adolescents (2 to <18 years) and assess the safety and tolerability of ferric maltol oral suspension in children (1 month to <2 years), in the treatment of iron deficiency anemia **Secondary** • To assess the PK in children and adolescents (2 to <18 years) after a single	Male and female pediatric subjects, aged 1 month to <18 years, with iron deficiency anemia	**Randomized:** Ferric Maltol: 35 Ferrous Sulfate: 30 **Total: 65** **Completed:** Ferric Maltol: 34 Ferrous Sulfate: 30 **Total: 64**	12 weeks

Trial	Trial Design	Regimen	Study Objectives	Study Population	# of patients enrolled	Treatment Duration
			dose of ferric maltol oral suspension, and after twice daily administration for at least 6 days, after a single morning dose • To assess the effect on iron markers in children and adolescents (1 month to <18 years) after twice daily administration of ferric maltol oral Suspension • To assess the PK, in children (1 month to <2 years) after a single dose of ferric maltol oral Suspension and after twice daily administration for at least 6 days, after a single morning dose • To assess the effect, in children (1 month to <2 years) after twice daily administration for at least 6 days, after a single morning dose • To assess the effect, in children (2 to <18 years) after a single dose of ferric maltol oral Suspension, and after twice daily administration for at least 6 days, after a single morning dose • To compare the palatability from age appropriate			

Trial	Trial Design	Regimen	Study Objectives	Study Population	# of patients enrolled	Treatment Duration
			scoring system of ferric maltol oral suspension and ferrous sulfate oral liquid			
ST10-01-103	Phase 1, randomized, open-label, parallel group, multicenter PK study	Ferric maltol, 7.8 mg, 16.6 mg, 30 mg capsules, twice daily oral on Days 1 to 9 Single dose, oral on Day 10.	**Primary** • To assess the PK and iron uptake of 3 doses of ferric maltol in children and adolescents **Secondary** • To assess the effects of 3 doses of ferric maltol in children and adolescents • To assess the safety and tolerability of ferric maltol in children and adolescents	Male and female pediatric subjects, aged 10 to <18 years old, with iron deficiency.	37	10 days
ST10-01-104	Phase 1, randomized, open-label, single dose, 4-way crossover study	Ferric maltol: • Capsules: 30 mg • Oral Suspension: 30 mg (5mL) Single dose, oral	**Primary** • To evaluate the PK of iron absorption, after a single 30 mg dose of ferric maltol, administered as a capsule or oral suspension (under fasted and fed conditions) based on primary parameters **Secondary** • To evaluate the PK after a single 30 mg dose of ferric maltol, administered as a capsule or oral suspension, (under fasted and fed conditions), based on TSAT,	Healthy adult subjects, 18 to 55 years of age	32	8 days

Trial	Trial Design	Regimen	Study Objectives	Study Population	# of patients enrolled	Treatment Duration
			TIBC, UIBC and plasma maltol and maltol glucuronide			

5.2 Review Strategy

The clinical review was primarily based on safety and efficacy data from study ST-10-01-305 and included the following:

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

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewers were performed using SAS/JMP 17.2 (SAS Institute, Inc., Cary, NC) and OCS Analysis Studio version 2.1.2. (Oracle Corporation, Redwood City, CA).

7. Review of Relevant Individual Trials Used to Support Efficacy

7.1. Review Strategy

The clinical review was primarily based on safety and efficacy data from study ST-10-01-305 and included the following:

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

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewers were performed using SAS/JMP 17.2 (SAS Institute, Inc., Cary, NC) and OCS Analysis Studio version 2.1.2. (Oracle Corporation, Redwood City, CA).

7.2. Study Design

Overview and Objective

Trial ID and Title:

ST-10-01-305 was a randomized, open-label, active-controlled, multicenter, comparative study.

The primary objective was to compare the safety and gastrointestinal tolerability of ferric maltol oral suspension and ferrous sulfate oral liquid in children and adolescents (2 years to < 18 years) and asses the safety and tolerability of ferric maltol in children (1 month to < 2 years), in treatment of iron deficiency anemia. The other primary objective was to assess the effect of hemoglobin on children and adolescents (1 month to < 18 years).

Trial Design

ST-10-01-305 was a Phase 3, randomized, open-label, active-controlled, multicenter, comparative study between ferric maltol oral suspension and ferrous sulfate oral liquid. Eligible patients aged 2 to 17 years were to be randomized at a ratio of 1:1 to ferric maltol or ferrous sulfate for a 12-week treatment period and subjects aged 1 month to less than 2 years were to be assigned to the ferric maltol group (assigned ferric maltol group).

Study Endpoints

Primary endpoint for efficacy of ferric maltol:

- Change in Hb concentration from baseline to Week 12.

Secondary endpoints for efficacy of ferric maltol:

- Changes in iron markers from baseline to Week 4.
- Changes in iron markers from baseline to Week 12.
- Achieving Hb concentration within normal range at Week 12.

Statistical Analysis Plan

Analysis day was calculated from the date of first dose of study drug in the treatment phase. The day of the first dose of study drug was considered as Day 1, and the day immediately before Day 1 as Day -1. There was no Day 0. Baseline was defined as the last measurement prior to the first treatment dose of study drug.

Determination of Sample Size

In total, up to 110 patients could have been recruited into the study. Up to 98 patients could

have been randomized in the 2 to less than 18 years cohort and up to 12 patients could have been assigned in the 1 month to less than 2 years cohort. The aim was to recruit up to 49 patients in each treatment group in the 2 to less than 18 years cohort. At least 12 patients in each age group (i.e., 24 patients in total) could have been included in the PK analysis of the ferric maltol oral suspension group.

A sample size of 49 patients in the ferric maltol group would have provided at least 80% power to demonstrate that the lower bound of the 95% CI for increase in Hb at 12 weeks, compared to baseline, was above 0. This approach assumed that the standard deviation (SD) of the change from baseline would be 1.2 g/dL or lower and the true mean change at least 0.5 g/dL.

Interim analysis

In Protocol Amendment 5, Version 4.1, dated 06 July 2023, a potential interim analysis and associated stopping rules were added to the study to address low recruitment rates. If fewer than 91 patients in total had been randomized when 32 ferric maltol patients had completed the 12- week primary treatment period, an interim analysis of the primary effectiveness endpoint (change in Hb concentration from baseline to Week 12) would be conducted. If change in Hb concentration from baseline to Week 12 was considered significant, the study would stop recruitment. If it had not been considered significant, the study would have continued (all patients would have been assigned to ferric maltol) until 54 patients had been recruited in the ferric maltol arm.

The interim analysis used a Pocock spending function. The interim analysis was based on a (100-3.45) % 2-sided CI. If the study had not stopped after the interim analysis, the final analysis would have been based on a (100-2.57) % 2-sided CI.

Analysis populations

The Intention-to-Treat (ITT) Population is defined as all patients who were randomized/assigned to treatment arms.

The modified ITT (mITT) Population is defined as all patients in the ITT Population who received at least 1 treatment dose.

