BMS-790052, a First-in-Class Potent Hepatitis C Virus NS5A Inhibitor, Demonstrates Multiple-Dose Proof-of-Concept in Subjects With Chronic GT1 HCV Infection

Nettles RE,1 Sevinsky H,1 Chung E,1 Burt D,2 Xiao H,1 Marbury T,1 Goldwater D,2 DeMicco M,1 Rodriguez-Torres M,3 Fuentes E,1 Vutikullud A,1 Lawitz E,3 Persson A,2 Bifano M,1 and Grasela DM*

1Bristol-Myers Squibb, Research and Development, Hopewell, NJ; 2Bristol-Myers Squibb, Research and Development, Princeton, NJ; 3Ontario Clinical Research Center, Orlando, FL; 4Astellas International, Burlingame, CA; 5Advanced Clinical Research Institute, Anaheim, CA; 6Fundacion de Investigacion de Diego, Santurce, Puerto Rico; 7Elite Research Institute, Miami, FL; 8West Coast Clinical Trials, Cypress, CA; 9Alamo Medical Research, San Antonio, TX.

ABSTRACT

Background: NS5A is a viral factor critical for HCV replication. BMS-790052 is a potent, orally available, pan-genotypic NS5A inhibitor with broad genetic coverage. In a multiple ascending dose (MAD) study with healthy volunteers, BMS-790052 was dosed in a blinded, randomized, placebo-controlled phase. Methods: The objectives of this study were to evaluate safety, tolerability, PK, antiviral activity, and vehicle acceptance of BMS-790052 in healthy male and female subjects with chronic GT1a or GT1b HCV infection. GT1b subjects were randomized to receive 1, 10, 30, 60, or 100 mg BMS-790052 QD, or 30 mg BID, or placebo. Results: Following oral administration of BMS-790052, subjects were randomized to receive 1, 10, 30, 60, or 100 mg BMS-790052 QD, or 30 mg BID, or placebo. Patients infected with HCV genotype 1b generally demonstrated greater antiviral responses compared to those infected with genotype 1a. The PK profile was supportive of once-daily dosing. Subjects were randomized to receive 1, 10, 30, 60, or 100 mg BMS-790052 QD, or 30 mg BID, or placebo. Results: Following oral administration of BMS-790052 at doses of 1 mg to 100 mg, BMS-790052 was readily absorbed with largely dose-proportional increases in exposure over the studied dose range. The mean terminal half-life of BMS-790052 was approximately 13 to 19 hours. Mean change in HCV RNA in genotype 1a and 1b subjects after multiple doses of 1, 10, 30, 60, and 100 mg BMS-790052 were as follows:

RESULTS

The most frequent treatment-emergent adverse event was headache (20.8% of subjects). The most frequent treatment-emergent adverse events in placebo recipients were headache (20.8% of subjects) and nausea (13.9% of subjects). There were no serious adverse events or discontinuations due to adverse events. The only adverse event that occurred in >10% of subjects in the GT1a and GT1b cohorts was headache, with 6% in GT1a and 10% in GT1b. Conclusions: BMS-790052 is a potent NS5A inhibitor that produces a robust decline in HCV RNA following multiple doses in subjects chronically infected with both HCV genotypes 1a and 1b. The PK profile of BMS-790052 is supportive of once-daily dosing. These results support the importance of initiating NS5A inhibitors in HCV infection. Further studies are under way to confirm the role of NS5A inhibitors in HCV infection.

METHODS – STUDY DESIGN

RESULTS

DISCLOSURES

AASLD, The Liver Meeting in Boston, MA, October 29 – November 2, 2010

1881