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ClinicalTrials Identifier: NCT00168701
Updated: 2005_09_14

Descriptive Information

Brief title Effacacy and Safety of BG00012 in MS

Official title Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Effacacy and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis

Brief summary

DMF, the active ingredient in BG00012, is an immunomodulator demonstrating definite therapeutic efficacy in psoriasis (Carboni et al, 2004; Altmeyer et al, 1994; Mrowietz et al, 1999) and possible therapeutic efficacy in MS (Schimrigk et al, 2001). However, the target site of action and the exact mechanism of action of DMF are unknown.

Like psoriasis, MS has been postulated to be driven by a Th1 cytokine reaction and to therapeutically respond to either immunosuppression or Th2 suppression (Weiner and Selkoe, 2002). Putative effects of BG00012 include suppression of circulating T cell population, down regulation of adhesion molecule expression, modulation of the Th1/Th2 cytokine expression profile, inhibition of neutrophil burst, and TNF-induced CD62E expression through suppression of NF-kB nuclear translocation.

Methyl fumaric acid esters (FUMADERMÒ) have been shown to reduce peripherally in vivo circulating CD4+, CD8+ and CD52+ mononuclear cells (Hoxtermann et al, 1998). This circulatory reduction has been associated with a decrease in intradermal mononuclear cell infiltration in psoriasis patients (another T cell-mediated disease) (Vandermeeren et al, 1997). DMF was recently shown to induce substantial plasma membrane alterations potentially linked to the deactivation via apoptosis of lymphocytes (Sebök et al, 2000).

Methylfumarates have been shown to modulate in vitro T cell cytokine profile from Th1 to Th2 (Ockenfels et al, 1998). DMF and MMF inhibit the proliferation of keratinocytes, possibly due to a temporary rise in the intracellular calcium concentration (Nibbering et al, 1993). Methylfumarates have been shown to prevent acute and chronic rejection in rat kidney transplantation models (Risch et al, 2001). It is difficult to assess the validity of some in vitro data that have been derived using doses that exceed serum levels found in human trials (Mrowietz et al, 1999).

In summary, the putative immunomodulatory effects, the psoriasis efficacy of FUMADERM®, and the efficacy data in the pilot MS study of BG00012 support a

proof of concept study in MS

Detailed description

The study will be divided into two parts: Part 1 will be a 24-week, blinded, placebo-controlled treatment phase followed by Part 2, a 24-week blinded, safety extension phase in which all subjects will receive BG00012.

All investigational drug (BG00012 or placebo) will be given orally.

In Part 1, subjects will be randomized in equal numbers to one of the following treatment groups:

Treatment Group BG00012 Dosing Regimen BG00012 Total Daily Dose
1 120 mg once a day (qd) 120 mg
2 120 mg three times a day (tid) 360 mg
3 240 mg tid 720 mg
4 Placebo Placebo

All subjects will be evaluated for tolerance to investigational drug after the first week of dosing. In addition, subjects in the highest dose group (Group 3) will dose at 120 mg tid for the first week. After 1 week, Group 3 subjects who tolerate 120 mg tid (as determined by the subject's tolerance of flushing episodes and gastrointestinal [GI] disturbances) will have their dose increased to 240 mg tid.

In Part 2, subjects who received BG00012 in Part 1 of the study will remain on the same BG00012 dose throughout the Part 2 extension phase. Subjects who received placebo in Part 1 of the study will receive BG00012 120 mg tid for one week in Part 2 and then, if well-tolerated, the BG00012 dose will be increased to 240 mg tid.

Dose reduction will be allowed for subjects who are unable to tolerate investigational drug. Dosing interruptions (or investigational drug discontinuation) will be required for significantly elevated liver or renal function tests or decreased white blood cell count (WBC). Any subject who prematurely discontinues BG00012 dosing should remain in the study for the time period specified in the protocol and continue protocol-scheduled evaluations.

Subject treatment assignments will remain blinded throughout the study. Safety will be monitored during the study by the Advisory Committee and the Clinical Safety Committee.

Phase	Phase 2
Study type	Interventional
Study design	Treatment
Study design	Randomized
Study design	Double Blind
Study design	Placebo Control
Study design	Parallel Assignment
Study design	Safety/Efficacy Study

Primary outcome	Measure: The primary endpoint for the primary objective is the total number of Gd-enhancing lesions over four scans at Weeks 12, 16, 20, and 24 (calculated as the sum of these four MRI scans).
Secondary outcome	Measure: Secondary MRI endpoints include:
Secondary outcome	Measure: · the cumulative number of new Gd-enhancing lesions from baseline to Week 24, and
Secondary outcome	Measure: · the number of new or newly-enlarging T2 hyperintense lesions at Week 24 compared to baseline.
Secondary outcome	Measure: Additional endpoints include:
Secondary outcome	Measure: · the number of new T1 hypointense lesions at Week 24 compared to baseline
Secondary outcome	Measure: · the incidence and severity of adverse events
Secondary outcome	Measure: · EDSS scores and change from baseline in EDSS scores at Weeks 12, 24, 36, and 48, and
Secondary outcome	Measure: · annualized relapse rate from Week 0 to Weeks 24 and 48, and the proportion of relapse-free subjects at Weeks 24 and 48.
Condition	Multiple Sclerosis
Intervention	Drug: BG00012

Recruitment Information

Status	No longer recruiting
Start date	2004-10

Criteria

Inclusion Criteria:

1. Must give written informed consent and authorize the release and use of protected health information (PHI), as required by local law.

