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Effect of BG-12 (Dimethyl Fumarate) in Newly Diagnosed RRMS Patients

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INTRODUCTION

- Oral BG-12 (dimethyl fumarate) is approved in the United States for the treatment of relapsing forms of MS.
- There is experimental evidence that BG-12 may provide anti-inflammatory and cytoprotective effects via the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway.[1,2]
- BG-12 demonstrated significant efficacy on clinical and MRI measures over 2 years in the Phase 3 DEFINE and CONFIRM studies in patients with relapsing–remitting MS (RRMS).[3-5]
  - Efficacy was consistent across a broad range of pre-specified patient subgroups from these studies.[6]
- A pre-specified integrated analysis of DEFINE and CONFIRM was conducted in order to provide a more precise estimate of the therapeutic effect of BG-12 relative to placebo than can be obtained from either study in isolation.

OBJECTIVE

- To report a post hoc analysis of the efficacy of BG-12 in the newly diagnosed RRMS patient population from the integrated DEFINE and CONFIRM data set.

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 to be conducted only if baseline characteristics and treatment effects were homogeneous across the studies.

Key Inclusion Criteria

- Age 18–55 years.
- Diagnosis of RRMS (McDonald criteria 2005).[7]
- 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).

Clinical Efficacy Endpoints

- In DEFINE, the primary endpoint was the proportion of patients relapsed at 2 years (this was a secondary endpoint in CONFIRM).
- In CONFIRM, the primary endpoint was annualized relapse rate (ARR) at 2 years (this was a secondary endpoint in DEFINE).
- Additional endpoints at 2 years included:
  - Time to 12-week confirmed disability progression on the EDSS
  - Number of Gd+ lesions
  - Number of new/enlarging T2 hyperintense lesions
  - Number of new T1 hypointense lesions.

Newly Diagnosed Population

- Newly diagnosed patients were defined as those diagnosed with RRMS within a year from study entry and who either had received no prior MS therapy (treatment naïve) or had been treated with steroids only.

RESULTS

Patients

- The ITT population for the integrated analysis comprised 2,301 patients.
  - Of these, 678 patients were newly diagnosed and were treated with BG-12 BID (n=221), BG-12 TID (n=234), or placebo (n=223), including 308 patients in the MRI cohort: BG-12 BID (n=99), BG-12 TID (n=109), or placebo (n=100).
- Baseline demographic and disease characteristics in the newly diagnosed population were generally well balanced across treatment groups (Table 1).

Relapses

- In newly diagnosed patients, BG-12 BID and BG-12 TID reduced the ARR at 2 years by 56% and 60%, respectively, compared with placebo (Figure 1).
- BG-12 BID and BG-12 TID reduced the risk of relapse at 2 years by 54% and 57%, respectively, compared with placebo (Figure 2).

Disability Progression

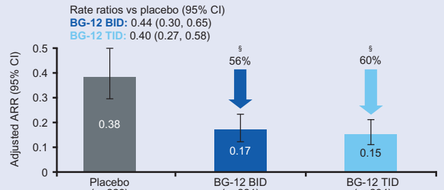
- BG-12 BID and BG-12 TID reduced the risk of 12-week confirmed disability progression at 2 years by 71% and 47%, respectively, compared with placebo (Figure 3).

Table 1: Baseline characteristics (newly diagnosed population)

Characteristic[a]	Placebo (n=223)	BG-12 BID (n=221)	BG-12 TID (n=234)
Age, years	36.5 (9.4)	35.3 (9.4)	36.6 (9.6)
Female, %	70	73	71
Time since first MS symptoms, years Median (min, max)	4.3 (5.3) 2.0 (0, 31)	4.3 (5.8) 2.0 (0, 42)	3.8 (4.1) 2.0 (0, 23)
Time since diagnosis, years Median (min, max)	0.5 (0.5) 1.0 (0, 1.0)	0.5 (0.5) 1.0 (0, 1.0)	0.5 (0.5) 1.0 (0, 1.0)
Prior MS treatment[b] naive, %	93	91	91
Relapses in prior year	1.4 (0.6)	1.4 (0.6)	1.5 (0.6)
McDonald criterion 1, %	75	68	69
EDSS score	2.2 (1.1)	2.1 (1.1)	2.0 (1.0)
Gd+ lesion volume,[c] cm^3	0.2 (0.4)	0.3 (0.9)	0.1 (0.3)
T2 lesion volume,[c] cm^3	8.7 (10.9)	8.5 (9.0)	7.7 (10.7)
T1 hypointense lesion volume,[c] cm^3	2.0 (3.6)	2.2 (3.3)	1.6 (2.7)

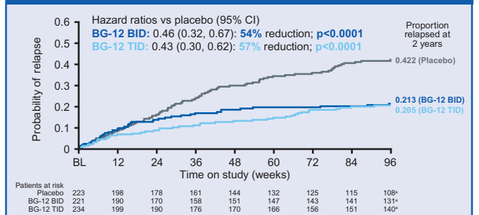
[a]Values are mean (standard deviation) unless otherwise stated; [b]Includes disease-modifying therapies (DMTs) and non-DMTs; [c]MRI cohort only.