Statistical analyses

Efficacy data are summarized by randomized/assigned treatment, based on the mITT population for the primary endpoint, and based on the ITT Population for the secondary endpoints. Sensitivity analyses were performed on the ITT Population for the primary endpoint.

Primary endpoint

The change in Hb concentration from baseline to Week 12 is summarized based on the mITT population for each treatment group using descriptive statistics summarized by mean, SD, median, and range (minimum and maximum).

A hypothesis testing was performed at the pre-specified interim analysis to test the hypothesis that the primary efficacy endpoint, Hb change from baseline to Week 12, in the ferric maltol arm is >0. The interim analysis was based on a (100-3.45) % 2-sided CI. The study was not designed for a formal efficacy comparison of ferric maltol to ferrous sulfate rather to assess the change in Hb concentration from baseline to Week 12 for ferric maltol as a single arm study. Therefore, efficacy results in the ferrous sulphate group are considered descriptive and no formal comparison was performed between ferric maltol and ferrous sulfate groups.

The efficacy of ferric maltol was assessed via the change in Hb concentration from baseline to Week 12 using a mixed model for repeated measures (MMRM) approach. The analysis included fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the baseline value as a continuous covariate. In the MMRM model, both assigned and randomized ferric maltol patients were included in the ferric maltol arm. A separate analysis was performed including only randomized patients.

Sensitivity analysis

The change in Hb concentration from baseline to Week 12 is also summarized and assessed for the ITT population.

Secondary endpoints

The secondary endpoints are reported for each treatment group using descriptive statistics summarized by mean, median, and range (minimum and maximum), and 95% confidence interval (CI) for the mean, where applicable, split by age group.

The secondary analysis of the change from baseline to Weeks 4 and also to Week 12 in iron markers (serum iron, serum corrected iron, transferrin, TSAT, TIBC, UIBC, and ferritin) are summarized using descriptive summary statistics. In this analysis, missing Week 4 and Week 12 values were imputed using a last observation carried forward (LOCF) approach, in which the last available post-baseline measurement was used in the analysis. It should be noted that LOCF assumes that missing data is completely random, that there are no changes after the last observation, which may not adequately account for the underlying pattern of missing data.

The number and percentage of patients achieving normal range, based on the central laboratory's reference range, at Week 12 is summarized by treatment group.

Study ST-10-01-305

7.2.1. 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 ST10-01-305.

Patient Disposition

The table below summarizes the patient disposition in the study. In summary, 56 out of 65 patients (86.2%) completed the study. The ferric maltol, ferrous sulfate, and ferric maltol assigned arm had completion rates of 90.3% (28/31 patients), 83.3% (25/30 patients), and 75.0% (3/4 patients), respectively. Only one patient discontinued due to an adverse event, which occurred in the ferrous sulfate group.

Table 9 ST10-01-305 Disposition (ITT Population)

Category	Ferric Maltol (N=31) n (%)	Ferrous Sulfate (N=30) n (%)	Ferric Maltol Assigned (N=4) n (%)	Total (N=65) n (%)
Enrolled	31 (100.0)	30 (100.0)	4 (100.0)	65 (100.0)
Randomized (ITT)	31 (100.0)	30 (100.0)	4 (100.0)	65 (100.0)
mITT	31 (100.0)	30 (100.0)	3 (75.0)	64 (98.5)
Treated	31 (100.0)	30 (100.0)	3 (75.0)	64 (98.5)
Discontinued Study early	3 (9.7)	5 (16.7)	1 (25.0)	9 (13.8)

Category	Ferric Maltol (N=31) n (%)	Ferrous Sulfate (N=30) n (%)	Ferric Maltol Assigned (N=4) n (%)	Total (N=65) n (%)
Withdrawal of consent	1 (3.2)	4 (13.3)	1 (25.0)	6 (9.2)
Adverse event	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.5)
Other	2 (6.5)	0 (0.0)	0 (0.0)	2 (3.1)
Discontinued early due to COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Completed the study	28 (90.3)	25 (83.3)	3 (75.0)	56 (86.2)

Source: FDA analysis of ADSL dataset

Protocol Violations/Deviations

Table 7 summarizes all protocol deviations in study ST-10-01-305. Most protocol deviations were related to investigational product and involved study drug compliance as less than 80% completion of the dosing diary.

The majority of protocol deviations in the ferric maltol treated arms were related to study procedures. Five patients in the randomized ferric maltol arm and three patients in the ferric maltol assigned arm had deviations in study procedures related to required PK assessments not completed or not completed correctly at a study visit.

Reviewer Comment: None of the protocol violations impacted the interpretability of Study ST-10-01-305.

Table 10 ST-10-01-305 Protocol Deviations (ITT Population)

Category	Ferric Maltol (N=31) n (%)	Ferrous Sulfate (N=30) n (%)	Ferric Maltol Assigned (N=4) n (%)	Total (N=65) n (%)
Any CSR-reportable protocol deviations	7 (22.6)	13 (43.3)	4 (100.0)	24 (36.9)

Category	Ferric Maltol (N=31) n (%)	Ferrous Sulfate (N=30) n (%)	Ferric Maltol Assigned (N=4) n (%)	Total (N=65) n (%)
Investigational Product	1 (3.2)	10 (33.3)	1 (25.0)	12 (18.5)
Study Procedures	5 (16.1)	1 (3.3)	3 (75.0)	9 (13.8)
Breaches in Good Clinical Practice	0 (0.0)	2 (6.7)	0 (0.0)	2 (3.1)
Restricted concomitant Medication Change	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.5)

Source: ST-10-01-305 Clinical Study Report, verified by FDA reviewer

Patients Baseline Demographics

The table below summarizes the baseline demographic characteristics across all treated patients. The modified intention to treat population (mITT) is summarized below to include patients that received at least one dose of ferric maltol. In summary, the study population was balanced between treatment groups with similar demographic distributions, though there was a predominance of female participants. Mean age was comparable between female participants and comprised approximately three-quarters of both treatment groups (74.2% ferric maltol vs 73.3% ferrous sulfate), which was consistent with the ferric maltol assigned infant group (75.0% female). Race was predominantly White (58.1% ferric maltol vs 53.3% ferrous sulfate), followed by Black or African American participants (29.0% vs 36.7%). The ferric maltol assigned infant group showed the same 33.3% classified as "White", “Asian” and “Other”. Ethnic distribution showed approximately 40% Hispanic or Latino participants in both 2 to less than 18 years treatment groups. Majority of the subjects are from United States.

