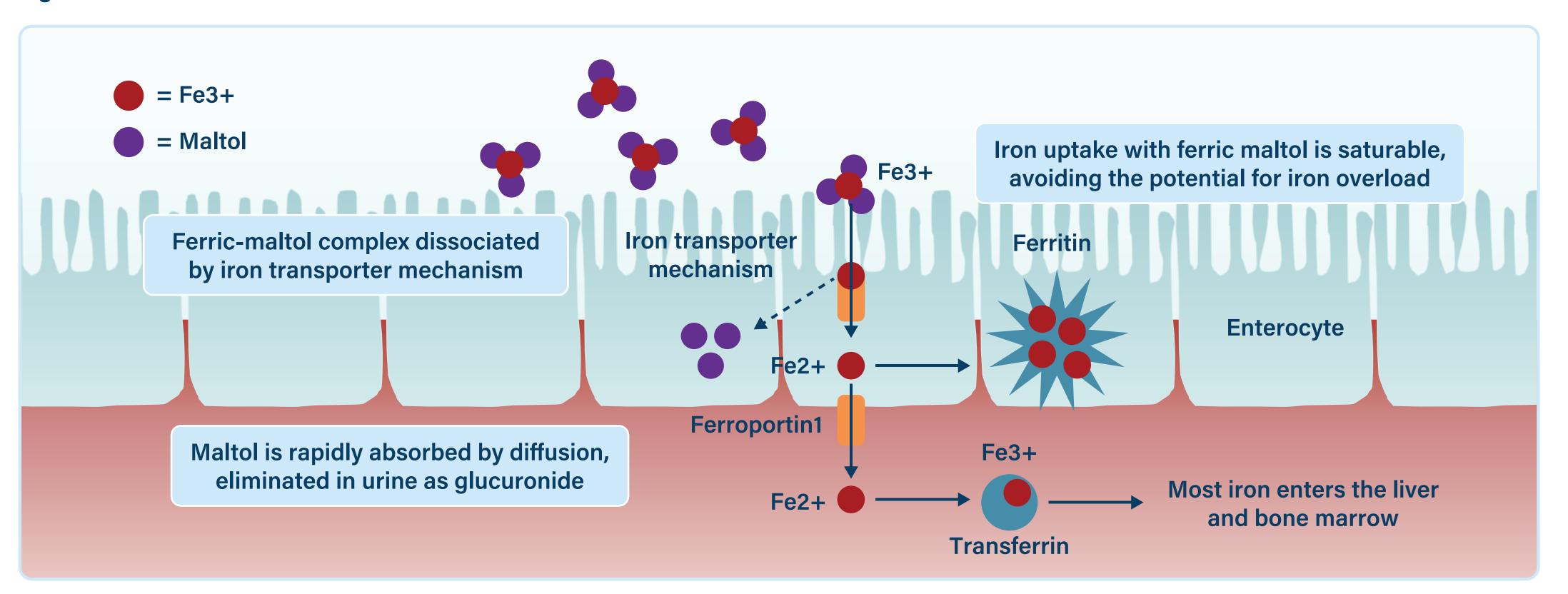
# Efficacy And Safety Of A Novel Oral Iron (Ferric Maltol) In Children And Adolescents; A Randomized, Multicenter, Open-Label, Active Comparator Study

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#### INTRODUCTION

- Ferric maltol is a novel oral iron complex engineered to address the limitations of traditional ferrous therapies. It delivers ferric iron (Fe³) chelated with high affinity to three maltol ligands — a naturally occurring compound with an established safety profile.¹ This formulation enhances absorption while minimizing mucosal toxicity compared to ferrous salts (Figure 1).1 Unlike ferrous sulfate, ferric maltol does not significantly alter the gut microbiome, as demonstrated in human fecal analyses.<sup>2</sup>
- Ferric maltol is approved by multiple regulatory agencies, including the European Medicines Agency and the US Food and Drug Administration, and is commercially available across Europe, Canada, and the United States for the treatment of iron deficiency in adults, regardless of anemia status.<sup>3,4</sup>

