Safety and Pharmacokinetics of BG-12 Given with and without Aspirin
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INTRODUCTION

- BG-325 (fingolimod) is a potential oral multiple sclerosis (MS) agent in development for relapse prevention in relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS).
- Two Phase 2 studies in patients with relapsing-remitting MS treated with oral BG-325 and interferon beta-1a or placebo showed a trend of reduced relapse rates and neuroimaging measures of MS disease activity, including significant reductions in T2 voxel counts and lesion volume by magnetic resonance imaging. [1]
- In studies to date, common adverse events (AEs) reported by subjects receiving BG-325 monotherapy included mild nausea and postural dizziness, both reported to be related to moderate in severity, with the incidence decreasing after the first month of treatment.

OBJECTIVES

- To investigate the safety, tolerability, and pharmacokinetics (PK) profiles of BG-12 (aspirin) administered with or without asparin during a day of dosing.
- To evaluate potential metabolites of BG-12 involved.

METHODS

- Subjects
  - Healthy volunteers aged 18-55 years were recruited to the study.
  - Subjects had a history of 60-120 days, or who had used non-steroidal anti-inflammatory drugs for over 90 days. All were free of major medical conditions.
  - 14 days prior to study Day 1, all subjects were excluded.

- Study Design and Treatment
  - Randomized, double-blind, placebo-controlled study.
  - Subjects were randomized into different treatment groups, which included the BG-325 dosing regimen in phase I studies (200, 300 mg) and the 100-mg daily dose (TDD) placebo, and assigned with or without aspirin for days 4 to 6 for a group of 12 subjects.
  - Other medications were administered at a standardized mean level immediately after dosing.

- Study Assessments
  - The PK profile of BG-12 on Day 12 was assessed by measuring the primary metabolites, MAF, in the plasma of subjects over 12 hours on Days 1 and 4.
  - PK parameters including area under the concentration-time curve (AUC), maximum plasma concentration (Cmax), time to reach Cmax (tmax), and terminal half-life (t1/2) were determined.
  - Flushing severity was assessed by two validated subject-reported measures: the Flush severity rating (FSR) (0-5 scale) and the total Flush Severity Scale (TFSS).

RESULTS

- All enrolled subjects received the study drug and completed the study.

PH-Profiles
- There was evidence of accumulation of MAF during the study, based on pre-dose plasma MAF levels at Day 1 and further evidenced by stability of the PK parameters throughout the study.
- The mean plasma concentration of MAF at each time point was higher in the placebo group compared to the aspirin group, with and without aspirin on Day 1 and Day 5, for each BG-12 regimen (Table 1).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 1</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>30.50</td>
<td>39.00</td>
</tr>
<tr>
<td>Aspirin</td>
<td>34.00</td>
<td>55.00</td>
</tr>
</tbody>
</table>

- Flushing severity was better in placebo groups than in aspirin groups, with mean scores less than 4.
- Mean CGR and TSS scores were lower in subjects treated with aspirin than in those who were not (Figure 1).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CGR</th>
<th>TSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.00</td>
<td>3.50</td>
</tr>
<tr>
<td>Aspirin</td>
<td>2.50</td>
<td>4.00</td>
</tr>
</tbody>
</table>

- In all treatment groups, mean flushing severity was rated highest on Day 3 for the CGR (subjective flushing) and on Day 5 for the TSS (objective flushing). On Day 1, the CGR scores increased from the first dose for both treatment groups. Mean TSS scores for placebo increased from the first dose for both treatment groups.

- AEs reported in the table were mostly mild in intensity.

- There were no apparent treatment- or dose-related differences in 4188 safety parameters and no evidence of a systemic component or any adverse effects on health or safety.

Potential Flushing Modulators
- Plasma concentrations of 11β-HSD, the major metabolite of ROS, were elevated at around 12 hours post-dosing at Day 1 in some subjects treated with BG-12. BG-12 metabolite was not in 11β-HSD, was not seen in subjects treated with the placebo.
- In aspirin-treated subjects, plasma concentrations of 11β-HSD were apparent in subjects treated with 12 aminophylline, and aspirin was elevated on Day 1 in some subjects treated with BG-12 alone; no elevations were seen in subjects treated with aspirin, and none had been reported on Day 1 in all subjects.
- No elevations in fosfomycin were noted in any groups.

Safety and Tolerability
- The most common AEs were flushing: the incidence was reduced in subjects treated with aspirin.
- In groups not receiving aspirin, flushing was reported for 26%, 50% and 66% of subjects on Days 1, 2 and 5, respectively.
- In the aspirin pre-treatment groups, flushing was reported for 75%, 30% and 45% of subjects treated with placebo, BG-325 and BG-12, respectively.
- The incidence and intensity of flushing decreased overtime with or without aspirin.
- Flushing severity was rated as mild to moderate on Day 1 for 2-3 days of dosing but only a few subjects reported flushing on Day 2.

DISCLOSURES
- Other AEs occurring more frequently with BG-12 than placebo were those affecting the GI system.
- In the aspirin groups, AEs related to subjects were reported for 36%, 33% and 30% subjects respectively.
- Subjects receiving aspirin reported for 38%, 33% and 30% of subjects on Days 1 and 5.
- Most AEs were assessed as mild or moderate in severity.
- No serious AEs or other clinically significant events were noted during the study. No subjects withdrew and there were no serious AEs or deaths during the study.

REFERENCES


ACKNOWLEDGMENT

For additional details on this study, please see the reference.