Table 11 ST-10-01 305 Patient Baseline Demographics (mITT Population)

	Ferric Maltol (N=31)	Ferrous Sulfate (N=30)	Assigned Ferric Maltol (N=3)
Age Mean (SD) Median (Min, Max)	 12.8 (3.8) 14.0 (4.0, 17.0)	 12.3 (4.6) 13.0 (2.0, 17.0)	 11.7 (0.6)* 12.0 (11.0, 12.0)
Age Group			
1 month to < 2 years	0	0	3 (100.0)
2 years to 9 years	7 (22.6)	7 (23.3)	0
10 years to 17 years	24 (77.4)	23 (76.7)	0
Sex			
Female	23 (74.2)	22 (73.3)	2 (66.7)
Male	8 (25.8)	8 (26.7)	1 (33.3)
Weight Mean (SD) Median (Min, Max)	 50.9 (19.5) 52.5 (16.1, 94.4)	 56.9 (25.7) 55.2 (12.0, 126.5)	 10.5 (0.8) 10.9 (9.6, 11.0)
Race			
Asian	3 (9.7)	3 (10.0)	1 (33.3)
Black or African American	9 (29.0)	11 (36.7)	0
Other	1 (3.2)	0	1 (33.3)
White	18 (58.1)	16 (53.3)	1 (33.3)
Ethnicity			
Hispanic or Latino	13 (41.9)	12 (40.0)	1 (33.3)
Not Hispanic or Latino	18 (58.1)	18 (60.0)	1 (33.3)
Unknown	0	0	1 (33.3)
Country			
United Kingdom	9 (29.0)	3 (10.0)	1 (33.3)
United States	22 (71.0)	27 (90.0)	2 (66.7)

Source: FDA analysis of ADDM dataset

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics were generally balanced between randomized ferric maltol and ferrous sulfate arms in study ST-10-01-305. The most commonly reported (>10%) medical history by System Organ Class (SOC) were blood and lymphatic system disorders (100%), metabolism and nutritional disorders (26.2%), gastrointestinal disorders (20%), respiratory and thoracic disorders (18.4%), psychiatric disorders and infections and infestations (15.4% each), and skin and subcutaneous disorders (12.4%).

Table 12 Medical History by System Organ Class in ≥ 5% of Patients (mITT Population)

	Assigned Ferric Maltol (N=3)	Ferric Maltol (N=31)	Ferrous Sulfate (N=30)	Total (N=65)
Medical History by System Organ Class				
Blood and lymphatic system disorders	3 (100.0)	31 (100.0)	30 (100.0)	65 (100.0)
Endocrine disorders	0	2 (6.5)	0	2 (3.1)
Eye disorders	0	0	2 (6.7)	2 (3.1)
Gastrointestinal disorders	0	8 (25.8)	5 (16.7)	13 (20.0)
Immune system disorders	0	1 (3.2)	4 (13.3)	5 (7.7)
Infections and infestations	1 (33.3)	4 (12.9)	5 (16.7)	10 (15.4)
Injury, poisoning and procedural complications	0	2 (6.5)	0	2 (3.1)
Investigations	0	5 (16.1)	1 (3.3)	6 (9.2)
Metabolism and nutrition disorders	0	8 (25.8)	9 (30.0)	17 (26.2)
Musculoskeletal and connective tissue disorders	0	2 (6.5)	0	2 (3.1)
Nervous system disorders	0	2 (6.5)	2 (6.7)	4 (6.2)
Psychiatric disorders	0	7 (22.6)	3 (10.0)	10 (15.4)
Reproductive system and breast disorders	0	3 (9.7)	1 (3.3)	4 (6.2)
Respiratory, thoracic and mediastinal disorders	1 (33.3)	6 (19.4)	5 (16.7)	12 (18.4)
Skin and subcutaneous tissue disorders	1 (33.3)	5 (16.1)	2 (6.7)	8 (12.3)

	Assigned Ferric Maltol (N=3)	Ferric Maltol (N=31)	Ferrous Sulfate (N=30)	Total (N=65)
Surgical and medical procedures	0	1 (3.2)	2 (6.7)	3(4.6)

Source: FDA analysis of ADMH dataset

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Similar treatment compliance was demonstrated between treatment groups with mean (SD) compliance rates of 88.5% (15.5), 95.9 (6.6), and 86.7(10.1) in the ferrous sulfate group, ferric maltol group, and assigned ferric maltol group, respectively.

Prior and Concomitant Medications

During the treatment phase, the most common medications (taken by at least 5% of patients) in the randomized ferric maltol treatment arm were paracetamol taken by 4 (12.7%) patients, followed by combined contraceptive pills taken by 3 (9.7%) patients, vitamin D and analogues, folic acid, and azathioprine each taken by 2 (6.5%) patients each.

Efficacy Results – Primary Endpoint

The table below summarizes the hemoglobin (Hb) concentration at baseline and Week 12 in the mITT population. In summary, both treatment groups increased hemoglobin levels from baseline to Week 12. At baseline, hemoglobin levels were similar between the ferrous sulfate group (107.1 g/L, standard deviation [SD]:8.84 g/L) and ferric maltol group (105.4 g/L, SD: 10.96 g/L), while the ferric maltol assigned infant group had descriptively lower baseline levels (98.0 g/L, SD: 8.00 g/L). At Week 12, the ferric maltol group demonstrated a 12.5 g/L change at week 12 compared to from baseline, SD: 13.89 g/L . The ferrous sulfate group demonstrated a 11.5 g/L change from baseline, SD: 13.97 g/L.

Table 13 ST10-01-305 Summary of Hb (g/L) Concentration (mITT Population)

Visit	Statistics	Ferric Maltol (N=31)	Ferrous Sulfate (N=30)	Ferric Maltol Assigned (N=3)	Total (N=64)
Hb Baseline, g/L	n	31	30	3	64
	Mean	105.4	107.1	98.0	105.8
	SD	10.96	8.84	8.00	9.95
	Median	108.0	108.0	98.0	108.0
	Min, Max	69, 118	72, 120	90, 106	69, 120
Hb Week 12, g/L	n	26	24	3	53
	Mean	117.6	118.6	115.7	117.9
	SD	7.97	10.44	6.43	8.99
	Median	118.5	120.0	113.0	119.0
	Min, Max	100, 136	94, 140	111, 123	94, 140
Change from baseline to Week 12, g/L	n	26	24	3	53
	Mean	12.5	11.5	17.7	12.3
	SD	13.89	13.97	13.61	13.72
	Median	8.5	9.0	13.0	9.0
	Min, Max	-7, 57	-7, 68	7, 33	-7, 68

Source: FDA analysis of ADSL and ADEFF1 datasets

The result for the primary endpoint, hemoglobin concentration changes from baseline to Week 12, using a mixed model for repeated measures (MMRM) is described in table below for the pediatric patients. Both treatment groups achieved improvements in hemoglobin levels. The least squares (LS) mean change from baseline to Week 12 was 12.5 g/L (standard error [SE]: 1.83) for the ferrous sulfate group and 11.0 g/L (SE: 1.68) for the ferric maltol group. The lower bound of the 96.55% confidence intervals for both groups excluded zero. Note that the 96.55% CI from Pocock spending function is used given this is an interim analysis.