#### Figure 1. Ferric maltol - Mechanism of Action



From August 2021 to August 2023, iron deficiency anemia (IDA) affected 9% of US individuals ≥2 years. Prevalence was higher in females (13%) than in males (6%), highest among Black populations (22%), and decreased with income (14% at <130% of the poverty level vs 6% at ≥350%).<sup>5,6</sup> Without correction, IDA in early life is associated with impaired physical growth and lasting cognitive and behavioral deficits.<sup>7,8</sup> Even in the absence of

anemia, mild iron deficiency has been linked to reduced academic performance in school-aged children.9,10,11 Oral iron is the standard treatment for pediatric IDA,5,11,13 but often poorly tolerated due to GI side effects,8-10 especially with ferrous sulfate, leading to poor adherence due to unabsorbed iron generating oxidative stress, mucosal injury, and microbiome disruption.<sup>5,13-16</sup>; while IV iron is an option for intolerant cases, safety concerns and access issues limit use in children. 10,11,16,17

These challenges highlight the need to trial the use of ferric maltol in pediatric populations.

- > This study reports the first randomized controlled trial to evaluate the safety, efficacy, and tolerability of age-appropriate doses of ferric maltol in pediatric patients — infants, children, and adolescents — with IDA. Primary endpoints were safety, gastrointestinal tolerability, treatment-emergent adverse events (TEAEs), and hemoglobin (Hb) response to ferric maltol over 12 weeks in children aged 1 month to 17 years with IDA. In patients aged 2–17 years, outcomes were compared with ferrous sulfate.
- Secondary endpoints were changes in iron markers at Weeks 4 and 12 and patient-reported outcomes on acceptability, palatability, and ease of use.

# **METHODS**

- This phase 3, multicenter, randomized trial (NCT05126901) at 23 US/UK sites compared ferric maltol suspension with ferrous sulfate liquid, with IRB/IEC approval.
- The 12-week open-label study randomized, using computer-randomized permutation, children aged 2-17 years 1:1 to ferric maltol suspension or ferrous sulfate liquid.
- Eligible patients were children aged 1 month to 17 years with IDA, defined by age and sex-specific Hb thresholds: <11.0 g/dL (1 month-<5 years), <11.5 g/dL (5-<12 years), <12.0 g/dL (12 years and females ≥13), and <13.0 g/dL (males ≥13). Ferritin was required to be  $<30 \mu g/L$ , or  $<50 \mu g/L$  with Transferrin Saturation (TSAT) < 20%.
- Infants aged 1 month to <2 years were recruited into an open-label ferric maltol arm for PK assessment. After individual confirmation of maltol metabolism and no accumulation, the infants continued as patients in a ferric maltol open label treatment arm (referred to as the assigned ferric maltol group).

Dosing schedule					
Age	Dose / Frequency	Suspension Equivalent			
Treatment - Ferric mal	tol oral suspension				
1 month - <2 years	0.6 mg iron equivalent/kg/dose, BID	0.1 mL/kg/dose			
2-11 years	15 mg iron equivalent per dose, BID	2.5 mL per dose			
12-17 years	30 mg iron equivalent per dose, BID	5 mL per dose			
Treatment - Ferrous sulfate oral liquid					
2-17 years	3 mg iron equivalent/kg/dose, BID	0.12 mL/kg/dose			
BID = twice daily					

Palatability, ease of use and acceptability assessment included the use of a 5-point Facial Hedonic Scale, with ratings provided by children or, for younger participants, by parents or clinicians.

# CONCLUSION

> Ferric maltol oral suspension improved Hb and iron stores significantly and was well tolerated across the full pediatric age range (1 month to 17 years), confirming its safety and efficacy with the studied dosing regimen and supporting its role as a well-tolerated and potentially more palatable alternative to ferrous sulfate.

# RESULTS

#### Patient Demographics

Demographics were similar across groups (Table 1). Most infants were female (75%) and Hispanic/Latino (50%), while most aged 2–17 years were female (73.8%), White (55.7%), and not Hispanic/Latino (59.0%).

