Effect of Montelukast on GI Tolerability in Patients With Relapsing-Remitting Multiple Sclerosis Receiving Delayed-release Dimethyl Fumarate: MITIGATE Study Results

P5450

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Conclusions

- Although enrollment into the study was closed early due to slow recruitment, the results suggest that montelukast may not reduce the severity of DMF-related GI events.
- The results support the established safety profile of DMF and no new safety or tolerability concerns for DMF were identified.
- Other studies have shown that a combination of real-world management strategies (e.g., taking DMF with food, titration schedule, symptomatic therapies), setting expectations on the intensity and duration of GI events, and providing rationale for therapy selection have been effective in improving persistence on DMF when experiencing DMF-associated GI AEs.[5,9]

Introduction

- As of January 31, 2018, >311,000 patients have chosen delayed-release dimethyl fumarate (DMF) treatment, representing >544,000 patient-years of exposure. Of these, ~6252 patients (~12,631 patient-years) were from clinical trials.
- DMF demonstrated strong and sustained efficacy on clinical and neuroradiological measures in Phase 3 studies and long-term extension trials of relapsing-remitting multiple sclerosis (RRMS).[1-3]
- Gastrointestinal (GI) symptoms, mostly mild or moderate in severity, are common adverse events (AEs) associated with DMF. GI AEs are more frequent during the first month of treatment and usually decrease over time.[4,5]
- A small (n=21) independent single-arm pilot study in patients with RRMS had previously suggested that DMF-related GI symptoms may be attenuated by montelukast — an oral therapy for asthma, exercise-induced bronchoconstriction, and allergic rhinitis.[6]
- Montelukast inhibits leukotriene D4, a chemotactic factor produced by eosinophils. It has been studied in other GI pathology such as eosinophilic esophagitis and eosinophilic gastroenteritis in addition to its use in approved indications.[7,8]

Objective

- The MITIGATE study (NCT02410278) evaluated whether montelukast reduced the severity of DMF-related GI events in patients with RRMS.

Methods

- MITIGATE was a randomized multicenter placebo-controlled Phase 4 study in patients with RRMS treated with DMF at 50 sites in the United States.

Patients

- Eligible patients were aged ≥18 years at the time of informed consent, diagnosed with RRMS, and had no significant background GI symptoms.
- Key exclusion criteria included: pregnancy or breastfeeding; a history of significant GI disease; chronic use (≥7 consecutive days) of bismuth subsalicylate; use of antiallergy medications; exposure to fumarates in the 3 months before screening; ≥1 major comorbidity that may affect the outcome of the study; a history of malignancy, severe allergic or anaphylactic reactions, or known drug hypersensitivity; abnormal laboratory results indicative of significant disease; and/or a major disease that would preclude participation in a clinical study.
- Enrollment into MITIGATE was closed before reaching the target sample size goal of 118 patients randomized to treatment (59 per arm) due to slow recruitment into the randomized study phase.

Study Design

- The MITIGATE study design is presented in Figure 1.
- Patients recorded GI symptoms in an e-diary daily using the Gastrointestinal Symptom Rating Scale (GSRS; Table 1) consisting of 15 items to assess GI symptoms for up to 4 weeks.
- Patients reaching a specific threshold GSRS score were randomized and blinded to symptomatic treatment (montelukast at a dose of 10 mg once daily in the evening or matching placebo; 1:1 randomization) taken with DMF for 8 weeks.

Endpoints

- The primary endpoint was the proportion of patients with worsening in severity of GI symptoms, measured by the average change from Day 0 to Day 10 in GSRS score, after oral administration of DMF (Day 0 was defined as the day before a patient started randomized treatment [if the GI threshold was reached 1 day previously], or the first day of randomized treatment if the threshold was reached that day. If the threshold was reached >1 day previously, then Day 0 was the last day when the threshold was reached, before the first dose).
  - Sensitivity analyses were based on the 5 dimension scores of the GSRS.
- Secondary endpoints evaluated whether taking montelukast after oral administration of DMF:
  - Decreased discontinuations due to GI events;
  - Reduced the number of patients taking symptomatic therapies for GI events; and
  - Reduced the incidence of flushing events.

Results

Demographics and Patient Disposition

- Baseline patient demographics were similar in the montelukast and placebo groups (Table 2).
- Of 148 patients screened, 102 met the criteria for e-diary compliance and absence of background GI symptoms, and were initiated on DMF.
- Of these, 64 (63%) patients developed GI symptoms that met the predefined study threshold and received montelukast or placebo treatment.