Table 14 ST10-01-305 Change from baseline to Week 12 in Hb Concentration (mITT Population)

Statistics	Ferric Maltol (N=34)	Ferrous Sulfate (N=30)
Change from baseline to Week 12		
N (%)	33 (97.1)	28 (93.3)
LS mean, SE (g/L)	11.0 (1.68)	12.5 (1.83)
96.55% CI	(7.3, 14.6)	(8.6, 16.5)

Source: FDA analysis of ADSL and ADEFF1 datasets
Abbreviations: LS: least square; SE: Standard error; CI: confidence interval.
Only participants with both baseline and at least one post-baseline measurement are included. Baseline was defined as the last measurement prior to the first treatment dose of study drug.
LS means, standard errors, and confidence intervals, were from an MMRM analysis with fixed effects for treatment, visit, treatment-by-visit interaction, and baseline Hb values as a continuous covariate.

Missing Data Summary

The table below summarizes the missing data patterns across different analysis stages. At baseline, data availability was 100% for both main treatment groups and only one missing value in the ferric maltol assigned group, showing 64/65 (98.5%) overall data availability. By Week 12, the ferric maltol group showing 26/31 (83.9%) available data, and the ferrous sulfate group showing 24/30 (80.0%) available data. The ferric maltol assigned group maintained 3 out of 4 (75.0%) data availability despite the small sample size. For the primary LS means analysis, which required both baseline and at least one post-baseline measurement, 30/31(96.8%) was available for the ferric maltol group, 28/30 (93.3%) was available for the ferrous sulfate group, and 3 out of 4 (75.0%) was available for the ferric maltol assigned group. Overall, 61/65 (93.8%) of participants were included in the primary analysis.

Table 15 ST10-01-305 Missing Data Summary for Hb (ITT population)

Analysis Stage	Ferric Maltol Assigned (N=4)	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)	Total (N=65)
Baseline n (%)				
Available for analysis	3 (75.0%)	30 (100.0%)	31 (100.0%)	64 (98.5%)
Missing data	1 (25.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Week 12 n (%)				
Available for analysis	3 (75.0%)	24 (80.0%)	26 (83.9%)	53 (82.8%)

Analysis Stage	Ferric Maltol Assigned (N=4)	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)	Total (N=65)
Missing data	1 (25.0%)	6 (20.0%)	5 (16.1%)	11 (17.2%)
Primary LS Means Analysis n (%)				
Included in analysis	3 (75.0%)	28 (93.3%)	30 (96.8%)	61 (93.8%)
Excluded (missing data)	1 (25.0%)	2 (6.7%)	1 (3.2%)	4 (6.2%)

Source: FDA analysis of ADSL dataset

The table below summarizes the primary efficacy analysis with ferric sulfate and ferric maltol group results. The ferrous sulfate group demonstrated an LS mean change of 12.4 g/L (96.55% CI: 8.3, 16.4), while the ferric maltol group showed a change of 10.7 g/L (96.55% CI: 6.8, 14.6). All confidence intervals exclude zero.

Table 16 ST10-01-305 Sensitivity Analysis – Analysis of Change in Hb Concentration (ITT Population – 2 Years to 17 Years)

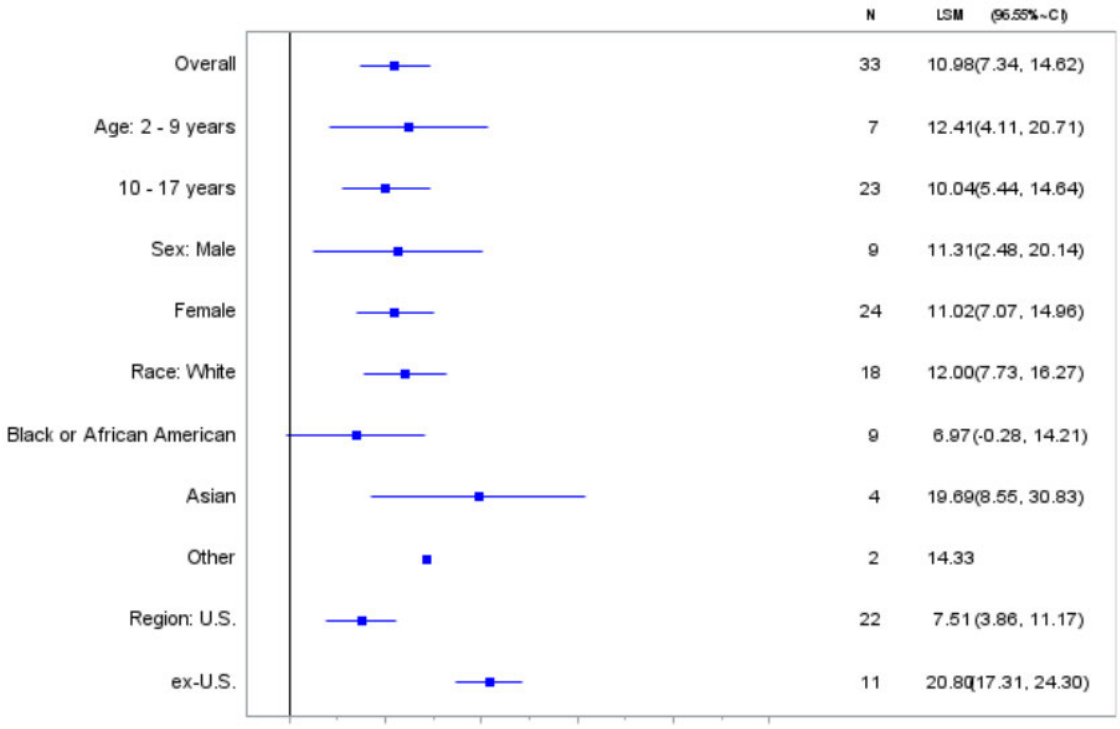
Statistics	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)
Primary LS Means Analysis		
n	28	30
LS mean (SE) (g/L)	12.4 (1.87)	10.7(1.80)
96.55% CI	(8.3, 16.4)	(6.8, 14.6)

Source: FDA analysis of ADSL and ADEFF1 datasets
Only participants with both baseline and at least 1 post-baseline measurement are included. Baseline was defined as the last measurement prior to the first treatment dose of study drug.
LS means, standard errors, confidence intervals, and p-values (which are <0.0001 compared with zero for individual drug arm) are from a MMRM analysis with fixed effects for treatment, visit, and treatment-by-visit interaction, and baseline values as a continuous covariate.

Subgroup Analysis

The figure below presents a forest plot showing the change in Hb concentration from baseline at Week 12 in the ferric maltol treatment group (blue squares) across various demographic subgroups, with least square means (LSM) and 96.55% confidence intervals displayed. Subgroup analyses were performed by age, sex, race, and region for the primary endpoint. The overall analysis shows ferric maltol achieving a LSM of 11.0 g/L (96.55% CI: 7.3, 14.6) in the mITT population that included both randomized and assigned patients to ferric maltol group(N=33). These results from the subgroup analyses were generally consistent across the different subgroups, no outliers observed. Only the "Black or African American" racial subgroup, which has a small sample size (n=9), had a 96.55% confidence interval that crossed zero. These results should be interpreted with caution considering the small sample size.