#### **Table 1. Patient Characteristics at Baseline**

Characteristic	Ferric Maltol Assigned (N=4)	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)	Randomized Total (N=61)
Age (months/years)	Months	Years	Years	Years
n	4	30	31	61
Mean (SD)	13 (2.71)	12.3 (4.63)	12.8 (3.80)	12.6 (4.2)
Sex, n (%)				
Female	3 (75.0)	22 (73.3)	23 (74.2)	45 (73.8)
Male	1 (25.0)	8 (26.7)	8 (25.8)	16 (26.2)
Childbearing potential, n (%)				
Yes	0 (0.0)	17 (77.3)	18 (78.3)	35 (77.2)
No	3 (100.0)	5 (22.7)	5 (21.7)	10 (21.7)
Ethnicity, n (%)				
Hispanic or Latino	2 (50.0)	12 (40.0)	13 (41.9)	25 (41.0)
Not Hispanic or Latino	1 (25.0)	18 (60.0)	18 (58.1)	36 (59.0)
Not reported	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race				
White	1 (25.0)	16 (53.3)	18 (58.1)	34 (55.7)
Black or African American	0 (0.0)	11 (36.7)	9 (29.0)	20 (32.8)
Asian	1 (25.0)	3 (10.0)	3 (9.7)	6 (9.8)
Other	2 (50.0)	0 (0.0)	1 (3.2)	1 (1.6)

The reported medical history suggests that patients had a range of medical backgrounds and disease types (Table 2).

# Table 2. Baseline Medical History by SOC for All Enrolled Patients

System Organ Class	Ferrous Sulfate (N=30) n (%)	Ferric Maltol (N=31) n (%)	Ferric Maltol Assigned (N=4) n (%)	Total (N=65) n (%)
Any medical history	30 (100.0)	31 (100.0)	4 (100.0)	65 (100.0)
Blood and lymphatic system disorders	30 (100.0)	31 (100.0)	4 (100.0)	65 (100.0)
Metabolism and nutrition disorders	9 (30.0)	8 (25.8)	0 (0.0)	17 (26.2)
Gastrointestinal disorders	5 (16.7)	8 (25.8)	0 (0.0)	13 (20.0)
Respiratory, thoracic, and mediastinal disorders	5 (16.7)	6 (19.4)	1 (25.0)	12 (18.5)
Infections and infestations	5 (16.7)	4 (12.9)	1 (25.0)	10 (15.4)
Psychiatric disorders	3 (10.0)	7 (22.6)	0 (0.0)	10 (15.4)
Skin and subcutaneous tissue disorders	2 (6.7)	5 (16.1)	1 (25.0)	8 (12.3)
Investigations	1 (3.3)	5 (16.1)	0 (0.0)	6 (9.2)
Immune system disorders	4 (13.3)	1 (3.2)	0 (0.0)	5 (7.7)
Nervous system disorders	2 (6.7)	2 (6.5)	0 (0.0)	4 (6.2)
Reproductive system and breast disorders	1 (3.3)	3 (9.7)	0 (0.0)	4 (6.2)
% = 100 × n/N.  Medical history reported terms were coded using the MedDRA Version 24.0			•	•

# RESULTS

#### Efficacy – Hb changes at Week 4 & Week 12

- After 32 subjects randomized to ferric maltol had completed the treatment period, an interim analysis for efficacy was performed. The Hb increase from baseline to Week 12 in the ferric maltol group (p<0.0001) was statistically significant and recruitment was halted. If recruitment had continued, final analysis was to be adjusted for multiple analysis.
- At Week 4, mean Hb ( $\pm$ SD) increase with ferrous sulfate was 8.9  $\pm$  9.6 g/L versus 6.0  $\pm$  8.5 g/L for ferric maltol . At Week 12, the mean ( $\pm$ SD) change from baseline Hb in the ferric maltol group was 12.5  $\pm$ 13.89 g/L compared to 11.5  $\pm$  13.97 g/L in the ferrous sulfate group (Figure 2). There was no statistically significant difference between groups.
- Similar trends were seen in the age/dose subgroups: a statistically significant increase vs. baseline, no statistical difference between treatment groups

