BMS-201038

Indication:	Hyperlipidemia
Protocol No.:	CV145-009
Phase:	I
Study Initiation Date:	19-Feb-1999
Study Completion Date:	22-Dec-1999
Report Date:	07-Jan-2002

THE EFFECTS OF CHRONIC DOSING OF BMS-201038 ON HEPATIC FAT ACCUMULATION AND REVERSIBILITY AS ASSESSED BY NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY (NMRS)

AN ABBREVIATED CLINICAL STUDY REPORT

Name and Affiliation of Principal Investigators:
William Insull, M.D. (Houston), Carlos Dujovne, M.D.(Kansas), Howard Knapp, M.D., Ph.D.(University of Iowa), Daniel Rader, M.D.(University of Pennsylvania), Evan Stein, M.D., Ph.D. (Cincinnati)

Company Signatory
Richard A. Reeves, M.D.
Bristol-Myers Squibb
Princeton, NJ 08543-4000
Tel: 609-252-3452
Fax: 609-252-6313

Department of Clinical Discovery
Drug Discovery and Exploratory Development
Bristol-Myers Squibb Pharmaceutical Research Institute
Bristol-Myers Squibb Company
Bristol-Myers Squibb
Princeton, NJ 08543-4000

FINAL REPORT SYNOPSIS

INTRODUCTION: BMS-201038 is an inhibitor of microsomal triglyceride transfer protein (MTP). In studies conducted in human volunteers BMS-201038 was shown to be a potent agent for lowering LDL-C and triglycerides. As an inhibitor of MTP it has the potential to increase hepatic fat content. To assess the possible accumulation of hepatic fat, a nuclear magnetic resonance spectroscopy (NMRS) technique was developed. This technique was originally described as a method to assess fat content in bone marrow, and subsequently developed as part of the MTP program to determine percent fat in the liver. In Protocol CV145-002, this technique demonstrated that at all doses of BMS-201038 from 10 mg QD to 100 mg QD, there appeared to be an increase in hepatic fat content. To further define the safety of this compound, a Reversibility Protocol, CV145-009, was developed to assess the extent of any hepatic fat accumulation and the degree of reversibility at 6 weeks post dosing of any accumulated hepatic fat. Based on the results of this trial, further clinical development on BMS-201038 was discontinued due to safety concerns. Therefore an Abbreviated Study Report is being issued.

TITLE OF STUDY: The Effects of Chronic Dosing of BMS-201038 on Hepatic Fat Accumulation and Reversibility as Assessed by Nuclear Magnetic Resonance Spectroscopy (NMRS)

INVESTIGATORS: Study conducted at 5 study centers in the U.S.A. The Principal investigators (site number) were William Insull, M.D. (001), Carlos Dujovne, M.D. (002), Howard Knapp, M.D., Ph.D. (003), Daniel Rader, M.D. (007), Evan Stein, M.D., Ph.D. (008)

STUDY CENTERS:
001: Lipid Research Clinic, Baylor College of Medicine, Houston, TX
002: Mid-Continent Clinical Trials, Overland, KS
003: Lipid Research Clinic, Iowa City, IA
004: Hospital of the University of Pennsylvania, Philadelphia, PA
008: Metabolic and Atherosclerosis Research Center, Cincinnati, OH

PUBLICATIONS: None

STUDY PERIOD: Date first subject enrolled: 19-Feb-1999
Date last subject completed: 22-Dec-1999

CLINICAL PHASE: I

OBJECTIVES: The primary objective of this study was to compare the effects of treatment with BMS-201038 25 mg QD x 4 weeks and treatment with matched placebo QD x 4 weeks on the reversibility of elevated hepatic fat content as measured by magnetic resonance imaging / nuclear magnetic resonance spectroscopy (MRI/NMRS) in subjects with hypercholesterolemia. Secondary objectives were to assess percent (%) change from baseline in total cholesterol (T-C), LDL-C, very low density lipoprotein cholesterol (VLDL-C), high density lipoprotein cholesterol (HDL-C), TG and apolipoprotein B (apo B).