Figure 7 ST-10-01-305 Subgroup Analysis for Change in Hb Concentration – Ferric Maltol



Source: FDA analysis of ADSL, ADEFF1, and DM datasets
Only participants who were randomized and assigned to ferric maltol treatment group with both baseline and at least 1 post-baseline measurement are included. Baseline was defined as the last measurement prior to the first treatment dose of study drug.

The analysis of patients aged 10 to less than 18 years in the ferric maltol group showed an LSM increase of 10.0 g/L (96.55% CI: 5.4, 14.6), which included 23 randomized patients (69.7% of the ferric maltol pediatric population in the overall mITT population). This group yielded similar results to the overall pediatric population.

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

The table below summarizes the observed changes in iron markers from baseline to Week 12 in the mITT population for ferrous sulfate (N=30), ferric maltol (N=31), and a small infant group that assigned to the ferric maltol arm (N=3). For ferritin, the ferrous sulfate group demonstrated a mean increase of 20.6 µg/L (SD: 30.97), ferric maltol group had a mean increase of 8.1 µg/L (SD: 1.06).

Ferric maltol group achieved a mean increase of 5.77 µmol/L (SD: 8.518) in iron level, and the ferrous sulfate group achieved a mean increase of 3.64 µmol/L (SD: 8.911). Ferric maltol group showed a mean increase of 7.7% (SD: 10.14%) for transferrin saturation, and ferrous sulfate showed a mean increase of 6.5% (SD: 12.39%).

Table 17 ST-10-01-305 Summary of Selected Iron Markers (mITT Population)

Efficacy Endpoints	Statistics	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)	Ferric Maltol Assigned (N=3)	Total (N=64)
Ferritin (µg/L)	n	28	31	3	62
	Mean	20.6	8.1	6.3	13.6
	SD*	30.97	11.06	8.74	22.97
	Median	3.5	5.0	4.0	5.0
	Min, Max*	19, 92	-11, 34	-1, 16	-19, 92
Iron (µmol/L)	n	28	31	3	62
	Mean	3.64	5.77	1.07	4.58
	SD	8.911	8.518	0.577	8.519
	Median	1.70	5.00	1.40	3.30
	Min, Max	-13.0, 33.3	-13.4, 31.3	0.4, 1.4	-13.4, 33.3
Transferrin saturation (%)	n	28	31	2	61
	Mean	6.5	7.7	2.0	7.0
	SD	12.39	10.14	0.00	11.03
	Median	3.0	5.0	2.0	4.0
	Min, Max	-17, 45	-16, 36	2, 2	-17, 45

Source: FDA analysis of ADSL and ADEFF1 datasets
Abbreviations: SD: Standard Deviation, Min: Minimum, Max: Maximum

The table below summarizes the proportion of patients achieving normal hemoglobin concentrations at Week 12, defined as responders. All three infant patients that were assigned to the ferric maltol group achieved response (100%). The ferrous sulfate group achieved a 53.3% response rate with 16 out of 30 patients reaching normal hemoglobin ranges. The ferric maltol group achieved a 38.7% response rate (12 out of 31 patients).

Table 18 ST-01-305 Summary of Hb Concentration Responders at Week 12 (mITT Population)

Category	Statistics	Ferric Maltol (N=31)	Ferrous Sulfate (N=30)	Ferric Maltol Assigned (N=3)
Responder	n (%)	12 (38.7)	16 (53.3)	3 (100.0)

Non-responder*	n (%)	61.3)	14 (46.7)	19 0 (0.0)

Source: FDA reviewer analysis of ADSL and ADEFF1 datasets
Patients with a missing Week 12 value were assumed to be non-responders.

Dose/Dose Response

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

Durability of Response

In Study ST10-01-305, patients were continued on treatment for up to 12 weeks. The increase in hemoglobin was demonstrated from baseline to Week 12 demonstrating durable effect of treatment.

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.

7.2.2. Conclusion on Efficacy

The efficacy of ferric maltol for the treatment of iron deficiency was evaluated in 24 patients ages 10 to less than 18 years (age range 10-17 years; 4 males and 20 females; with iron deficiency who received aged-based dosing of ferric maltol twice daily in Study ST-10-01-305. Patients aged 10-11 years received 15 mg twice daily while patients 12 to less than 18 years received 30 mg twice daily. Although Study ST-10-01-305 was a randomized trial (ferric maltol versus ferrous sulfate), the statistical methodology of the trial was designed to assess efficacy based on evaluation of the mean change in hemoglobin at Week 12 from baseline in the ferric maltol arm only. While Study ST-10-01-305 evaluated 65 patients with iron deficiency anemia, 34 of whom received ferric maltol, the Applicant is currently seeking an indication for pediatric patients aged 10 years and older as the available formulation at this time is the approved 30 mg capsule. The Applicant intends to submit a new drug application and expand the indication to pediatric patients (b) (4) once the oral suspension is available for commercial use.

The efficacy findings in participants aged 10 to less than 18 years (n=24) are as follows:

- The baseline Hb concentration (g/dL) was 10.73 (SD 0.89) in the 10 to < 18 years (n=24) and the mean change from baseline to week 12 was 1.10 (SD 1.06).

- Mean ferritin levels at baseline were 11.4 mcg/L [SD 10.06] and the mean ferritin levels at Week 12 were 20 mcg/L [SD 13.51] with a mean overall improvement of 8.6 mcg/L [SD 10.29].
- There was a higher mean change in hemoglobin from baseline at Week 12 in participants who received ferric maltol 30 mg twice daily (n=21) compared to those that received ferric maltol 15 mg twice daily (n=3) (1.23 vs. -0.15 g/dL) supporting the use of 30 mg twice daily (capsule formulation) dose for pediatric patients aged 10 years and older.
- The oral suspension was utilized in the pediatric Study ST10-01-305, making the bridge between suspension and capsule formulations critical for approval of capsules for pediatric subjects in the current submission. Given that the capsule formulation demonstrates higher exposure levels, efficacy is adequately bridged for using the capsules in pediatric subjects greater than 10 years of age.
- The pediatric dose selection was grounded on extensive adult clinical data with ferric maltol. The approved adult dose of 30 mg twice daily (BID) was established through Phase 3 studies demonstrating efficacy and safety in adults with iron deficiency anemia (IDA) associated with inflammatory bowel disease (IBD) and chronic kidney disease (CKD).
- Efficacy was also based on partial extrapolation from adequate and well controlled studies in the adult population.
- An observed increase in hemoglobin from baseline at 12 weeks is sufficient to demonstrate clinical benefit in pediatric patients with iron deficiency.

8. Review of Safety

8.1. Safety Review Approach

The safety review was primarily based on Study ST-10-01-305. Adverse events were analyzed based on data review comparing the randomized ferric maltol and ferrous sulfate treatment arms. Data from Study ST-10-01-103 was also reviewed and summarized in this section. Further details regarding respective study design and protocols are provided in section 5.1 of this review.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The treatment period for the study was 12 weeks (84 days). Study drug exposure was

similar across treatment groups. The mean (±SD) days of exposure to study drug were 86.0 (±1.7) days, 82.8 (±11.6) days, and 77.7 (±20.5) days for the assigned ferric maltol group, ferric maltol group, and ferrous sulfate group, respectively.