2. Must be 18 to 55 years old, inclusive, at the time of informed consent.

3. Must have a confirmed diagnosis of relapsing-remitting MS according to McDonald criteria #1-4 (McDonald et al, 2001; Appendix 2).

4. Must have a baseline EDSS between 0.0 and 5.0, inclusive.

5. Must meet one of the following two criteria:

a) have experienced at least one relapse within the 12 months prior to randomization, with a prior cranial MRI demonstrating lesion(s) consistent with MS (it is not necessary to obtain a current scan if a scan performed previously is available from the subject's history; if a scan is not available from the subject's history, then the baseline scan may be used). For inclusion purposes, a relapse is defined as neurologic signs and/or symptoms documented by a neurologist in the medical record and of at least 24-hours duration to be determined by the investigator or the

relapse onset,

OR

b) show evidence of Gd-enhancing lesions of the brain on an MRI performed within the 6 weeks prior to randomization (if a scan is not available from the subject's history, then the baseline scan may be used).

6. Male and female subjects must be willing to take appropriate measures to prevent pregnancy while participating in this study. Male subjects and female subjects of child-bearing potential must use adequate contraception as appropriate (either intra-uterine device, oral or depot contraceptive, or barrier plus spermicide) and be willing and able to continue contraception for 30 days after their last dose of investigational drug. The rhythm method is not to be used as the sole method of contraception. Females who have not been stable on oral or depot contraceptives for 3 months prior to the first dose of investigational drug must also agree to use a barrier method throughout the study. Female subjects are exempt from contraceptive use if they are post-menopausal for at least 1 year prior to the start of the study or are surgically sterile (females need to have either no uterus or no ovaries to be considered surgically sterile; males or females who have tubes tied or cut are not considered surgically sterile).

All female subjects who are not post-menopausal or surgically sterile must have a negative pregnancy test at screening and at various time points throughout the study to receive investigational drug.

Exclusion Criteria:
1. Primary progressive, secondary progressive, or progressive relapsing MS (as defined by Lublin and Reingold, 1996 [Appendix 3]). These conditions require the presence of continuous clinical disease worsening over a period of at least 3 months. Patients with these conditions may also have superimposed relapses, but are distinguished from relapsing-remitting patients by the lack of clinically stable periods or clinical improvement.

2. History of malignancy unless an exception is granted by the Biogen Idec Medical Director.

3. History of severe allergic or anaphylactic reactions or known drug hypersensitivity.

4. History of abnormal laboratory results indicative of any significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurologic (other than MS), and/or other major disease that would preclude administration of BG00012.

5. History of human immunodeficiency virus (HIV).

6. History of drug or alcohol abuse (as defined by the Investigator) within the 2 years prior to randomization.

AND/OR the subject has not stabilized from a previous relapse prior to randomization.

8. Body weight >100 kg.

9. Positive for hepatitis C antibody and/or positive for hepatitis B surface antigen (HBsAg) at screening.

10. Any of the following abnormal blood tests at screening:
· alanine transaminate/serum glutamate-pyruvate transaminase (ALT/SGPT), or aspartate transaminase/serum glutamic-oxaloacetic transaminase (AST/SGOT), or gamma-glutamyl-transferase (GGT) >2 times the upper limit of normal (ULN)
· leukocytes <3500/mm3
· eosinophils >0.7 x 10^3/mL or >0.7 GI/L, and
· serum creatinine >ULN.
11. Any previous treatment with FUMADERM®, FAG-201, or BG00012.

12. Prior treatment with the any of the following:
· total lymphoid irradiation
· cladribine
· T-cell or T-cell receptor vaccination
· any therapeutic monoclonal antibody, with the exception of ANTEGREN® (natalizumab) (see exclusion #14)

13. Prior treatment with any of the following within 1 year prior to randomization:
· mitoxantrone
· cyclophosphamide

14. Prior treatment with any of the following medications or procedures within the 6 months prior to randomization:
· cyclosporine
· azathioprine
· methotrexate
· natalizumab
· intravenous immunoglobulin (IVIg)
· plasmapheresis or cytapheresis.

15. Prior treatment with any of the following within the 3 months prior to randomization:
· subcutaneous or oral glatiramer acetate
· interferon-alpha
· interferon-beta (subjects who are positive for neutralizing antibodies to interferon-beta may receive interferon-beta treatment up to 2 weeks prior to randomization).

16. Treatment with any of the following medications within the 30 days prior to randomization:
· IV corticosteroid treatment
· oral corticosteroid treatment
· 4-aminopyridine or related products.

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