BG00012 in RRMS: Update From Phase 2 Study.

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Rationale for the Use of DMF in RRMS.

- Rationale:
  - **In vitro:**
    - Th1→Th2 cytokine profile shift. *Ockenfels et al. 1998. Asadulah et al. 1997. De Jong et al. 1996.*
    - MHF and DMF inhibited monocyte differentiation into dendritic cells. *Zhu and Mrowietz, 2001.*
    - Decrease TNF α induced endothelial adhesion molecule (e-selectin, VCAM1, ICAM1) expression. *Vandermeeren et al. 1997.*
    - Dimethylfumarate inhibits tumor-necrosis-factor-induced CD62E expression in an NF-kb-dependent manner *Loewe et al 2001.*
    - Decreases TNF-induced nuclear entry of NF-kappa b/p65 in human endothelial cells. *Loewe et al 2002.*
  - **In vivo:**
    - ↓ Acute and chronic rejection. *Risch et al. 2001. Lehmann 2002,*
  - **In man (oral DMF/MHF):**
    - Decrease Gd enhancing lesions in MS. *Schimrigk et al. #S46.003, AAN 2005.*
    - Decrease circulating T cells. *Treumer et al. 2003. Hoxtermann et al. 1998.*

Double-blind, Placebo Controlled, Dose Ranging Study to Determine the Efficacy and Safety of BG00012 in Subjects With RRMS.

(clinicaltrials.gov # NCT00168701)

- 24 weeks therapy; 4 arms:
  - Placebo; 120 qd; 120 TID; 240 TID.
- Primary efficacy endpoint:
  - Total # of Gd-enhancing lesions over four scans at weeks 12, 16, 20 & 24 vs. Placebo (EEP).
- Additional MRI efficacy endpoints:
  - Cumulative # of Gd-enhancing lesions over six scans at weeks 4, 8, 12, 16, 20 & 24 vs. Placebo (EEP).
  - # Of new or newly enlarging T2 hyper-intense lesions at week 24 compared to baseline (EEP).

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