Table 19 ST-10-01-305 Duration of Exposure (Safety Population)

	Ferric Maltol (N=31)	Ferrous Sulfate (N=30)	Assigned Ferric Maltol* (N=3)	Total (N=64)
Duration of treatment, days **Mean (SD)** **Median (Min, Max)**	82.8 (11.6) 85.0 (45.0, 103.0)	77.7 (20.5) 84.5 (2.0, 91.0)	86.0 (1.7) 85.0 (85.0, 88.0)	80.5 (16.3) 85.0 (2.0, 103.0)
Patients treated, by duration				
≤ 6 days	0	1 (3.3)	0	1 (1.6)
7 – 27 days	0	0	0	0
≥ 84 days	25 (80.6)	22 (73.3)	3 (100.0)	50 (78.1)
28 - 55 days	2 (6.5)	3 (10.0)	0	5 (7.8)
56 - 83 days	3 (9.7)	4 (13.3)	0	7 (10.9)

Source: FDA reviewer analysis of ADEX dataset

8.2.2. Relevant characteristics of the safety population:

Safety population demographic characteristics and baseline characteristics for ST-10-01-305 are summarized in Section 6.1.2.

8.2.3. Adequacy of the safety database:

Ferric maltol was approved in 2019 for the treatment of IDA in adult patients; the safety database of ferric maltol in adult patients is adequate. However, there is limited clinical experience in the pediatric population. The Applicant's safety database of ferric maltol in pediatric patients available in the NDA consists of a total of 70 subjects, 33 subjects from study ST-10-01-305, and 37 subjects from ST-10-01-305, an open-label PK study evaluating ferric maltol in children aged 10 to less than 18 years and is acceptable for the pediatric population for proposed indication.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall quality of data was adequate to allow safety evaluation. No major concerns regarding data integrity were identified during the safety review.

8.3.2. Categorization of Adverse Events

In Study ST-10-01-305, AEs were reported using the verbatim term and coding using MedDRA terminology version 24.0. Mapping of the verbatim AE terms to MedDRA Preferred Term and System Organ Class (SOC) was acceptable. The intensity of AEs was graded according to the National Cancer Institute Common Technology Criteria for Adverse Events (NCI-CTCAE) criteria.

8.3.3. Routine Clinical Tests

In Study ST-10-01-305, vital signs, hematology, and chemistry laboratory parameters, and iron indices were obtained during screening, Days 0, 7 (vital signs only) 28 (no clinical chemistry), and 84.

8.4. Safety Results

The table below summarizes the overall safety results of Study ST-10-01-305. The overall incidence of TEAEs was the same in the randomized ferric maltol and ferrous sulfate arms. No deaths were reported in the study. One SAE deemed unlikely related to study drug occurred in the ferric maltol assigned arm. Most of the TEAEs were mild in severity.

Table 20 ST-10-01-305 Overall Summary of Safety (Safety Population)

	Ferric Maltol (N=31)	**Ferrous Sulfate (N=30)**	**Ferric Maltol Assigned (N=3)**
TEAEs	9 (30.0)	9 (30.0)	2 (66.7)
Any AEs by maximum severity	7 (23.3)	7 (23.3)	2(66.7)

	Ferric Maltol (N=31)	Ferrous Sulfate (N=30)	Ferric Maltol Assigned (N=3)
Mild **Moderate** **Severe**	2 (6.5) 0 (0.0)	2 (6.7) 0 (0.0)	1(33.3) 0(0.0)
TESAEs	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs considered related to study treatment	2 (6.5)	4 (13.3)	1 (33.3)
TEAEs leading to any study drug discontinuation	0 (0.0)	1 (3.3)	0 (0.0)
Deaths	(0.0)	(0.0)	(0.0)

Source: FDA analysis of ADSL and ADAE datasets
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.

8.4.1. Deaths

No deaths were reported in study ST-10-01-305.

8.4.2. Serious Adverse Events

In Study ST-01-10-305, one serious adverse event of wheezing occurred in a 15-month-old participant with a history of bronchiolitis and eczema treated with ferric maltol requiring hospitalization for treatment with corticosteroids and nebulizer treatments.

Reviewer comment: The serious adverse event of wheezing was likely related to underlying bronchiolitis. Wheezing or symptoms associated with anaphylaxis are not known adverse events related to oral use of iron products to include ferric maltol use.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No adverse events leading to drug discontinuation were reported in ferric maltol arms in Study ST-10-01-305.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

The overall incidence of TEAEs was similar between the randomized ferric maltol and ferrous sulfate arms (30.0% vs. 29.0%, respectively). The most frequently reported TEAEs (>5%) in the ferric maltol arm were nausea and gastroenteritis.

Table 21 ST-10-01-305 Treatment-Emergent Adverse Events that Occurred in ≥ 1 Patients

	Ferric Maltol (N=31)	Ferrous Sulfate (N=30)	Ferric Maltol Assigned (N=3)
All			
Infections and Infestations			
Ear infection	1 (3.2)	0 (0.0)	0 (0.0)
Gastroenteritis	2 (6.4)	0 (0.0)	0 (0.0)
Conjunctivitis	0 (0.0)	0 (0.0)	1 (33.3)
Respiratory, thoracic, and mediastinal disorders			
Cough	1(3.2)	0(0.0)	1 (33.3)
Gastrointestinal disorders			
Nausea	2 (6.5)	3 (10.0)	0 (0.0)
Abdominal pain	1 (3.2)	1 (3.3)	0(0.0)
Vomiting	1 (3.2)	1 (3.3)	0(0.0)
Defecation urgency	1 (3.2)	0(0.0)	0(0.0)
Diarrhea	1 (3.2)	0(0.0)	1 (33.3)
Discolored feces	1 (3.2)	0(0.0)	0(0.0)
Nervous system disorders			
Dizziness	1 (3.2)	0(0.0)	0(0.0)
Headache	1 (3.2)	0(0.0)	0(0.0)

Source: FDA analysis of ADAE dataset
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.

Treatment-Emergent AEs that were considered study treatment related occurred in 16.1% and 16.7% in the ferric maltol and ferrous sulfate arms, respectively. The most common reported TEAEs considered related to study treatment in the ferric maltol arm (≥ 1%) were nausea abdominal pain, vomiting, defecation urgency, diarrhea, discolored feces, dizziness, and headache.