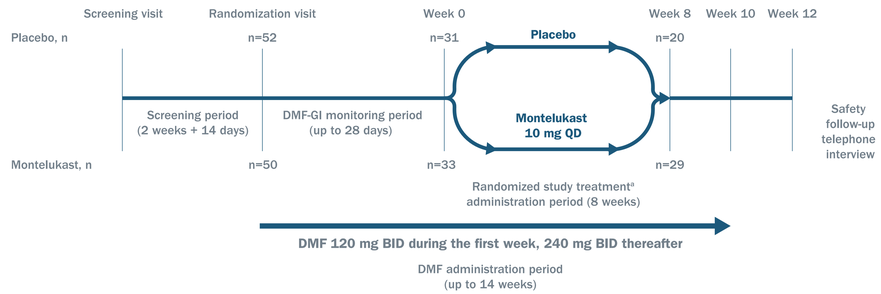
Efficacy

- Efficacy endpoints were assessed in a modified intention-to-treat (ITT) population (n=63). The modified ITT population consisted of all patients who were randomized, received ≥1 dose of DMF treatment, received ≥1 dose of study treatment (montelukast or placebo) on/after the first DMF dose date, and had ≥1 GSRS score measurement during the Day 1 to Day 10 period.
- There was no statistically significant difference between the proportion of patients with worsening of GI symptoms in the 2 treatment groups (Figure 2).
- Similarly, while GI symptoms decreased in both treatment groups, there was no significant difference between the placebo and montelukast groups in average change in severity score from Day 1 to Day 10 (adjusted mean difference, montelukast vs. placebo: 0.084 [95% CI, –0.104 to 0.273]; *P*=.3753; Table 3).
  - By-dimension analyses of abdominal pain, reflux syndrome, diarrhea syndrome, indigestion, and constipation also showed no significant difference in symptom score (Table 3).
- There was no notable difference in time to first worsening of GSRS score or time to recovery to the Day 0 score from the worst GSRS score in patients on montelukast vs. placebo. Similarly, there was no significant difference in discontinuation of DMF due to GI-related AEs between treatment groups or number of patients taking GI symptomatic therapy as recorded in the e-diary.

Safety

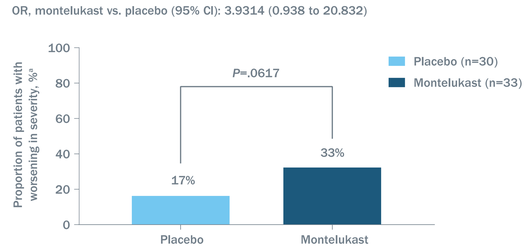
- The incidence of AEs was similar between treatment groups; 40 (63%) of patients reported ≥1 AE (Table 4).
- Flushing and viral upper respiratory tract infection were the most frequently reported AEs (<5% difference in incidence between the 2 treatment groups).

Figure 1. MITIGATE study design



BID = twice daily; DMF = delayed-release dimethyl fumarate; GI = gastrointestinal; QD = once daily
[a]Use of symptomatic therapies, as specified in the protocol, was permitted from Day 10 onward

Figure 2. Proportion of patients with worsening in GI symptom severity



CI = profile likelihood confidence interval; GI = gastrointestinal; OR = odds ratio
[a]Worsening in severity defined as a positive average change from baseline (Day 0) to Day 10 in Gastrointestinal Symptom Rating Scale (GSRS) score. Average change of the GSRS score from Day 0 to Day 10 calculated as the sum of changes from baseline in GSRS score over the first 10 days divided by the total number of days with GSRS score. Results obtained from a weighted logistic regression model comparing the 2 treatment groups, adjusted for baseline age, weight, and GSRS score. Weights for the model defined as the proportions of days with GSRS score recorded. OR refers to the odds of an event in the montelukast treatment group divided by the odds of an event in the placebo treatment group. *P* value derived from the likelihood ratio test that the OR is 1

Table 1. Gastrointestinal Symptom Rating Scale (GSRS)

GSRS is an interview-based rating scale consisting of 15 items for assessment of GI symptoms:
Pain or discomfort in the upper abdomen or the pit of the stomach
Heartburn
Acid reflux
Hunger pains
Nausea
Rumbling in the stomach
Stomach feeling bloated
Burping
Passing gas or flatus
Constipation
Diarrhea
Loose stools
Hard stools
Urgent need to have a bowel movement
Sensation of not completely emptying the bowels
For each question, the following response choices are offered:
No discomfort at all
Minor discomfort
Mild discomfort
Moderate discomfort
Moderately severe discomfort
Severe discomfort
Very severe discomfort
Items were scored for intensity on a 7-grade Likert scale, from 0 (no discomfort) to 6 (very severe discomfort)
The overall GSRS score is the mean of these 15 items, varying from 0 to 6; a score of 0 indicates that no symptoms are present, and a score of 6 indicates the worst possible degree of all symptoms
Further, these 15 items can be grouped into 5 dimensions:
Abdominal pain syndrome
Reflux syndrome
Indigestion syndrome
Diarrhea syndrome
Constipation syndrome
A dimension score is calculated as the mean of the items belonging to the specific syndrome