Figure 1: ARR at 2 years



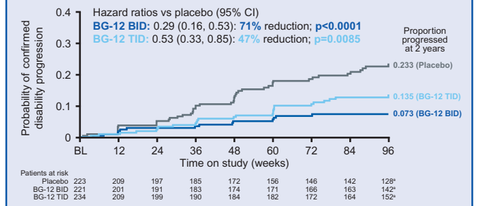
§p<0.0001 vs placebo.
ARR calculated with negative binomial regression, adjusted for baseline EDSS score (≤2.0 vs >2.0), baseline age (<40 vs ≥40), study, region, and number of relapses in the year prior to study entry. CI = confidence interval.

Figure 2: Proportion of patients relapsed at 2 years



Estimated proportion of patients relapsed at Week 96 was derived using Kaplan–Meier analysis. Hazard ratios, 95% CI, and p-values were based on a stratified Cox proportional hazards model with study as the stratifying variable, adjusted for baseline EDSS score (≤2.0 vs >2.0), baseline age (<40 vs ≥40), region, and number of relapses in the year prior to study entry.
*Numbers at risk 5 days prior to Week 96 (earlier window of Week 96 visit). BL = baseline.

Figure 3: Time to 12-week confirmed disability progression at 2 years

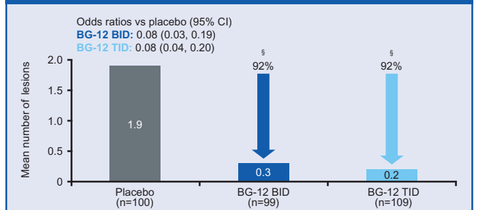


Estimated proportion of patients with progression at Week 96 was derived using Kaplan–Meier analysis. Hazard ratios, 95% CI, and p-values were based on a stratified Cox proportional hazards model with study as the stratifying variable, adjusted for baseline EDSS score, baseline age (<40 vs ≥40), and region.
*Numbers at risk 5 days prior to Week 96 (earlier window of Week 96 visit).

MRI Results

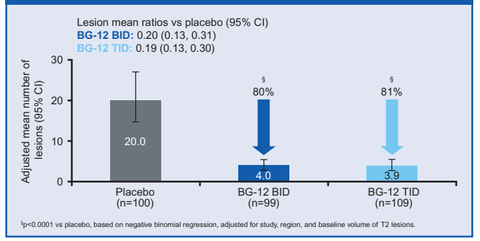
- Compared with placebo, BG-12 BID and BG-12 TID reduced:
  - Gd+ lesion activity by 92% (both dosages; Figure 4a)
  - The number of new/enlarging T2 hyperintense lesions by 80% and 81% (Figure 4b)
  - The number of new T1 hypointense lesions by 68% and 70% (Figure 4c), respectively.

Figure 4a: Gd+ lesions at 2 years



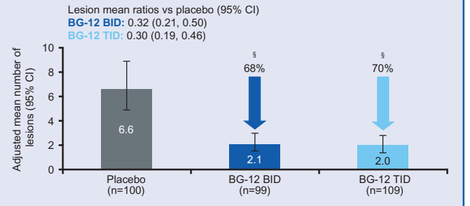
§p<0.0001 vs placebo, based on ordinal logistic regression, adjusted for study, region, and baseline number of Gd+ lesions; percentages are the reduction in odds of having greater Gd+ lesion activity, compared with placebo.

Figure 4b: New/enlarging T2 hyperintense lesions at 2 years



§p<0.0001 vs placebo, based on negative binomial regression, adjusted for study, region, and baseline volume of T2 lesions.

Figure 4c: New T1 hypointense lesions at 2 years



§p<0.0001 vs placebo, based on negative binomial regression, adjusted for study, region, and baseline volume of T1 lesions.

CONCLUSIONS

- This post hoc analysis demonstrates that patients participating in the Phase 3 DEFINE and CONFIRM studies who are newly diagnosed with RRMS derived clinical and neuroradiologic benefit with BG-12 treatment relative to placebo.
- The findings in newly diagnosed patients mirror the results reported for the overall DEFINE and CONFIRM study populations evaluated in the integrated analysis,[5] supporting the consistent efficacy of BG-12 in subpopulations of patients from these studies.
- Together with an acceptable safety profile in the overall study populations,[3,4] this analysis supports BG-12 as a valuable oral treatment option for newly diagnosed RRMS patients.

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DISCLOSURES

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