Table 22 ST-10-01-305 TEAEs Assessed as Drug-Related (Safety Population)

	Ferric Maltol (N=31)	Ferrous Sulfate (N=30)	Ferric Maltol Assigned (N=3)
All	5/31 (16.1)	5/30 (16.7)	1 (33.3)
Gastrointestinal disorders			
Nausea	2 (6.5)	3 (10.0)	0 (0.0)
Abdominal pain	1 (3.2)	1 (3.3)	0(0.0)
Vomiting	1 (3.2)	1 (3.3)	0(0.0)
Defecation urgency	1 (3.2)	0(0.0)	0(0.0)
Diarrhea	1 (3.2)	0(0.0)	1 (33.3)
Discolored feces	1 (3.2)	0(0.0)	0(0.0)
Nervous system disorders			
Dizziness	1 (3.2)	0(0.0)	0(0.0)
Headache	1 (3.2)	0(0.0)	0(0.0)

Source: FDA analysis of ADAE dataset
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.

8.4.5. Laboratory Findings

There were no clinically significant changes in chemistry parameters in any treatment group.

8.4.6. Vital Signs

In Study ST-10-01-305, there were no clinically relevant changes from baseline for vital signs (systolic and diastolic blood pressure, heart rate or temperature).

8.4.7. Electrocardiograms (ECGs)

In Study ST-10-01-305, there were no clinically meaningful mean changes from baseline in ECG parameters and no subjects had clinically significant abnormal ECG results.

8.4.8. Immunogenicity

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

8.5. Analysis of Submission-Specific Safety Issues

The safety profile of maltol was reviewed in the original NDA submission for the adult approval. 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. Refer to the clinical pharmacology sections of this review for additional details regarding the data reviewed to support the safety of maltol in the formulation of ferric maltol in pediatric patients > 10 years of age.

8.6. Safety Analyses by Demographic Subgroups

Table 23 ST-10-01-305: Overall Summary of Safety by Age Group (Safety Population)

	Ferric Maltol (N=31)		Ferrous Sulfate (N=30)	
	2 to 9 years (n=7)	10 to 17 years (n=24)	2 to 9 years (n=7)	10 to 17 years (n=23)
Deaths	0	0	0	0
TESAEs	0	0	0	0
TEAEs	2 (28.5%)	5 (20.8%)	0	3 (13.0%)
Grade 3 or 4 TEAEs	0	0	0	0
TEAEs leading to any study drug discontinuation	0	0	0	0

Source: FDA analysis of ADAE dataset
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.

Table 24 ST-10-01-305: Overall Summary of Safety by Gender (Safety Population)

	Ferric Maltol (N=31)		Ferrous Sulfate (N=30)	
	Male (n=8)	Female (n=23)	Male (n=8)	Female (n=22)
Deaths	0	0	0	0
TESAEs	0	0	0	0
TEAEs	1 (12.5%)	6 (26.1%)	0	3 (13.6%)
Grade 3 or 4 TEAEs	0	0	0	0

TEAEs leading to any study drug discontinuation	0	0	0	0

Source: FDA analysis of ADAE dataset

Reviewer Comment: The results above should be interpreted with caution given the low number of events and small number of patients in the subgroups as summarized in the tables above.

Safety Summary of ST-10-01-103

ST-10-01-103 was a phase 1, randomized, open-label, parallel group, multicenter pediatric PK study. Eligible subjects aged 10 to 17 years who were randomized at a ratio of 1:1:1 to 1 of 3 doses of ferric maltol (7.8 mg, 16.6 mg, or 30 mg BID) for 9 days (Days 1 to 9); and a final dose was to be administered on the morning of Day 10. During the treatment period (Days 1 to 10), subjects were to visit the site for PK blood sampling sessions on Days 1 and 10.

Thirty-seven subjects aged 10-17 years received ferric maltol during the 10-day treatment period; 12 subjects in the 7.8 mg dose group, 13 subjects in the 16.6 mg dose group, and 12 subjects in the 30 mg dose group. Rates of TEAEs were generally similar across dose groups, (58.3% in 7.8 mg dose group, 46.2% in 16.6 mg dose group, and 58.3% in 30 mg dose group). The most frequently reported TEAEs were headache (18.9%), feces discolored (13.5%), fatigue (10.8%), diarrhea, and dizziness (8.1% subjects each), and nausea, vomiting, and cough (5.4% of subjects each). One TEAE of tonsilitis in one subject in the 16.6 mg group lead to drug discontinuation. There were no SAEs or death reported in the study.

The safety findings of ST-10-01-103 are consistent with findings observed in ST-10-01-305 and the adult population.

8.7. Specific Safety Studies/Clinical Trials

This section is not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Carcinogenicity studies were not conducted.

8.8.2. Human Reproduction and Pregnancy

The current label for ferric maltol contains the following in the pregnancy subsection of the Use in Specific Populations section:

Ferric Maltol is not absorbed systemically as an intact complex following oral administration, and maternal use is not expected to result in fetal exposure to the drug.

8.8.3. Pediatrics and Assessment of Effects on Growth

Assessments of effects on growth were not conducted.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no incidences of overdose reported during ST-10-01-305 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.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There has been no commercial exposure of ferric maltol in the pediatric population as of submission of the annual report covering the period from 25 July 2024 to 24 July 2025. No new safety signals were reported from review of the Periodic Adverse Drug Experience Report for Accrufer from 19 August 2024 to 8 August 2025.

8.9.2. Additional Safety Issues From Other Disciplines

Use of capsule formulation in 10 to less than 18-year age group and 30 mg twice daily dosing for 10-11 year age group

The Applicant is seeking approval for the use of the adult-approved capsule formulation to be administered on an empty stomach to pediatric patients 10 years and older as per the product insert; however, the oral suspension formulation was used to dose all pediatric patients in Study ST-10-01-305. Furthermore, the baseline corrected serum iron levels was approximately one-third for the suspension compared to the capsule both administered under fasting conditions in Study ST-10-01-104 corresponding to a greater exposure to peak serum iron levels (approximately 3-fold higher) for the capsule when compared to the clinical trial experience. Additionally, the Applicant proposed with this supplement submission to administer a higher dose of 30 mg twice daily in patients 10 to 11 years old while patients in Study ST-10-01-305 in this age group received 15 mg twice daily.

An Information Request was submitted to the Applicant to provide rationale justifying the safety for the expected higher serum iron levels in pediatric patients, to clarify the rationale to administer the product in a fasted state to pediatric patients, and to provide justification for recommendation of a 30 mg twice daily capsule dose the 10-11 year age group.

