A pooled analysis of early and sustained response in patients with IBD with iron deficiency anemia who were treated with ferric maltol

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INTRODUCTION

Iron deficiency (ID) accounts for around half of the estimated 2.2 billion cases of anemia globally.[1] In Western countries about 3.4% of the general population is anemic, and up to 30% of patients with inflammatory bowel disease (IBD) are reported to have ID anemia (IDA).[2]

Patients with IBD experience ID associated with chronic gastrointestinal blood loss, impaired absorption across damaged bowel mucosa, and inflammation-associated downregulation of absorption.[1]

Unabsorbed iron, which commonly remains in the gut following traditional ferrous iron replacement therapy, can trigger disease flares in patients with IBD.[1] Unabsorbed iron contributes to gut damage and mucosal irritation, and manifests as commonly experienced adverse events including nausea, abdominal discomfort, diarrhea, or constipation.

Ferric maltol (FM) has been designed to optimize iron absorption, thus reducing gastrointestinal adverse events associated with suboptimal tolerability in traditional oral ferrous sulfate options.[3] Previous studies have demonstrated an improved tolerability profile for FM compared with traditional ferrous iron treatment.[1] FM is indicated for the treatment of ID in adults, with or without anemia.[4]

Because IDA can lead to a meaningful reduction in quality of life (resulting from headaches, fatigue, and loss of productivity) and can worsen concomitant IBD, it is important that iron replacement treatment is not only both tolerable and effective for the longer term, but also effective in achieving early hemoglobin (Hb) normalization in the management of IDA. Meaningful change in Hb (>1 g/dL from baseline (BL) in the weeks immediately following iron replacement therapy is a key goal of IDA treatment.

OBJECTIVES

The aim of this study was to perform a novel pooled efficacy assessment of FM in the treatment of IDA at Week 4 to evaluate early response, and at Week 12 to demonstrate the durability of any early effect.

Assess the proportion of patients with meaningful (>1 g/dL) increases in Hb from BL and with 'normalization' of Hb following treatment initiation or placebo.

METHODS

This analysis pooled patients from the combined phase 3 AEGIS 1 and 2 (301/2; NCT01352221) studies, and a phase 3b study (304; NCT02680756) which included adults with a diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) and IDA.

Data were pooled for summary analyses, and participants assigned to comparator and treatment (FM) groups. The FM group was made up of participants from studies 301/2 and 304; because study 304 did not have a placebo arm, the placebo population presented here is informed by study 301/2 only.

Individuals were excluded from a particular summary if they had no value recorded for that measure or for one of its components. Values were averaged for patients with multiple measurements at a single timepoint.

IDA was defined as Hb ≥9.5–<12.0 g/dL for women and ≥9.5–<13.0 g/dL for men in study 301/2 and as Hb ≥8.0–≤11.0 g/dL for women and ≥8.0–≤12.0 g/dL for men in study 304. All included patients had ID defined as ferritin <30 µg/L at screening.

In the pooled analysis, change in Hb concentration from BL at Week 4 and at Week 12 was assessed. Normalization of Hb was assessed at Week 4 and Week 12; 'normal Hb' was defined as ≥13 g/dL for men and ≥12 g/dL for women.

RESULTS

In study 301/2, the mean age was 39.3 years and 65% of participants were women; 55% had CD and 45% had UC. In study 304, the mean age was 40.2 years and 58% were women; 62% had CD and 37% had UC. Patient demographics for the pooled group are shown in **Table 1**.

At Week 4 (**Figure 1**), the 301/2 population (n=59) had a mean improvement in Hb from BL of 1.08 g/dL (95% confidence interval [CI], 0.91–1.25) and the 304 population (n=125) had a mean increase of 1.27 g/dL (95% CI, 1.10–1.44). At Week 12 (**Figure 2**), those in 301/2 (n=58) had a mean gain in Hb from BL of 2.26 g/dL (95% CI, 1.96–2.56) and patients in 304 (n=125) had a mean increase of 2.45 g/dL (95% CI, 2.20–2.70).

