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Effect of BG-12 (Dimethyl Fumarate) on Quality of Life in Patients with MS

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INTRODUCTION

- Patients with multiple sclerosis (MS) often experience impaired health-related quality of life (HRQoL) that deteriorates with disease progression, affecting family life, social functioning and employment status.[1,2] Common features of MS such as depression, fatigue, and cognitive dysfunction also impact HRQoL.[1–4]
- Patients with MS rank their HRQoL lower than that of the general population and individuals with other chronic diseases.[5]
  - Hence, it is useful to assess HRQoL alongside efficacy and safety outcomes when evaluating the effects of potential treatments for MS.
- Oral BG-12 (dimethyl fumarate) is approved in the United States for the treatment of relapsing forms of MS.
- BG-12 has shown significant clinical and MRI efficacy and an acceptable safety profile in the Phase 3 DEFINE and CONFIRM studies in patients with relapsing–remitting MS (RRMS).[4,7]
- The efficacy of BG-12 was further supported in a pre-specified integrated analysis of data from DEFINE and CONFIRM.[8]
  - This analysis was conducted 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.

OBJECTIVES

- To report the effects of BG-12 on pre-specified HRQoL endpoints over 2 years in a pre-specified integrated analysis of DEFINE and CONFIRM in patients with RRMS.
- To describe the impact of MS on patient HRQoL at baseline.

METHODS

Study Design

- DEFINE and CONFIRM enrolled patients with an established diagnosis of RRMS according to McDonald criteria (2005)[9] and an Expanded Disability Status Scale (EDSS) score of 0–5.0.
- 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.
- 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.
- Patient-reported HRQoL was assessed as a tertiary endpoint in both studies.

Short Form-36 Health Survey (SF-36)

- An SF-36 questionnaire measuring patients' health status and HRQoL was administered at baseline and at 6, 12, and 24 months.
  - The SF-36 consists of eight multi-item domains with scores ranging from 0 to 100, where higher scores indicate better HRQoL.[10]
  - Data outputs are grouped into two summary scores; the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

Global Impression of Well-being

- Patients' global impression of well-being was assessed at baseline and every 3 months thereafter using a 100-point visual analog scale (VAS), ranging from 'poor' (score of 0) to 'excellent' (score of 100).

European Quality of Life – 5 Dimensions Health Survey (EQ-5D)

- Patients indicate whether they have 'no problems' (level 1), 'some problems' (level 2), or 'severe problems' (level 3) in five dimensions of health status. The scores are combined to give the summary EQ-5D index score.
- The EQ-5D was administered at baseline and at 6, 12, and 24 months.

Statistical Analyses

- Treatment effects were assessed in the intent-to-treat (ITT) population based on mean changes from baseline to 2 years in SF-36, global impression of well-being, and EQ-5D scores, using analysis of covariance adjusted for study, region, and baseline values for the respective HRQoL measure.
  - Missing data were imputed using a random effects model.
- The proportion of patients showing a clinically relevant 5-point improvement[11,12] from baseline to 2 years on the PCS and MCS subscales was determined by a post hoc ordinal logistic regression analysis, adjusted for region and corresponding baseline SF-36 component score.
- Baseline SF-36 summary scores were assessed relative to baseline EDSS scores in a post hoc analysis to explore the impact of MS disability status on HRQoL.

RESULTS

Patients

- The ITT population for the integrated analysis comprised 2,301 patients treated with placebo (n=771), BG-12 BID (n=769), and BG-12 TID (n=761).
- Baseline demographic and disease characteristics were generally well balanced across the treatment groups in the individual studies, and in the integrated analysis (Table 1).

Table 1: Baseline demographic and disease 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)
Time since diagnosis, years	5.3 (5.5)	5.3 (5.3)	4.9 (5.3)
Prior approved MS treatments,[b] %	37	34	35
Relapses in previous 3 years	2.5 (1.5)	2.5 (1.4)	2.5 (1.4)
Relapses in prior year	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)
Time since most recent pre-study relapse, months	6.6 (6.6)	6.4 (5.9)	6.5 (6.6)
EDSS score	2.5 (1.2)	2.5 (1.3)	2.4 (1.2)

[a]Values are mean (standard deviation [SD]) unless otherwise stated; [b]Interferon beta-1a, interferon beta-1b, natalizumab or GA.

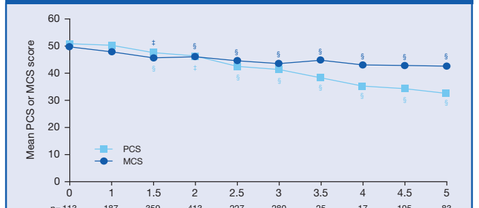
Impact of MS on Patient HRQoL at Baseline

- Mean baseline PCS scores ± SD were 43.1 ± 10.1, 43.0 ± 10.0, and 43.4 ± 10.4 in the placebo, BG-12 BID, and BG-12 TID groups, respectively.
- Corresponding mean MCS scores were 45.3 ± 11.0, 45.3 ± 11.1, and 45.0 ± 10.7.
  - These scores are lower than those for the general US population (50 for each component summary).[10]
- At baseline, HRQoL impairment was greater with increasing EDSS scores: patients with baseline EDSS scores ≥1.5 had significantly lower mean PCS and MCS scores than those with an EDSS score of 0 (Figure 1).
  - Patients with an EDSS score ≥2.5 had clinically meaningful impairment (≥5 point deficit) in mean PCS and MCS scale scores relative to those with EDSS score of 0.