Reviewer Comment: *The Applicant provided rationale for recommending a 30 mg twice daily capsule in the 10-11 year age group based on hemoglobin efficacy data and iron exposure PK data (see Clinical Pharmacology review for details). In summary, the mean rise in hemoglobin at Week 12 was comparable in patients aged 2-9 years (17.5 g/L) receiving 15mg twice daily to patients aged 12 to less than 18 years (12.3g/L) receiving 30mg twice daily . However, the mean rise in patients aged 10-11 years receiving 15mg twice daily was lower (-1.5g/L). The Applicant states the hemoglobin response difference is likely explained by body weight, body composition, and iron demand in the slightly older age group. From a safety perspective, although safety data for 30 mg twice daily exposure (capsule formulation) in 10-11 year subgroup is limited to one subject in Study ST-10-01-103 who received treatment for 10 days, the subject did not have any significant adverse events. Rates of adverse events were similar among patients who received 30 mg twice daily compared to subjects who received lower doses across Studies ST-10-01-103 and ST-10-01-305. Furthermore, there was no evidence of maltol accumulation in pediatric subjects leading to toxicity. From a clinical standpoint, it is reasonable to allow 10 and 11 years with iron deficiency to receive the 30 mg twice daily dosing.*

8.10. Integrated Assessment of Safety

The safety evaluation of ferric maltol in pediatric patients with ID was primarily based on a total of 65 patients (ferric maltol: 31, ferrous sulfate: 30, ferric maltol assigned: 4) who participated in Study ST-10-01-305. In Study ST-10-01-305, subjects 1 month to less than 2 years received ferric maltol at 0.6 mg/kg/dose twice daily (BID), subjects 2 to 11 years received 15 mg twice daily, and subjects 12 to less than 18 years received 30 mg twice daily. Subjects randomized to receive ferrous sulfate received 3 mg/kg/dose of elemental iron twice daily. The safety findings of Study ST-10-01-305 were as follows:

- No deaths were reported.
- No adverse events led to study drug discontinuation in ferric maltol arm.
- One patient in the ferric maltol assigned arm (1 month to < 2 years) experienced a serious adverse event of wheezing unlikely to be attributed to ferric maltol use.
- The overall incidence of TEAEs was similar between the randomized ferric maltol and ferrous sulfate arms (30.0% vs. 29.0%, respectively). The most frequently reported TEAEs (>5%) in the ferric maltol arm were nausea and gastroenteritis.
- TEAEs that were considered study treatment related occurred in 16.1% and 16.7% in the ferric maltol and ferrous sulfate arms, respectively. The most common reported TEAEs considered related to study treatment in the ferric maltol arm (≥ 1%) were nausea abdominal pain, vomiting, defecation urgency, diarrhea, discolored feces,

dizziness, and headache.

Additional safety data from Study ST-10-01-103 did not reveal new safety signals. The safety profile observed in the pediatric Studies ST-10-01-305 and ST-10-01-103 were similar to that observed in the adult population.

Advisory Committee Meeting and Other External Consultations

Advisory committee or any other external consultations were not required for this sNDA.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

The following are recommended major changes to the Accrufer prescribing information based on this review:

1 INDICATIONS AND USAGE: Revise the indication to treatment of iron deficiency to include pediatric patients aged 10 years and older

2 DOSAGE AND ADMINISTRATION: Addition of route of administration (oral) and timing of administration (1 hour before or 2 hours after meals).

6 ADVERSE REACTIONS: Add brief description of pediatric patients aged 10 years and older in Study ST-10-01-305 and summarizing safety profile in pediatric patients consistent with the adult population.

8 USE IN SPECIFIC POPULATIONS: Add that the safety and effectiveness of Accrufer for the treatment of iron deficiency in pediatric patients aged 10 years and older established by evidence from adequate and well-controlled studies of Accrufer in adults with additional data from an adequate and well-controlled study conducted in pediatric patients aged 10 years and older.

12 CLINICAL PHARMACOLOGY: Added summary of pediatric pharmacokinetic data.

14 CLINICAL STUDIES: Revised efficacy results of Study ST-10-01-305 to only include subgroup analysis in pediatric patients aged 10 to 17 years because the proposed indication is for pediatric patients 10 years of age and older.

10. Risk Evaluation and Mitigation Strategies (REMS)

REMS is not required for this sNDA.

11. Postmarketing Requirements and Commitments

No clinical PMCs or PMRs are necessary for this sNDA.

This submission fulfills the pediatric studies requirements for PMR 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.

12. Appendices

12.1. Protocol Amendments

Table 25 ST-10-01-305 Protocol Amendments

Date	Amendment(s)
May 18, 2021	Protocol Amendment 1 • Addition of baseline pre-dose urine sample during pre-assignment PK phase.
October 28, 2021	Protocol Amendment 2 • Exclusion criteria include patients with history of active peptic ulcer disease.
November 3, 2021	Protocol Amendment 3 • After review by investigator and medical monitors, urine analysis to evaluate clearance of maltol and maltol glucuronide to not be

	performed after first 6 subjects screened in 1 month to less than 2 years group perform pre-assignment PK phase and demonstrate adequate elimination. • Allow for over-the-counter supplements/multivitamin preparations including those that contain iron; however, subjects should keep same dose throughout the study. • Clarification that the use of any other single agent prescribed iron medication may be discontinued prematurely during the study.
March 14, 2023	Protocol Amendment 4 • After 25 subjects aged 2-17 have been randomized 1:1 to receive ferric maltol or ferrous sulfate oral suspension, subjects thereafter will be assigned to receive ferric maltol oral suspension. • Treatment assignment from 1:1 to 2:1 with reduction in subjects in ferrous sulfate arm from 49 to 25 subjects due to slow recruitment and to allow PK sub study to complete closer to time full study would complete. • Change in hemoglobin concentration from baseline to Week 12 moved from secondary to primary endpoint.
July 6, 2023	Protocol Amendment 5 • Addition of potential interim analysis and associated stopping rules. • Removal of blood sample to evaluate clearance of maltol and maltol glucuronide after data demonstrated urine analysis satisfactory surrogate for plasma clearance.

Reviewer Comment: *ST-10-01-305 underwent changes between planning and execution due to recruitment difficulty and high screen failure. In the initial approach outlined in Protocol Version 1 from March 2021, prior to study initiation in November 2021, the Applicant indicated that the study would be analyzed using descriptive statistics only, with efficacy demonstrated if the lower bound of the 95% confidence interval for hemoglobin increase at 12 weeks compared to baseline was above zero, assuming a standard deviation of 1.2 g/dL or lower and a true mean change of at least 0.5 g/dL. By Protocol Version 4.1 dated July 2023, before study completion in June 2024, the Applicant had added an interim analysis with Pocock spending function to test for significance of hemoglobin increase in the ferric maltol arm from baseline to Week 12 compared with zero, with the provision that if fewer than 91 subjects total had been randomized when 32 ferric maltol subjects completed treatment and the results were significant, recruitment would stop. The study results included in this review were based on the interim analysis.*

12.2. List of PMRs/Deferred Pediatric Assessments

Table 26 Deferred Pediatric Assessments Issued as Postmarketing Requirements for NDA 212320

PMR Number	Description
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.
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.
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.
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.
3667-5	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.

12.3. References

1. Williams AMea. Anemia Prevalence: United States, August 2021- August 2023. 2024:519.
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3. WHO. WHO Guidelines Approved by the Guidelines Review Committee. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: World Health Organization
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7. Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. Am J Hematol. 2016;91(1):31-8.

8. Pantopoulos K. Oral iron supplementation: new formulations, old questions. Haematologica. 2024;109(9):2790-801.

12.4. Financial Disclosure

Covered Clinical Study (Name and/or Number): Protocol ST-10-01-305, ST10-01-103, ST10-01-104

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 21 for 305, 9 for 103, and 1 for 104		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/

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