DX18

Effect of Bismuth Subsalicylate on Gastrointestinal Tolerability in Healthy Volunteers Receiving Delayed-Release Dimethyl Fumarate

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2014 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC) and the 6th Cooperative Meeting with Americas Committee for Treatment and Reserach in Multiple Sclerosis (ACTRIMS)

May 28 – 31, 2014

Dallas, Texas

INTRODUCTION

Delayed-release dimethyl fumarate (DMF) is approved in the United States, Canada, Australia, and the European Union for the treatment of multiple sclerosis (MS).

Commonly reported adverse events (AEs) among the 1,534 delayed-release DMF-treated patients enrolled in pivotal Phase 3 studies included flushing and gastrointestinal (GI)-related events[1,2].

These events were typically mild or moderate in severity and decreased substantially in incidence after the first month of treatment.

Mitigation strategies for GI events are needed. Facilitating management of GI tolerability may improve adherence.

OBJECTIVE

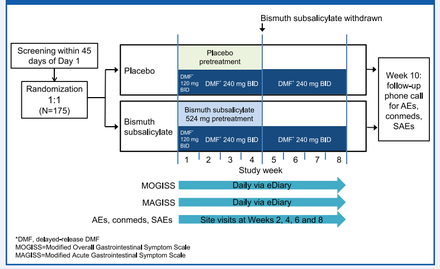
- The objective was to evaluate the effect of bismuth subsalicylate on GI events in healthy volunteers receiving delayed-release DMF, in an 8-week, randomized, double-blind, placebo-controlled study
- The primary endpoint was the time to first GI-related event
- Secondary endpoints included the frequency, severity, and duration of GI-related events and the percentage of subjects who discontinued delayed-release DMF due to GI-related events

METHODS

Study design

- PREVENT is an 8-week, double-blind, placebo-controlled, Phase 1 study conducted to evaluate the effect of bismuth subsalicylate on GI events in healthy volunteers receiving delayed-release DMF (Figure 1)
- Key eligibility criteria for the study were age 18−65 years, in good health based on medical history and screening evaluations, BMI of 18.0 to 34.0 kg/m^2, and naïve to delayed-release DMF or fumaric acid esters. Among the exclusion criteria were a history of clinically significant GI disease, active GI disease, or other clinically significant or major disease
- Patients recorded pertinent information regarding any GI-related events occurring within 10 hours of each dose of delayed-release DMF using an eDiary device and the Modified Overall Gastrointestinal Symptom Scale (MOGISS) and Modified Acute Gastrointestinal Symptoms Scale (MAGISS)
- MOGISS and MAGISS are numerical rating scales in which the severity of the event is rated from 0–10 as follows: 0 = no event; 1–3 = mild event; 4–6 = moderate event; 7–9 = severe event; and 10 = extreme event
- After the screening/baseline visit, patients were evaluated for AEs, serious AEs (SAEs), and concomitant medications in site visits at Weeks 2, 4, 6, and 8 and in a follow-up phone call at Week 10

Figure 1: PREVENT study schematic



*DMF, delayed-release DMF
MOGISS=Modified Overall Gastrointestinal Symptom Scale
MAGISS=Modified Acute Gastrointestinal Symptom Scale

RESULTS

Patients

- A total of 175 subjects were dosed, including 87 and 88 in the placebo and bismuth subsalicylate groups, respectively (Table 1)
- Mean study medication adherence (defined as the number of days that the medication was actually taken divided by number of days that the medication was expected to be taken) for delayed-release DMF was 91.3% in the placebo group and 91.7% in the bismuth subsalicylate group; for placebo was 88.6% (placebo group); and for bismuth subsalicylate was 89.6% (bismuth subsalicylate group)
- A total of 17 subjects discontinued the study, including 8 (9.1%) and 9 (10.3%) in the placebo and bismuth subsalicylate groups, respectively; among them, 3 (3.4%) and 7 (8.0%) discontinued due to AEs, and 2 (2.3%) and 1 (1.1%) withdrew consent