SF-36 Summary Scores

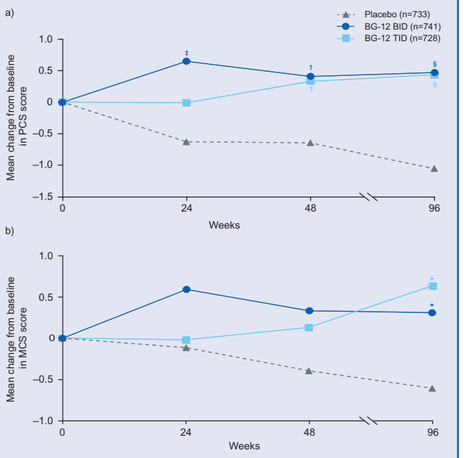
- Patients treated with BG-12 reported significant increases in mean PCS and MCS scores at 2 years, indicating improvement in their physical and mental functioning, while placebo-treated patients showed a decrease in mean PCS and MCS scores (Figure 2).

Figure 1: Higher EDSS scores associated with lower mean SF-36 PCS and MCS scores at baseline



‡p<0.001, §p<0.0001 for mean score vs mean score at a baseline EDSS score of 0 (t-test).

Figure 2: SF-36 mean change from baseline in a) PCS, and b) MCS score over time

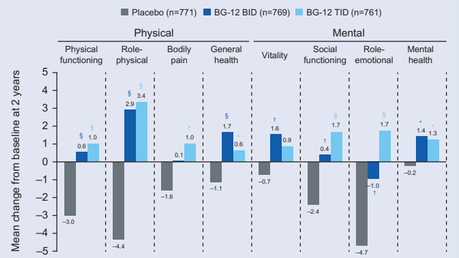


*p<0.05, †p<0.01, ‡p<0.001, §p≤0.0001 vs placebo.

SF-36 Subscale Scores

- At 2 years, BG-12-treated patients reported no change or overall improvement from baseline in all SF-36 subscale scores, except for mean role-emotional score for the BG-12 BID group, while placebo-treated patients reported lower SF-36 subscale scores versus baseline (Figure 3).
  - Improvements were significant for BG-12 BID versus placebo on all PCS and MCS subscales except bodily pain.
  - Significant improvements were reported with BG-12 TID compared with placebo on all PCS and MCS subscales except vitality.

Figure 3: SF-36 subscale scores: mean change from baseline to 2 years



*p<0.05, †p<0.01, ‡p≤0.0001 vs placebo.

Clinically Relevant (≥5 Points) Improvement in SF-36 Summary Scores

- The proportion of patients who achieved a clinically relevant 5-point improvement in PCS and MCS scores was significantly higher in the BG-12 groups than in the placebo group (Table 2).

Table 2: Patients with 5-point change in SF-36 component scores from baseline to 2 years

	Placebo (n=733)	BG-12 BID (n=741)	BG-12 TID (n=728)
PCS, n (%)			
Improved	169 (23.1)	197 (26.6)	219 (30.1)
Stable	351 (47.9)	354 (47.8)	341 (46.8)
Worsened	213 (29.1)	190 (25.6)	168 (23.1)
Odds ratio (95% CI)[a,b]		1.26 (1.03, 1.54)	1.48 (1.21, 1.81)
p-value[a]		0.0221	0.0001
MCS, n (%)			
Improved	129 (17.6)	162 (21.9)	182 (25.0)
Stable	417 (56.9)	439 (59.2)	408 (56.0)
Worsened	187 (25.5)	140 (18.9)	138 (19.0)
Odds ratio (95% CI)[a,b]		1.42 (1.16, 1.73)	1.63 (1.33, 2.00)
p-value[a]		0.0008	<0.0001

Post hoc analysis.
[a]Comparison vs placebo based on ordinal logistic regression model; [b]Odds for improvement from stable to improved or from worsened to stable. CI = confidence interval.

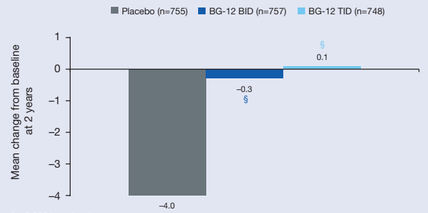
Global Impression of Well-being (VAS)

- Mean baseline scores ± SD were similar in the placebo (63.7 ± 22.5), BG-12 BID (64.7 ± 21.6) and BG-12 TID (64.6 ± 22.7) groups.
- At 2 years, patients in the BG-12 groups reported a significantly better sense of well-being than patients in the placebo group.
  - The mean change from baseline to 2 years in the VAS score in the placebo group was –4.0 compared with –0.3 in the BG-12 BID group and 0.1 in the BG-12 TID group (both p<0.0001; Figure 4).

EQ-5D

- Mean EQ-5D index baseline scores ± SD were similar in the placebo, BG-12 BID and BG-12 TID groups: 0.71 ± 0.23, 0.72 ± 0.22, and 0.71 ± 0.23, respectively.
- At 2 years, BG-12-treated patients reported significantly improved health status according to the EQ-5D index score compared with placebo-treated patients.

Figure 4: Global assessment of well-being (VAS): mean change from baseline at 2 years



§p≤0.0001 vs placebo.

CONCLUSIONS

- BG-12 treatment resulted in significant improvements in physical and mental aspects of health and functioning, general well-being, and overall health status compared with placebo in patients with RRMS.
  - By contrast, patients receiving placebo generally reported a decline in their HRQoL throughout the study.
- Alongside significant improvements in efficacy outcomes and an acceptable safety profile,[4–8] the demonstrated benefits of BG-12 on patient-reported HRQoL further support BG-12 as a valuable oral treatment option for patients with relapsing MS.

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