Table 1. BL characteristics for the pooled dataset

Characteristic	Mean	Standard Deviation
Age (years)	39.59	13.73
Height (cm)	170.70	8.88
Weight (kg)	70.30	14.17
BL Hb (g/dL)	10.53	1.16
	Men/Women	Total
Sex	150/102	252

Figure 1. Change in Hb from BL at Week 4 (each study and pooled)

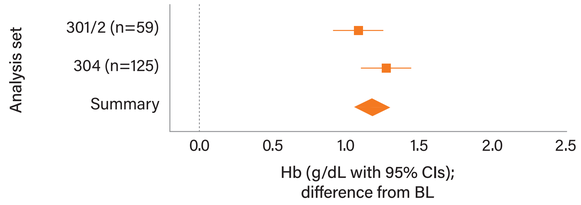
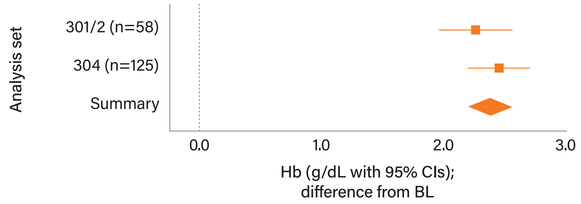


Figure 2. Change in Hb from BL at Week 12 (each study and pooled)



The pooled analysis showed a mean increase in Hb from BL of 1.18 g/dL (95% CI, 1.05–1.30) at Week 4 (n=184) and of 2.37 g/dL (95% CI, 2.18–2.57) at Week 12 (n=183).

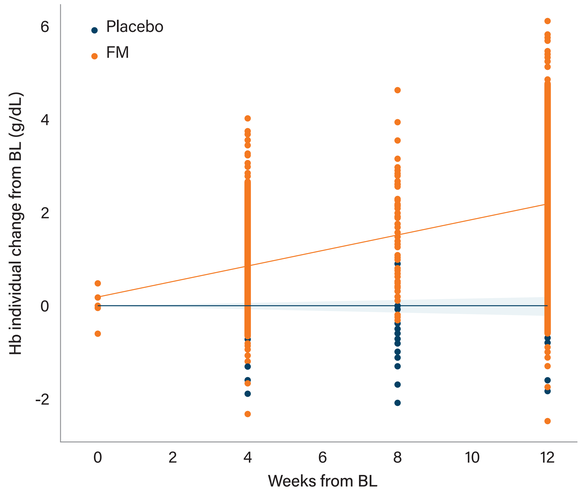
The proportion of patients achieving a meaningful increase in Hb from BL and/or normalization of Hb was markedly greater with FM than with placebo at both Week 4 and Week 12 (**Table 2**).

The overall increase in Hb over 12 weeks was greater with FM than with placebo (**Figure 3**), with the degree of improvement with FM increasing with the duration of treatment.

Table 2. Patients with Hb in normal range and with change >1 g/dL

Visit	Condition	FM		Placebo	
		n/N	%	n/N	%
Week 4	Normal range Hb	55/186	29.57	4/64	6.25
	Rise of >1 g/dL from BL	102/186	54.84	2/64	3.13
Week 12	Normal range Hb	113/182	62.09	10/54	18.52
	Rise of >1 g/dL from BL	155/182	85.16	5/54	9.26

Figure 3. Pooled analysis of Hb change with FM versus placebo



DISCUSSION

Patients with IBD and IDA who received FM had a clinically meaningful (>1.0 g/dL) mean improvement in Hb at Week 4 and a >2.0 g/dL increase at Week 12 in a pooled analysis of pivotal randomized controlled trials.

Early and sustained improvement in Hb is key to optimizing the management of IDA in patients with IBD; this was achieved with FM, contributing to a greater attainment of Hb normalization over 12 weeks versus placebo.

CONCLUSIONS

These findings support physicians in making treatment decisions for iron replacement in patients with IBD and IDA.

FM provides early and efficacious improvement in Hb, aiding rapid Hb normalization following initiation and Hb maintenance for up to 52–64 weeks.[1] FM provides an effective iron replacement option for patients and is well-tolerated.

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