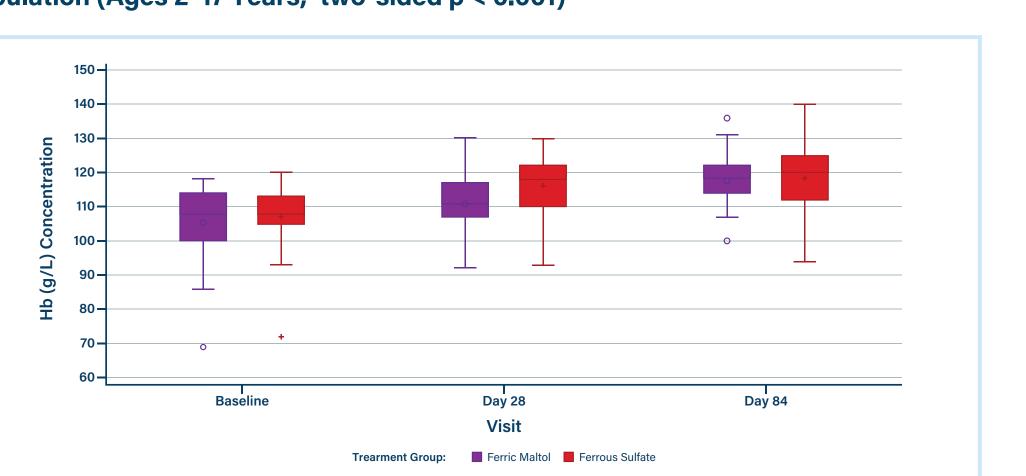
(n = 7, two-sided p = 0.003)

1 Month to <2 Years)

change at Week 4 or 12 (Figure 6 & 7).

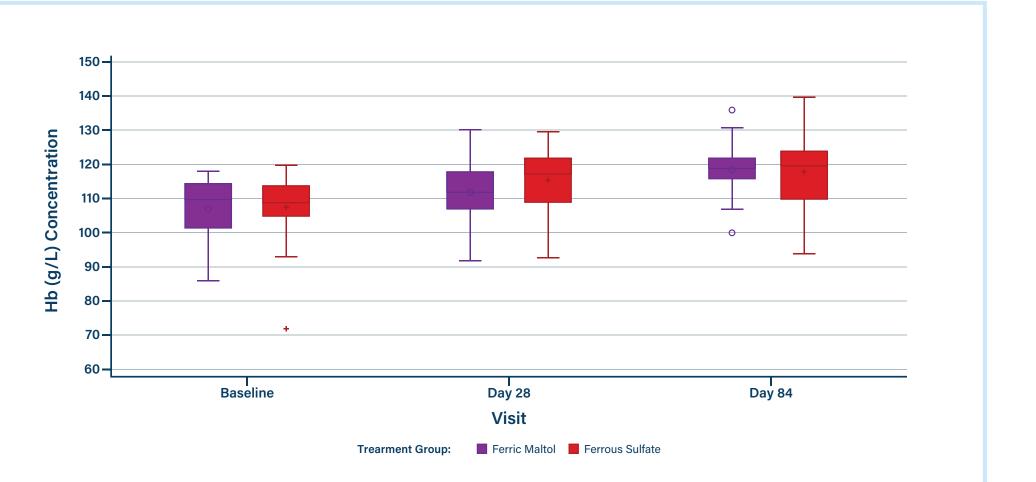
The mean ( $\pm$ SD) change from baseline Hb reported for the assigned ferric maltol group at Week 12 was 17.7  $\pm$  13.61 g/L (Figure 5).

#### Figure 2. Boxplot of Hb (g/L) from Baseline to Week 12 in the mITT Population (Ages 2–17 Years; two-sided p < 0.001)

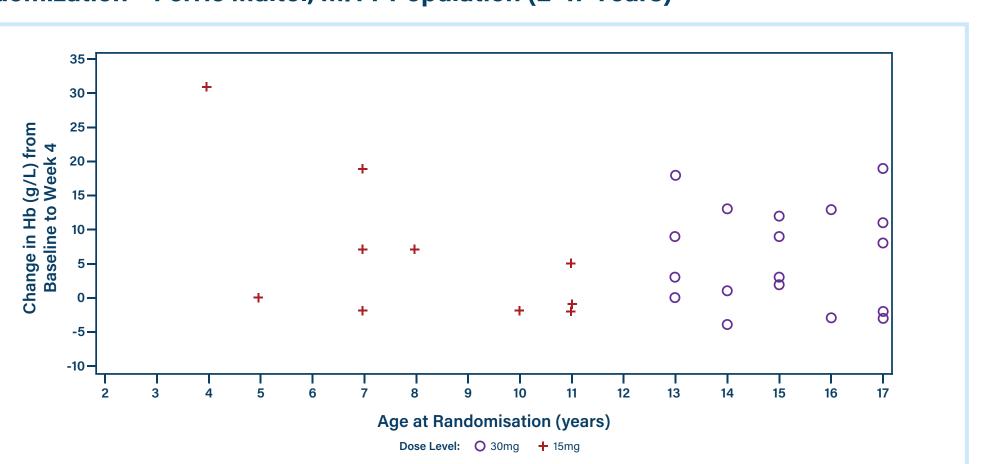








#### Figure 6. Scatterplot of Hb (g/L) Change from Baseline to Week 4 by Age at Randomization - Ferric Maltol, mITT Population (2-17 Years)