Table 1: Baseline demographics

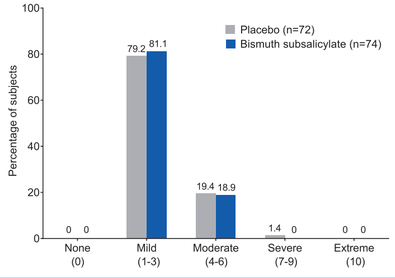
Characteristic	Placebo (n=87)	Bismuth subsalicylate (n=88)
Age (years)	36.4 (20.0, 63.0)	38.1 (18.0, 64.0)
Female (%)	49.4	52.3
Race (% White)	71.3	64.8
BMI (kg/m^2)	26.4 (18.6, 33.3)	26.3 (20.0, 33.0)
Weight (kg)	76.1 (52.6, 108.8)	75.6 (48.7, 104.6)
Height (cm)	169.3 (147.9, 187.7)	169.1 (143.5, 198.5)

Values are mean (range) unless otherwise stated.

First GI-Related Event

- A total of 146 subjects reported at least one GI event via eDiary, including 72 (82.8%) and 74 (84.1%) in the placebo and bismuth subsalicylate groups, respectively
- Across the 8−week study period, the most commonly reported GI events in the placebo vs bismuth subsalicylate groups included flatulence (51.8% vs 43.2%), diarrhea (52.9% vs 39.8%), lower abdominal pain (38.8% vs 42.0%), nausea (34.1% bs 45.5%), and bloating (37.6% vs 40.9%)
- The mean time (± SD) from initiation of study treatment to first GI event was similar in the placebo group (5.4 ± 8.73 days) and bismuth subsalicylate group (5.6 ± 10.87 days)
- The severity of the first GI event was similar in the placebo group and bismuth subsalicylate group (Figure 2). The majority (~80%) of subjects in both groups reported a first GI event of mild severity

Figure 2: Severity of first GI event



GI Event Rates Over Time

- The overall GI event rate (MOGISS) was highest in Week 1 and declined thereafter (Figure 3)
- There were no appreciable differences between groups in GI event rates over time from week 1 to week 8 (Week 1: 50.0% for placebo vs 55.7% for bismuth subsalicylate; Week 8: 26.6% for placebo vs 21.3% for bismuth subsalicylate)
- The incidence of individual acute GI events (MAGISS) in Weeks 1−4 were generally comparable in the placebo vs bismuth subsalicylate groups, except for flatulence and diarrhea (Figure 4)
- The incidences of flatulence (50.6% vs 38.6%) and diarrhea (48.2% vs 36.4%), were numerically but not statistically lower in the bismuth subsalicylate group

Figure 3: Overall GI event (MOGISS) rates over time

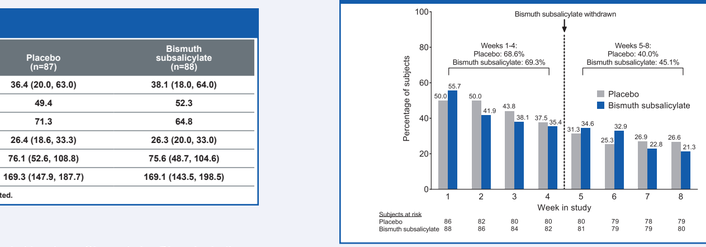
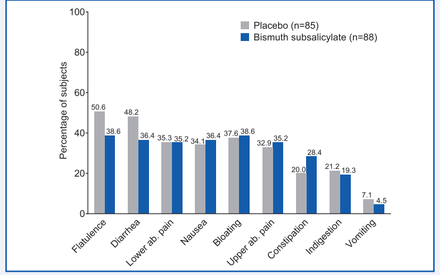


Figure 4: Incidence of acute GI events (MAGISS) in Weeks 1−4



Severity of GI Events

- The worst severity scores for overall GI events (MOGISS; Figure 5) and mean worst severity scores for individual acute GI events (MAGISS; Figure 6) in Weeks 1−4 were generally comparable between groups
- The mean worst severity scores for flatulence (1.1 vs 1.8; LS mean difference [95% CI]: 0.7 [0.1, 1.3]) and diarrhea (1.0 vs 1.6; LS mean difference [95% CI]: 0.6 [0.0, 1.2] were significantly lower in the bismuth subsalicylate group compared with the placebo group (Figure 6)
- Percentages of subjects reporting worst severity scores of "severe" (7−9) and "extreme" (10) were lower in the bismuth subsalicylate group vs the placebo group for flatulence, diarrhea, upper abdominal pain, indigestion, and vomiting (Figure 7)

