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BG-12 (Dimethyl Fumarate) with Aspirin Pretreatment or Slow Dose Titration

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INTRODUCTION

- Oral BG-12 (dimethyl fumarate) is approved in the United States for the treatment of relapsing forms of MS.
- BG-12 demonstrated significant clinical and neuroradiologic efficacy over 2 years in the Phase 3 DEFINE and CONFIRM studies in patients with relapsing–remitting MS (RRMS).[1,2]
- In the Phase 3 studies, the most common adverse events associated with BG-12 included flushing and gastrointestinal (GI) events.[1,2]
  - For most patients, these events were mild or moderate in severity and decreased in incidence after the first month of treatment.

OBJECTIVE

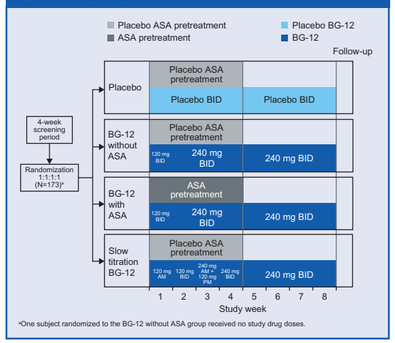
- To evaluate the effects of non-enteric coated aspirin (ASA) pretreatment or slow dose titration of BG-12 on flushing and GI events associated with BG-12 in an 8-week, randomized, double-blind, Phase 3b study in healthy volunteers. This time period represents the peak incidence of these events during the Phase 3 trials.

METHODS

Study Design

- Study subjects were randomized to receive oral BG-12 twice daily (BID), with or without ASA, BG-12 placebo with ASA placebo, or slow titrated (over 3 weeks) BG-12 without ASA (Figure 1).

Figure 1: Study design



aOne subject randomized to the BG-12 without ASA group received no study drug doses.

- Study drug administration was as follows:
  - Placebo group
    - BG-12 placebo for 8 weeks plus ASA placebo in Weeks 1–4
  - BG-12 without ASA group
    - BG-12 120 mg BID for 1 week then 240 mg BID for 7 weeks, plus ASA placebo in Weeks 1–4
  - BG-12 with ASA group
    - BG-12 120 mg BID for 1 week, then 240 mg BID for 7 weeks plus ASA 325 mg in Weeks 1–4
  - Slow titration BG-12 group
    - BG-12 120 mg once daily for 1 week, 120 mg BID in Week 2, 240 mg am/120 mg pm in Week 3, then 240 mg BID in Weeks 4–8.

Key Inclusion Criteria

- Age 25–55 years.
- Must be in good health, as determined by the investigator.
- Body mass index of 18.0 to 34.0 kg/m^2.
- Ability to complete the assessment scales using an eDiary device.

Key Exclusion Criteria

- Diarrhea, constipation, abdominal pain, flushing, or nausea within 28 days prior to study Day 1.
- Treatment with any prescription medication within 28 days prior to study Day 1.
- Clinically significant abnormal laboratory test values, as determined by the investigator.

Flushing and GI Event Reporting

- Study volunteers recorded flushing and GI events via an eDiary device using the following four subject-reported scales:
  - Flushing
    - Modified Global Flushing Severity Scale (MGFSS)
    - Modified Flushing Severity Scale (MFSS)
  - GI events
    - Modified Overall GI Symptom Scale (MOGISS)
    - Modified Acute GI Symptom Scale (MAGISS).
- All four scales are visual analog 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.
- The flushing scales were modified from the validated niacin flushing scale develop by Norquist et al.[3] and the GI scales were developed internally to obtain relevant data in a similar manner to the flushing scales.
- The MGFSS and MOGISS scales reflect the impact of flushing and GI events on the subject during the 24 hours prior to data entry while the MFSS and MAGISS scales assess the acute effect of flushing and GI events after each administration of study drug.
- This poster will focus on the acute scales (MFSS and MAGISS).

Endpoints

- The primary endpoint was the incidence and severity of flushing as measured by MFSS and MGFSS and the incidence and severity of GI events as measured by MAGISS and MOGISS.
- Secondary endpoints included safety assessments and the onset and duration of flushing and GI events.
- The primary analysis was focused on the comparisons between the BG-12 with ASA and BG-12 without ASA groups, and between the slow-titrated BG-12 and BG-12 without ASA groups.

RESULTS

Patients

- A total of 173 subjects were randomized and 172 were dosed as follows: placebo (n=44), BG-12 without ASA (n=43), BG-12 with ASA (n=43), or slow titration BG-12 (n=42).
- Study drug adherence for the duration of the study was high, with mean adherence ranging from 97.8% to 99.0%.
- Baseline demographics were generally similar across study groups (Table 1), although there were slight differences between groups in terms of gender and race.

Table 1: Demographics

Characteristic	Placebo (n=44)	BG-12 without ASA (n=43)	BG-12 with ASA (n=43)	Slow titration BG-12 (n=42)
Mean age, years	35.5	39.0	38.1	36.2
Gender				
Male, n (%)	30 (68)	22 (51)	26 (60)	22 (52)
Race				
Caucasian, n (%)	34 (77)	34 (79)	37 (86)	36 (86)
Mean weight, kg	83.0	81.5	84.6	79.2

- There were no discontinuations due to flushing events.
- Discontinuations due to GI events were as follows:
  - Placebo (n=1)
  - BG-12 without ASA (n=3)
  - BG-12 with ASA (n=6)
  - Slow titration BG-12 (n=2).