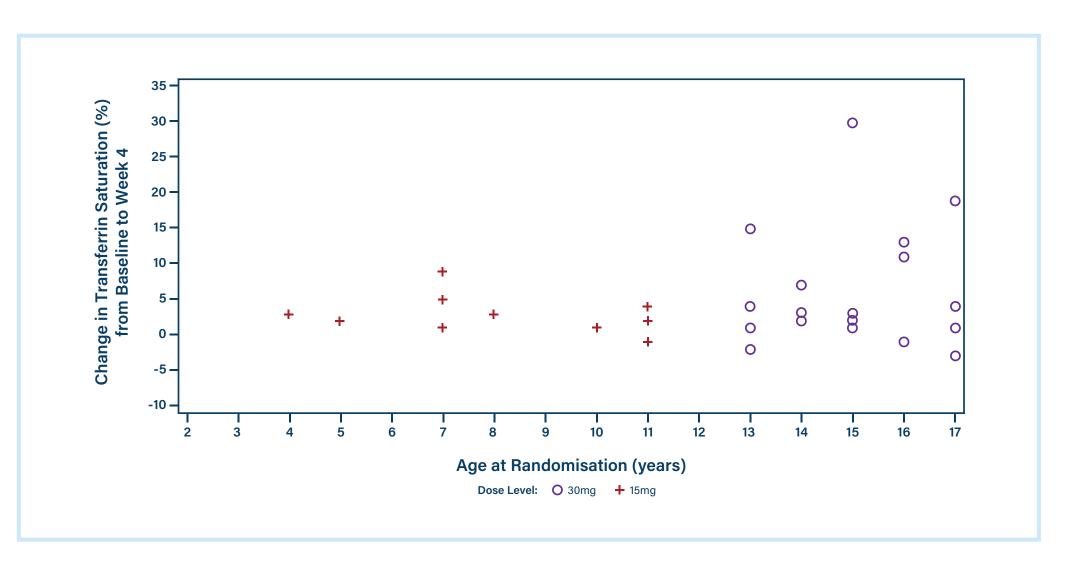
#### Baseline was defined as the last measurement prior to the first treatment dose of study drug Age was calculated based on the patient's informed consent date and year of birth and was set to align with the collected age group classification specified on the case report form. Hb = hemoglobin; mITT = modified Intention-to-Treat; defined as all patients in the ITT Population who received at least 1 treatment dose.

# Efficacy – Change in Iron Markers by Week 12

## In the ferric maltol group:

Serum iron increased significantly from baseline to Week 12 in all age groups: 4.92 g/L in ages 2–17 years (p = 0.001), 5.89 g/L in ages 2–9 years (p = 0.008), and 4.64 g/L in ages 10-17 years (p = 0.014). TSAT increased significantly from baseline to Week 12 (Figure 8 & 9): 6.91% in ages 2–17 years (p = 0.001), 7.65% in ages 2–9 (p = 0.027), and 6.66% in ages 10-17 (p = 0.011).

#### Figure 8. TSAT (%) Change from Baseline to Week 4 vs. Age at Randomization - Ferric Maltol, mITT Population (2-17 Years)



## In the ferrous sulfate group:

Serum iron increased significantly from baseline to Week 12 in all age: 4.55 g/L in ages 2–17 years (p = 0.006), 5.83 g/L in ages 2–9 years (p = 0.012), and 4.19 g/L in ages 10–17 years (p = 0.048). TSAT increased significantly from baseline to Week 12: 7.30 g/L in ages 2–17 years (p = 0.002), 9.68 g/L in ages 2–9 years (p = 0.012), and 6.63 g/L in ages 10–17 years (p = 0.024). The difference between treatment groups was not statistically significant.