GI = gastrointestinal

Table 2. Patient baseline characteristics (MITT population)

Type	Placebo n=30	Montelukast n=33	Total n=63
Age, y			
Mean (SD)	43.6 (13.0)	44.9 (10.4)	44.3 (11.6)
Median	45.0	47.0	47.0
Female, n (%)	23 (77)	27 (82)	50 (79)
Body mass index, kg/m²			
Mean (SD)	28.9 (5.5)	30.3 (7.8)	29.7 (6.8)
Median	28.9	27.5	28.8
Systolic blood pressure			
Mean (SD)	124.4 (19.0)	124.7 (14.7)	124.6 (16.8)
Median	121.0	127.0	123.0
Diastolic blood pressure			
Mean (SD)	77.4 (10.7)	78.2 (9.1)	77.8 (9.8)
Median	76.5	78.0	78.0

MITT = modified intention-to-treat

Table 3. Mean change from baseline in GSRS, Day 1 to Day 10, overall and by dimension analysis

	Placebo n=30	Montelukast n=33	Adjusted mean difference, montelukast vs. placebo	*P* value[a]
Overall score				
Mean (SD) average change	–0.28 (0.695)	–0.23 (0.499)		
Adjusted mean average change (95% CI)[a]	–0.333 (–0.469 to –0.197)	–0.249 (–0.379 to –0.120)	0.084 (–0.104 to 0.273)	.3753
Abdominal pain score				
Mean (SD) average change	–0.38 (0.977)	–0.19 (0.787)		
Adjusted mean average change (95% CI)[a]	–0.479 (–0.685 to –0.274)	–0.235 (–0.430 to –0.040)	0.244 (–0.040 to 0.529)	.0912
Reflux syndrome score				
Mean (SD) average change	–0.24 (0.833)	–0.12 (0.811)		
Adjusted mean average change (95% CI)[a]	–0.252 (–0.398 to –0.107)	–0.121 (–0.260 to 0.017)	0.131 (–0.071 to 0.333)	.1982
Diarrhea syndrome score				
Mean (SD) average change	–0.33 (1.375)	–0.43 (0.898)		
Adjusted mean average change (95% CI)[a]	–0.446 (–0.608 to –0.284)	–0.377 (–0.531 to –0.222)	0.069 (–0.156 to 0.294)	.5422
Indigestion syndrome score				
Mean (SD) average change	–0.35 (0.790)	–0.31 (0.781)		
Adjusted mean average change (95% CI)[a]	–0.371 (–0.554 to –0.188)	–0.342 (–0.516 to –0.169)	0.029 (–0.225 to 0.282)	.8228
Constipation syndrome score				
Mean (SD) average change	–0.07 (0.716)	–0.02 (0.582)		
Adjusted mean average change (95% CI)[a]	–0.079 (–0.305 to 0.148)	–0.059 (–0.276 to 0.157)	0.019 (–0.295 to 0.334)	.9019

GSRS = Gastrointestinal Symptom Rating Scale
[a]Results obtained from an analysis of covariance model for comparing average GSRS score change in the 2 treatment groups, adjusted for age, weight, and baseline GSRS score. Weights, defined as the proportions of days with GSRS score recorded during the Day 1 to Day 10 period, were applied to adjust for missing data

Table 4. Incidence of AEs[a]

AE, n (%)	Placebo n=31	Montelukast n=33
Patients with ≥1 AE	19 (61)	21 (64)
Blood and lymphatic disorders	1 (3)	0
Eye disorders	0	1 (3)
Gastrointestinal disorders	3 (10)	3 (9)
General disorders and administration site conditions	4 (13)	4 (12)
Immune system disorders	1 (3)	0
Injury, poisoning, and procedural complications	1 (3)	1 (3)
Infections and infestations	6 (19)	5 (15)
Viral upper respiratory tract infection	5 (16)	4 (12)
Investigations	1 (3)	8 (24)
Increased ALT	1 (3)	2 (6)
Increased AST	1 (3)	1 (3)
Increased creatine phosphokinase	0	2 (6)
Increased hepatic enzyme	0	2 (6)
Metabolism and nutritional disorders	0	1 (3)
Muscular and connective tissue disorders	5 (16)	3 (9)
Neoplasms (benign, malignant, and unspecified)	0	1 (3)
Nervous system disorders	5 (16)	5 (15)
Psychiatric disorders	2 (6)	0
Respiratory, thoracic, and mediastinal disorders	1 (3)	3 (9)
Skin and subcutaneous tissue disorders	3 (10)	0
Vascular disorders	4 (13)	5 (15)
Flushing	4 (13)	5 (15)

AE = adverse event; ALT = alanine aminotransaminase; AST = aspartate aminotransaminase
[a]Results from the montelukast/placebo safety analysis population (defined as all patients who received ≥1 dose of randomized study treatment (montelukast or placebo)

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