For most patients, these events were mild or moderate in severity and decreased in incidence after the first month of treatment: 83.0% of patients experienced flushing with ASA pretreatment and 81.5% of patients experienced flushing with slow titration BG-12 (Table 1). The median number of flushing events was lower in the BG-12 with ASA group, when compared with BG-12 alone or slow titration BG-12 (Figure 1).

### RESULTS

**Flushing Events**
- Flushing events were common in all groups, including placebo, but were more common in subjects treated with ASA in Weeks 1–4 compared to 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.
- 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=1), and slow titration BG-12 (n=1).
- 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 mean worst severity scores seen in the BG-12 without ASA group (Figure 6).
- Flushing severity was assessed by dividing the total area under the curve (AUC) from Weeks 1–4 by the median number of flushing events (Figure 6).

**GI Events**
- GI events were relatively common in BG-12–treated subjects (Figure 4).
- 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 first 4 weeks of the study.

### CONCLUSIONS

- Flushing events in the BG-12 groups were common and were managed by the subjects as mild to moderate. No subject discontinued due to flushing.
- The incidence of flushing and GI events in all groups, including placebo, were higher than those reported previously in the pivotal Phase 3 trials. However, a similar trend was observed in this study assessed patient-reported events daily, whereas events occurring in the confirmatory studies were assessed monthly by study investigators.
- ASA reduced the incidence and severity of flushing events, whereas slow titration of BG-12 apparently had no effect.
- GI events were relatively common and were reported as mild by the subjects. ASA administration appeared to worsen GI symptoms and slow 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 temporary.

### METHODS

**Study Design**
- Study subjects were randomized to receive oral BG-12 twice daily (BID), 360 mg without ASA, 360 mg with ASA plaques, or slow titrated over 3 weeks without ASA (BG-12 without ASA (Figure 1)).

**Flushing and GI Event Reporting**
- Study volunteers recorded flushing and GI events via an eDiary device using t-MFSS and m-MGFISS scales. The flushing scales were modified in a similar manner to the flushing scales developed by Norquist et al. and the GI scales were modified internally to obtain relevant data in a similar manner to the flushing scales. The t-MFSS and m-MGFISS scales reflect the impact of flushing and GI events on the subject during the 24 hours prior to data collection.
- 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 mean worst severity scores seen in the BG-12 without ASA group (Figure 6).
- Flushing severity was assessed by dividing the total area under the curve (AUC) from Weeks 1–4 by the median number of flushing events (Figure 6).

**RESULTS**

**Objective**
- To evaluate the effects of non-steroidal anti-inflammatory drug (NSAID) pretreatment or slow dose titration of BG-12 on flushing and GI events associated with BG-12 on 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.

**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 radiologic efficacy over 2 years in the Phase 3a DEFINE and CONFIRM studies in patients with relapsing–remitting MS (RRMS).
- In the Phase 3a studies, the most common adverse events associated with BG-12 included flushing and gastrointestinal (GI) events. For most patients, these events were mild or moderate in severity and decreased in incidence after the first month of treatment.

**Methods**

**Study Design**
- Study subjects were randomized to receive oral BG-12 twice daily (BID), 360 mg with ASA, 360 mg with ASA plaques, or slow titrated over 3 weeks without ASA (BG-12 without ASA (Figure 1)).

**Flushing and GI Event Reporting**
- Study volunteers recorded flushing and GI events via an eDiary device using t-MFSS and m-MGFISS scales. The flushing scales were modified in a similar manner to the flushing scales developed by Norquist et al. and the GI scales were modified internally to obtain relevant data in a similar manner to the flushing scales. The t-MFSS and m-MGFISS scales reflect the impact of flushing and GI events on the subject during the 24 hours prior to data collection.
- 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 mean worst severity scores seen in the BG-12 without ASA group (Figure 6).
- Flushing severity was assessed by dividing the total area under the curve (AUC) from Weeks 1–4 by the median number of flushing events (Figure 6).

**Endpoints**
- The primary endpoint was the incidence and severity of flushing as measured by t-MFSS and m-MGFISS and the incidence and severity of GI events as measured by t-MFSS and m-MGFISS.