2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

Dose Level: O 30mg + 15mg

Figure 3. Boxplot of Hb (g/L) from Baseline to Week 12 in the mITT Population

Trearment Group: Ferric Maltol Ferrous Sulfate

(Ages 2-9): Ferrous sulfate (n = 7, two-sided p < 0.001) and ferric maltol

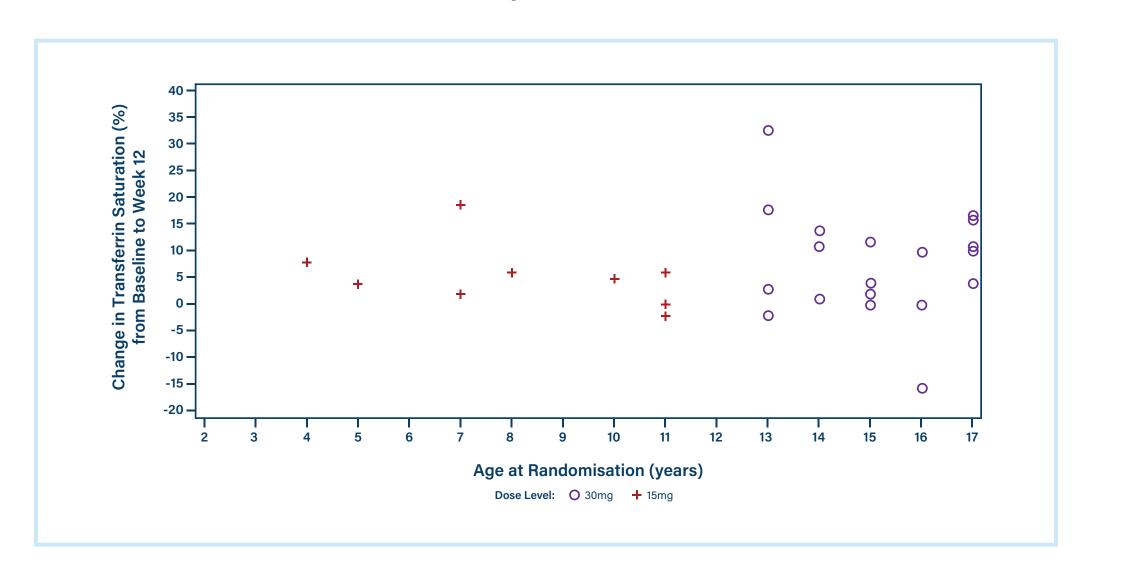
Figure 5. Change in Hb(g/L) - Assigned Ferric Maltol (mITT Population)

The scatterplots show no significant correlation was found between age at randomization and Hb

Figure 7. Scatterplot of Hb (g/L) Change from Baseline to Week 12

by Age at Randomization - Ferric Maltol, mITT Population (2-17 Years)

#### Figure 9. TSAT (%) Change from Baseline to Week 12 vs. Age at Randomization - Ferric Maltol, mITT Population (2-17 Years)



# PALATABILITY

At both Day 1 and Day 28, ferric maltol had much lower odds of being rated "Bad" or "Very Bad" compared with ferrous sulfate (Tables 3-4), with odds ratios of 0.06 (95% CI: 0.00-0.49, p = 0.003) and 0.05 (95% CI: 0.00-0.45, p = 0.001), respectively. For taste, ferric maltol also showed lower odds of being rated "Bad" or "Very Bad" compared with ferrous sulfate, demonstrating a potential advantage in palatability.

#### Table 3. Palatability - Response to smell at Day 1 & Day 28 (Age 6-17 years)

Visit	Category	Ferrous Sulfate (N=26) n (%)	Ferric Maltol (N=29) n (%)	Odds Ratio	95% CI	p-value (two-sided)
Day 1	Bad or Very Bad	9 (39.1%)	1 (3.4%)	0.06	(0.00, 0.49)	0.003
	OK, Good, or Very Good	14 (60.9%)	28 (96.6%)	_	_	_
Day 28	Bad or Very Bad	10 (41.7%)	1 (3.6%)	0.05	(0.00, 0.45)	0.001
	OK, Good, or Very Good	14 (58.3%)	27 (96.4%)	_	_	_