Figure 5: Worst severity scores for overall GI events (MOGISS) in Weeks 1−4

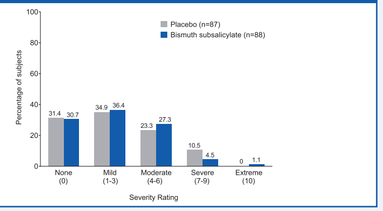


Figure 6: Mean worst severity scores for individual acute GI events (MAGISS) in Weeks 1−4

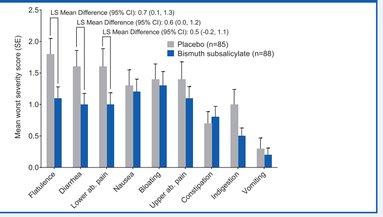
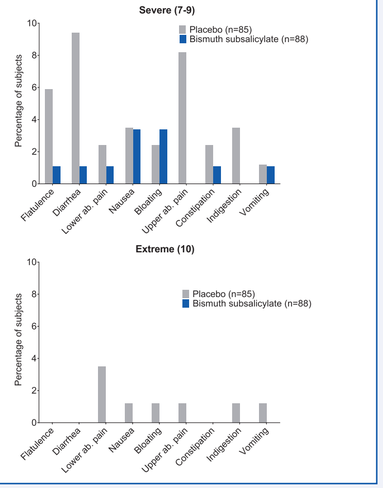


Figure 7: Percentages of subjects reporting worst severity scores of "severe" (7−9) or "extreme" (10) for individual acute GI events (MAGISS) in Weeks 1−4



Duration of GI Events

- The percentage of days with individual acute GI events (MAGISS; Figure 8) and the median duration (hours) of individual acute GI events (MAGISS; Figure 9) in Weeks 1−4 were generally comparable between groups

Figure 8: Percentage of days with individual acute GI events (MAGISS) in Weeks 1−4

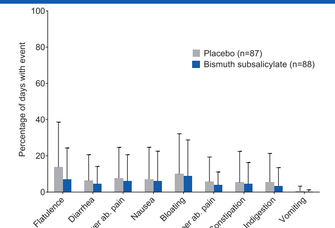
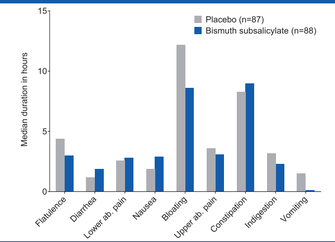


Figure 9: Median duration of individual acute GI events (MAGISS) in Weeks 1−4



CONCLUSIONS

- Coadministration of bismuth subsalicylate with delayed-release DMF significantly reduced the severity and numerically reduced the incidence of flatulence and diarrhea
- Percentages of subjects reporting worst severity scores of "severe" (7−9) and "extreme" (10) were lower in the bismuth subsalicylate group compared with the placebo group for flatulence, diarrhea, upper abdominal pain, indigestion, and vomiting
- The placebo and bismuth salicylate groups were comparable in terms of:
  - Time to onset of first GI event and severity of first GI event
  - Prevalence of overall GI events over time
  - Worst severity scores for overall GI events in Weeks 1−4
  - Percentage of days with and median duration of acute GI events in Weeks 1−4

References

1. Gold R, Kappos L, Arnold DL, et al. *N Engl J Med* 2012;367:1098–1107.
2. Fox RJ, Miller DH, Phillips JT, et al. *N Engl J Med* 2012;367:1087–1097.

Acknowledgements

This study was sponsored by Biogen Idec (Cambridge, MA, USA).

Disclosures

JL, CvH, JW, JZ: employees of Biogen Idec, Inc.;*TM:* employee of PharmStats, Inc.

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