Flushing Events

- Flushing events were common in subjects in all groups, including placebo, but were more common in subjects receiving BG-12 alone or slow titration BG-12 (Figure 2).
- The incidence of flushing was lower in subjects receiving BG-12 with ASA than in subjects receiving BG-12 alone or slow titration BG-12.
  - After withdrawal of ASA at the start of Week 5 in the BG-12 with ASA group, the incidence of flushing increased slightly from Weeks 5–8 but was consistently lower than the incidence in the BG-12 without ASA group.
- Flushing severity was assessed by dividing the total area under the curve (AUC) for severity scores by the number of days a severity score was reported (Figure 3). The mean AUCs for flushing severity were generally low across all groups.

Figure 2: Percentage of subjects experiencing flushing events

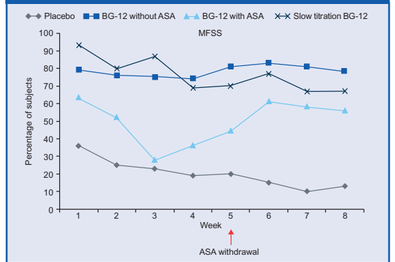
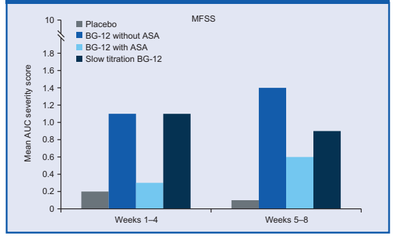
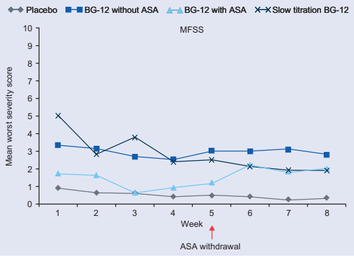


Figure 3: Summary of severity scores for overall flushing events



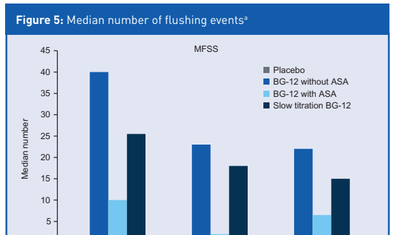
- Mean worst severity scores are shown in Figure 4.
  - Pretreatment with ASA reduced the severity of flushing.
  - Mean worst severity scores in the BG-12 with ASA group were higher in Weeks 5–8 (ie, after withdrawal of ASA) than in Weeks 1–4 but were consistently lower than the mean worst severity scores seen in the BG-12 without ASA group (Figure 4).

Figure 4: Worst severity scores for flushing events



- The median number of flushing events was lowest in the BG-12 with ASA group, when compared with BG-12 alone or slow titration BG-12 (Figure 5).

Figure 5: Median number of flushing events[a]

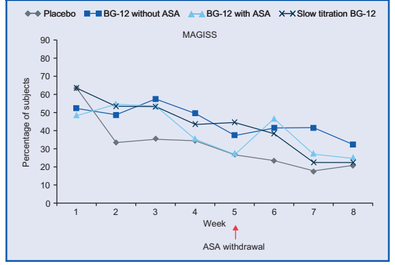


aThe median number of flushing events in the placebo group was zero overall, for Weeks 1–4, and for Weeks 5–8.

GI Events

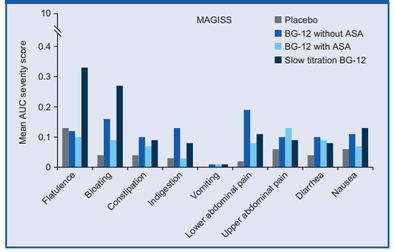
- GI events were relatively common in BG-12-treated subjects (Figure 6).
  - By Week 4, the percentage of subjects who experienced GI events was lower in the BG-12 with ASA group than in the other BG-12 treatment groups. Proportions in the BG-12 alone and slow titration BG-12 groups were similar throughout the 8 weeks of the study.

Figure 6: Percentage of subjects experiencing GI events



- Mean severity scores (AUC) for any given GI symptom were low in Weeks 1–4 (Figure 7). Mean AUC severity scores in Weeks 5–8 were lower for all GI symptoms and for all groups (data not shown).

Figure 7: Summary of severity scores for acute GI events (Weeks 1–4)



CONCLUSIONS

- Flushing events in the BG-12 groups were common and were assessed by the subjects as mild to moderate. No subject discontinued due to flushing.
- The incidences of flushing and GI events for all groups, including placebo, were higher than those reported previously in the pivotal Phase 3 trials; however, it should be noted that this study assessed patient-reported events daily, whereas events occurring in the DEFINE and CONFIRM studies were assessed monthly by study investigators.
- ASA reduced both the incidence and severity of flushing events, whereas slow titration of BG-12 appeared to have no effect.
- GI events were relatively common and were reported as mild by the subjects. ASA administration did not appear to worsen GI symptoms and slow dose titration of BG-12 had no effect.
- Overall, these results suggest that flushing and GI events associated with BG-12 are mild to moderate and manageable.

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DISCLOSURES

HR: employee of PROMETRIKA, LLC. JOG, JL, GP, VV: employees of Biogen Idec.

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