#### Table 4. Palatability - Response to taste at Day 1 & Day 28 (Age 2-17 years)

Visit	Category	Ferrous Sulfate (N) n (%)	Ferric Maltol (N) n (%)	Odds Ratio	95% CI	p-value (two-sided)
Day 1	Bad or Very Bad	15 (50.0%)	8 (25.8%)	0.35	(0.10, 1.15)	0.067
	OK, Good, or Very Good	15 (50.0%)	23 (74.2%)	_	_	_
ay 28	Bad or Very Bad	13 (50.0%)	7 (23.3%)	0.30	(0.08, 1.09)	0.052
	OK, Good, or Very Good	13 (50.0%)	23 (76.7%)	_	_	_

# SAFETY

In patients aged 1 month to <2 years, all experienced AEs (n=3), with 2 reporting mild Treatment-Emergent Adverse Events (TEAEs, n=6). One subject had mild diarrhea and teething events (Table 6). A single Serious AE (viral-induced wheeze) occurred prior to dosing and was not drug-related.

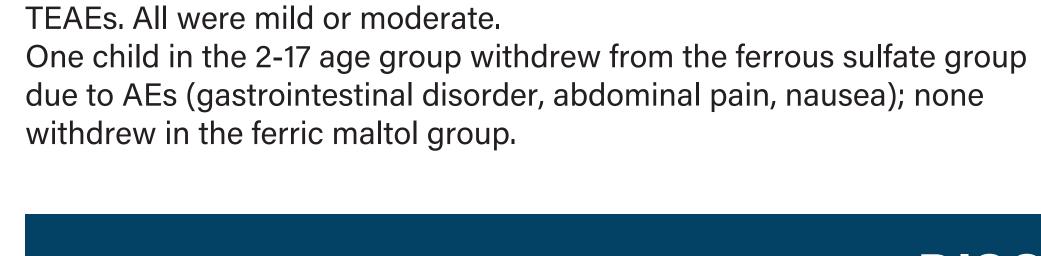
No TEAEs were study drug-related, and no discontinuations occurred.

#### **Table 6. TEAEs by System Organ Class and Preferred Term** - Safety Population (1 Month to <2 Years )

	Ferric Maltol Assigned (N=3) n (%) e	
Any TEAEs	2 (66.7) 6	
Blood and lymphatic system disorders	1 (33.3) 1	
Iron deficiency anaemia	1 (33.3) 1	
Gastrointestinal disorders	1 (33.3) 1	
Diarrhoea	1 (33.3) 1	
Teething	1 (33.3) 1	
Infections and infestations	1 (33.3) 1	
Conjunctivitis	1 (33.3) 1	
Respiratory, thoracic, and mediastinal disorders	1 (33.3) 1	
Cough	1 (33.3) 1	
Wheezing	1 (33.3) 1	
% = 100 × n/N. e = number of events.  TEAEs were defined as AEs that started after the first dose of study drug.  For programming purposes, AEs that occurred on the same date as the first dose date were flagged as TEAEs, regardless of the time of day.  AE reported terms were coded using MedDRA Version 24.0.  AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.		

