BRISTOL-MYERS SQUIBB COMPANY

BMS-201038

INVESTIGATOR BROCHURE GENERAL ADDENDUM

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matched placebo. One subject who received 100 mg of BMS-201038 had six AE's, one of which was severe; these were all in association with a vasovagal reaction and felt by the investigator to be unrelated to study drug. Another subject had eight AE's; all appeared to be in association with an upper respiratory infection. The remaining 11 adverse events were minor complaints such as lightheadedness, weakness, salty taste, or nausea and considered by the investigator in each case to be unassessable as to causal relationship to study drug administration. There were two laboratory AE's of an increased CK in one subject and asymptomatic pyuria in two others.[27]

3.1.2 CV145-002, Multiple Dose PO

In this protocol, 36 hypercholesterolemic (fasting total cholesterol of ≥200 mg/dL) healthy volunteers were recruited in four groups of nine subjects each to receive in an ascending fashion doses of BMS-201038 of 10, 25, 50 or 100 mg or matched placebo capsules QD for 14 days. Due to AE's (predominantly gastrointestinal AE's), subjects in the 100 mg group were discontinued at Day 8. All subjects entered for a seven day dietary lead-in with an AHA Step I diet which was maintained throughout the study. Within each group six subjects received active drug and three subjects received placebo. In the course of the study plasma samples for analysis of BMS-201038, BMS-203304 and BMS-203215 were obtained at specified time points post-dosing. Plasma concentrations of BMS-203304 were predominant. The mean $T_{½}$ for both BMS-203334 and BMS-203215 was approximately 21 hours. The accumulation index (AI) for the parent compound was calculated from AUC_{tau} Day 14/AUC_{tau} Day 1. At doses of 25 mg QD there was no significant accumulation of BMS-201038.

BMS-201038 had a marked dose and time related effect on cholesterol and triglycerides. By Day 14 the mean fasting LDL cholesterol at 25 mg QD

compared to baseline was -56%, at 50 mg QD - 73% (mean placebo -1%) and on Day 8 of 100 mg QD - 82% (mean placebo - 8%). The mean triglycerides at 25 mg QD on Day 14 were - 12% from baseline, at 50 mg QD - 54% (mean placebo -2%) and on Day 8 of 100 mg QD - 62% (mean placebo +54%).

Additional pharmacodynamic measures were also performed. These included Magnetic Resonance Imaging (MRI) and Nuclear Magnetic Resonance Spectroscopy (NMRS) of the liver, techniques which use no ionizing radiation, to assess for potential accumulation of hepatic fat content which may occur as an extension of the pharmacologic effect. These procedures were performed at baseline before dosing and at end of the study. The spectroscopic results indicate that in comparison with baseline and with placebo, there appeared to be some increase in hepatic fat content at all doses. Preliminary results from the NMRS data indicate for the dose groups 10 mg, 25 mg and 50 mg QD x 14 days, the mean hepatic fat content at baseline was in the range of 1.9% and at the end of the study was in the range of 8.8%. Following the discontinuation of dosing at 100 mg QD, an additional MRI/NMRS was obtained on Day 8. There was a clear indication that fat accumulation had occurred after eight days of dosing; when measured again at Day 14 there was virtually no change from Day 8.

There were no SAE's. A total of 111 AE's were reported, 95 in the treated groups and 16 in the placebo group. Most of these events occurred pre-dosing, were judged by the investigator as unrelated to administration of BMS-201038 or matched placebo, or the same AE was reported on multiple occasions for a subject. The frequency of AE's was dose-related: three in the 25 mg QD group, 26 at 50 mg QD group, and 57 at 100 mg QD group.

Of the 95 AE's in the drug treated groups, 72 were gastrointestinal in origin including nausea, flatulence, abdominal cramping and loose stools or diarrhea. In association with these symptoms, subjects complained of gaseousness or flatulence type symptoms with some associated abdominal cramping. After a week of dosing at 100 mg QD the subjects were discontinued from dosing due to intolerable adverse gastrointestinal effects. One subject was discontinued for a five-fold increase in ALT. The investigator reported that all symptoms and signs resolved within a week following discharge.[28]

3.1.3 CV145-003, Single Dose IV

In this protocol, 32 hypercholesterolemic healthy volunteers were recruited in four groups of eight subjects each to receive in an ascending fashion single IV doses of BMS-201038 of 7.5, 15, 30 or 60 mg or matched placebo administered as a constant rate 30 minute IV infusion. All subjects entered for a two day lead-in with an AHA Step I diet which was maintained throughout the study. Within each group six subjects received active drug and two subjects received placebo. Plasma samples for analysis of BMS-201038, BMS-203304 and BMS-203215 were obtained at specified time points for 72 hours post-dosing. Concentrations of BMS-203304 were predominant. The mean $T_{½}$ for BMS-201038 was approximately 25 hours.

Several pharmacodynamic measures of BMS-201038 on lipid lowering were obtained by frequent post dose monitoring of lipid profiles; including frequent post dose triglycerides, cholesterol, LDL-C, HDL-C, VLDL-C and Apo B. BMS-201038 had a marked dose- and time-related effect on cholesterol and triglyceride lowering. The mean post dose LDL-C at 60 mg was reduced by