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# Timecourse of Treatment Effects of BG-12 (Dimethyl Fumarate) in MS

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## INTRODUCTION

- Oral BG-12 (dimethyl fumarate) is approved in the United States for relapsing forms of MS.
- Experimental evidence shows that BG-12 may have anti-inflammatory and cytoprotective activity via the nuclear factor (erythroid-derived 2) -like 2 (Nrf2) transcriptional pathway.[1,2]
- In a Phase 2 study, significantly reduced MRI activity with BG-12 versus placebo was observed from Week 12.[3]
- BG-12 has demonstrated significant reductions in relapses and brain MRI activity over 2 years in patients with relapsing-remitting MS (RRMS) in the Phase 3 DEFINE and CONFIRM studies.[4,5]

## OBJECTIVE

- To characterize the temporal profile of BG-12 treatment efficacy in an integrated analysis of data from DEFINE and CONFIRM.

## METHODS

### Study Design

- Patients were randomized to receive oral BG-12 240 mg twice daily (BID) or three times daily (TID) or matching placebo for 2 years.
  - CONFIRM also included glatiramer acetate (GA) as a reference comparator.
- Clinical efficacy was assessed in the intent-to-treat (ITT) population; MRI assessments were performed in a cohort of patients at sites with MRI capabilities.
- The integrated analysis plan was finalized prior to unblinding of CONFIRM and was conducted because baseline characteristics and treatment effects were homogeneous across the studies.[4,5]

### Key Inclusion Criteria

- Age 18–55 years.
- Diagnosis of RRMS (McDonald criteria 2005).[6]
- Expanded Disability Status Scale (EDSS) score of 0–5.0.
- ≥1 relapse in the 12 months prior to randomization or ≥1 gadolinium-enhancing (Gd+) lesion on brain MRI within 6 weeks prior to randomization.

### Key Exclusion Criteria

- Progressive forms of MS.
- Other significant illness or pre-specified abnormal laboratory parameters.
- A relapse or corticosteroids within 50 days prior to randomization.
- Prior treatment with GA:
  - Within the past 3 months (DEFINE)
  - At any time (CONFIRM).

### Analysis of Timecourse

- The pre-specified integrated analysis of DEFINE and CONFIRM studies assessed annualized relapse rate (ARR), time to first relapse (weeks), and number of new/enlarging T2 hyperintense lesions and Gd+ lesions over 2 years.
- To assess the onset of BG-12 treatment efficacy a post hoc analysis of ARR by 3-month interval, time to first relapse (weeks) over 2 years, T2 lesions at Week 24, Weeks 24–48, and Weeks 48–96 and Gd+ lesions at Weeks 24, 48, and 96 were conducted.

## RESULTS

### Patients

- The ITT population for the integrated analysis comprised 769, 761 and 771 patients assigned to BG-12 BID, TID and placebo, respectively (MRI cohort: 345, 354 and 347 patients, respectively) (Table 1).
- Baseline demographic and disease characteristics were generally well balanced across treatment groups.

**Table 1:** Demographics and baseline characteristics

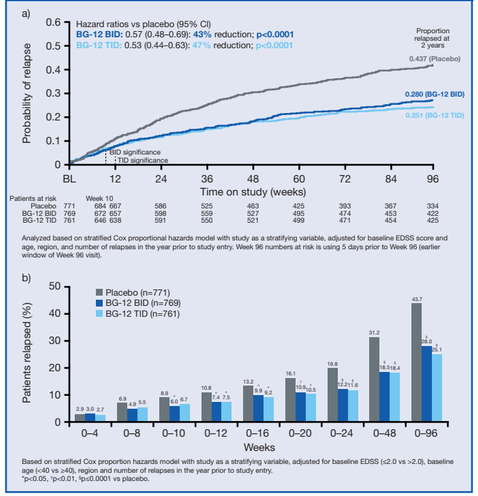
| Characteristic[a] | Placebo (n=771) | BG-12 BID (n=769) | BG-12 TID (n=761) |
|---|---|---|---|
| Age, years | 37.7 (9.2) | 37.9 (9.2) | 38.3 (9.1) |
| Female, % | 72 | 70 | 73 |
| Time since first MS symptoms, years | 8.1 (6.5) | 8.3 (6.8) | 7.8 (6.5) |
| Prior approved MS treatments,[b] % | 37 | 34 | 35 |
| Relapses in prior year | 1.3 (0.7) | 1.3 (0.7) | 1.3 (0.7) |
| EDSS score | 2.5 (1.2) | 2.5 (1.3) | 2.4 (1.2) |
| Patients with Gd+ lesion(s),[c] % | 45 | 41 | 37 |
| T2 lesion volume,[c] cm$^3$ | 10.4 (11.4) | 11.1 (12.1) | 10.8 (12.7) |

[a]Values are means (standard deviation) unless otherwise stated; [b]Interferon beta-1a (24%), interferon beta-1b (13%), natalizumab (2%), GA (8%); [c]Performed in a subset of patients (n=1,046 [347, 345, 354 in placebo, BG-12 BID, and BG-12 TID groups, respectively)].