Among patients aged 2 to 17 years, four (4) (13.3%) had 6 TEAEs in the

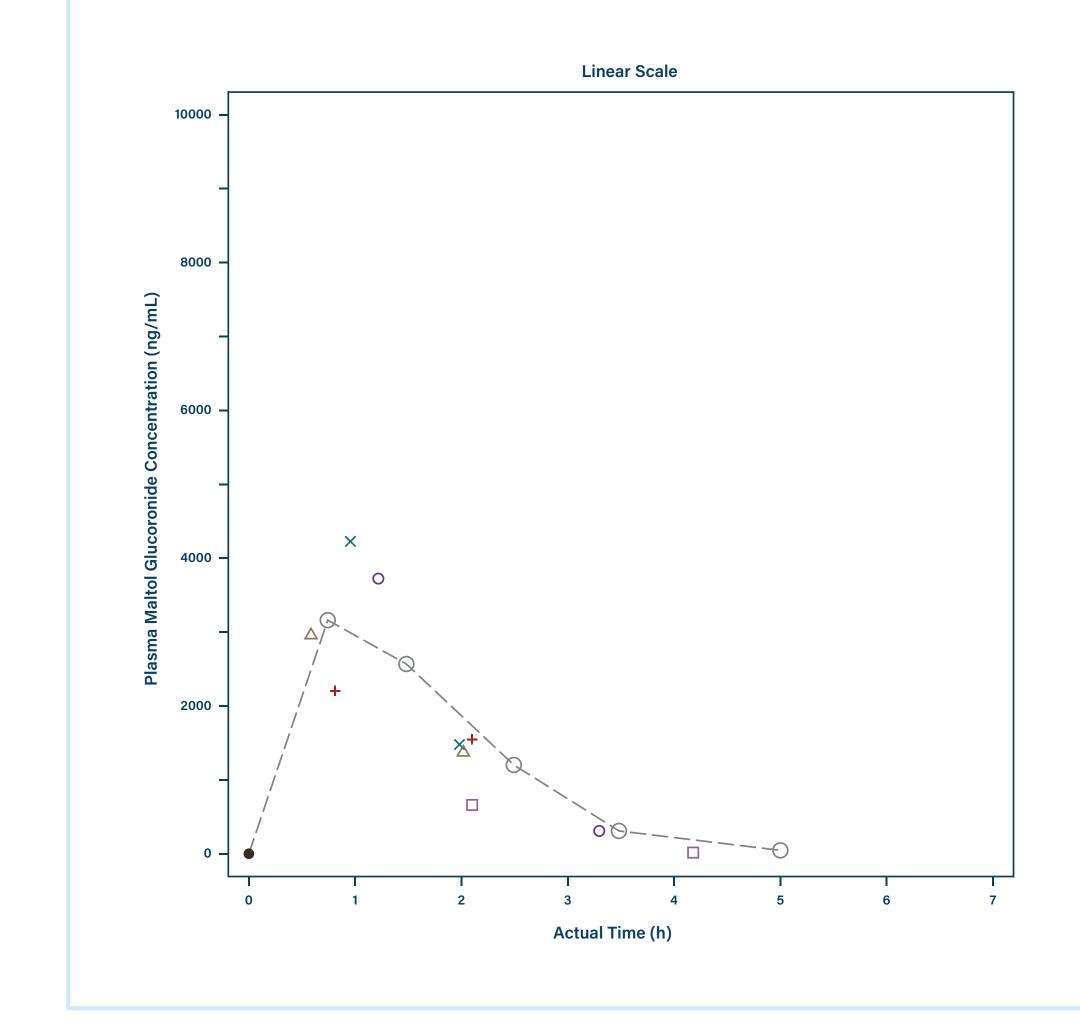
due to AEs (gastrointestinal disorder, abdominal pain, nausea); none



ferrous sulfate group; in the ferric maltol group, 2 (6.5%) experienced 10

# MALTOL CLEARANCE

- No notable accumulation of maltol glucuronide was observed across age groups, including infants aged 1 month to <2 years, demonstrating metabolic clearance across the pediatric population.
- Plasma Maltol Glucuronide Levels (ng/mL) on Day 2 Following Ferric Maltol 15 mg dosing in Children Aged 2-9 Years, showing a typical profile for plasma clearance in 2-9 year olds; profiles were similar in other age groups



# DISCUSSION

- > Clinically and statistically significant Hb improvements vs. baseline were observed across all groups (assigned ferric maltol, ferric maltol, and ferrous sulfate groups), starting with similar baseline Hb levels, demonstrating the efficacy of ferric maltol. As expected, there was no difference in Hb improvement between groups at week 12 as the study was not designed or powered to show this (p >0.05). Pharmacokinetic analysis showed that maltol was rapidly converted to maltol glucuronide, with no notable accumulation observed across any age group, including infants aged 1 month to <2 years.
- Pediatric Hb response to ferric maltol aligned with outcomes observed in adult IDA populations, showing comparable efficacy to prior studies in CKD and IBD.15,18
- Across all palatability assessments, ferric maltol was consistently associated with markedly lower odds of patients reporting their condition as "Bad" or "Very Bad" compared with ferrous sulfate, translating to a 65–95% reduction in the likelihood of poor ratings. Ferric maltol was well tolerated across all age groups (1 month to <2 years and 2 to 17 years), with a similar incidence and profile of TEAEs compared to ferrous sulfate. All reported TEAEs were mild or moderate in severity.

# REFERENCES

Medical history reported terms were coded using the MedDRA Version 24.0.

MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.