### Relapses

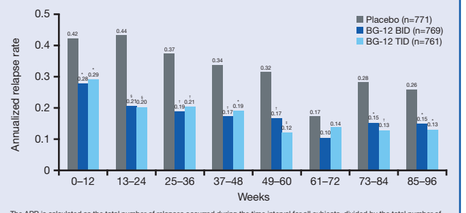
- BG-12 reduced the proportion of patients relapsed, with significant separation versus placebo achieved at Week 10 for BG-12 BID and Week 12 for BG-12 TID (post hoc analyses) (Figure 1).
  - Risk of relapse hazard ratio (95% confidence interval [CI]) at Week 10 was 0.68 (0.46–0.99) in the BID group (p=0.0427) and 0.77 (0.53–1.12) in the TID group (p=0.1682).
  - Risk of relapse hazard ratio (95% CI) at Week 12 was 0.68 (0.48–0.96) in the BID group (p=0.0276) and 0.70 (0.50–0.99) in the TID group (p=0.0451).

**Figure 1:** Proportion of patients relapsed a) Time to first relapse and b) Cumulative risk of relapse




- Separation was maintained at 2 years, with reductions in risk of relapse of 43% and 47% in patients receiving BG-12 BID and BG-12 TID, respectively, versus placebo (p<0.0001) (Figure 1).
- BG-12 treatment reduced ARR with significant separation versus placebo at Week 12 for both doses (Figure 2).
  - The rate ratio (95% CI) for ARR at Week 12 was 0.66 (0.47–0.93) (BID; p=0.0159) and 0.69 (0.49–0.97) (TID; p=0.0314).

**Figure 2:** ARR over time




- Significant separation was maintained thereafter; at 2 years, BG-12 BID and TID reduced ARR by 49% for both (p<0.0001) compared with placebo.

### MRI Results

- Statistically significant reductions relative to placebo in the number of new/enlarging T2 lesions and number of Gd+ lesions were observed from the first post-baseline MRI assessment at 24 weeks in patients treated with BG-12.
  - Reductions in adjusted mean numbers of new/enlarging T2 hyperintense lesions versus placebo at 24 weeks (Figure 3) were:
    - 72% with BG-12 BID (lesion mean ratio [95% CI]: 0.28 [0.22–0.36]; p<0.0001)
    - 67% with BG-12 TID (lesion mean ratio [95% CI]: 0.33 [0.26–0.41]; p<0.0001).
  - Reductions in Gd+ lesion activity at Week 24 (Figure 4) were:
    - 88% with BG-12 BID (odds ratio [95% CI]: 0.12 [0.08–0.20]; p<0.0001)
    - 75% with BG-12 TID (odds ratio [95% CI]: 0.25 [0.17–0.36]; p<0.0001).

**Figure 3:** Number of new/enlarging T2 lesions

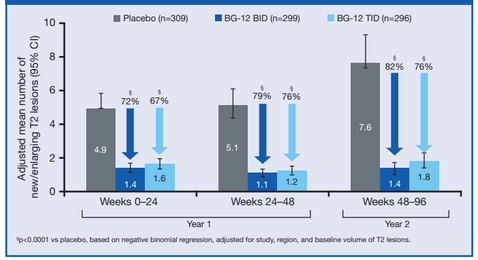
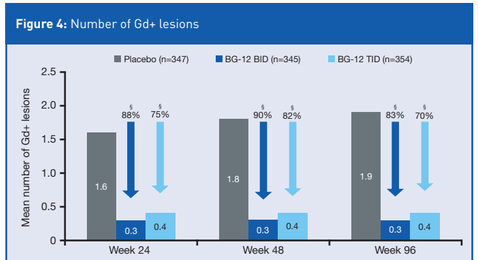



**Figure 4:** Number of Gd+ lesions




- Reductions in Gd+ lesion activity versus placebo were observed within the first 24 weeks of the study and were sustained at Year 1 and Year 2 of the study.

## CONCLUSIONS

- BG-12 treatment resulted in significant improvements in disease activity over placebo that were apparent by Weeks 10–12 and sustained over 2 years.
- Similar efficacy results were observed between the two BG-12 dosing regimens.
- Significant treatment benefits were observed from the first post-treatment assessment of MRI activity at 24 weeks.
- The early and sustained treatment effects, together with an acceptable safety profile, support BG-12 as a valuable oral treatment for patients with relapsing forms of MS.

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## DISCLOSURES

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