METHODOLOGY: A multicenter, randomized, double-blind, parallel design was used. After adherence to a low-fat, low-cholesterol diet conforming to the National Cholesterol Education Program (NCEP) Step One diet for at least 2 weeks and no treatment with lipid-lowering agents for a minimum of 4 weeks, subjects entered into a 4-week single-blind placebo lead-in period (Period A). During this time the subjects were counseled regarding their need to maintain their normal level of physical activity and to refrain from unaccustomed physical activity. After successful completion of the dietary and placebo lead in, including

capsule compliance checks and baseline pulmonary function tests (PFTs: spirometry with DLCO) and MRI/NMRS at the end of the placebo lead-in period, 76 subjects with LDL-C ≥ 160 mg/dL and TG ≤ 500 mg/dL were randomized in a 1:1 ratio to receive once-daily doses of BMS-201038 25 mg QD x 4 weeks or matched placebo QD x 4 weeks (Period B). Subjects were instructed to take their study medications in the morning. During the double-blind period, subjects were seen for clinic visits during weeks 1, 2, 3, 4, and 5 of Period B, and 6 weeks following the last dose of Period B study medication.

Subjects returned to the clinic for subsequent hepatic MRI/NMRS after 4 weeks of dosing (Week B5) and after 6 weeks post dosing (Week B11). PFTs were repeated during Week B5. Following satisfactory completion of the discharge evaluation (Week B11), subjects were discharged from the study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: To be eligible for randomization, subjects must have had a mean (2 samples) LDL-C ≥ 160 mg/dL and a mean serum TG ≤ 500 mg/dL. The qualifying lipid value was calculated from the mean of two determinations during the single-blind placebo lead-in period, at Weeks A2 and A3. The LDL-C concentration of the lower qualifying specimen must have been within 15% of the higher qualifying specimen. If they were not within 15%, a third sample was to be obtained during Week A4. Blood samples for all laboratory measurements were to be obtained in the morning after an overnight fast of at least 10 hours.

STUDY POPULATION: The demographic characteristics of the subjects are listed in Appendix 1 and summarized in the following table.

Demographic Characteristics

Demographic Parameter	Treatment	
	Placebo (n = 38)	BMS-201038 (n = 38)
Age (y)		
Mean (SD)	52 (10.3)	51 (9.1)
Range	24-65	29-65
Height (cm)		
Mean (SD)	172.4 (8.8)	171.2 (11.1)
Range	156.0-190.0	147.3-191.3
Weight (kg)		
Mean (SD)	81.6 (14.7)	83.9 (13.8)
Range	53.1-113.2	47.3-111.6
Gender (%)		
Male	24 (63.2)	24 (63.2)
Female	14 (36.8)	14 (36.8)
Race (%)		
White	35 (92.1)	34 (89.5)
Black	3 (7.9)	3 (7.9)
Other	0	1 (2.6)

NUMBER OF SUBJECTS/PATIENTS: Seventy-six (76) subjects were randomized to either the BMS-201038 (38 subjects) or placebo (38 subjects) dose groups in Period B, and 64 subjects completed the study, as presented in Appendix 2. The complete Drug Administration Summary by subject is given in Appendix 3.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: BMS-201038, 25 mg capsule. PO. batch number N97018.

DURATION OF TREATMENT: Subjects were entered into a 4-5 week single-blind placebo lead-in period (Period A), and then those subjects who qualified were randomized in a 1:1 ratio to receive once-daily doses of BMS-201038 25 mg or matched placebo QD x 4 weeks (Period B).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Placebo capsule matching the BMS-201038 25 mg capsule , PO, batch number N97014.

SAFETY RESULTS: Safety assessments were based on medical review of adverse events and the results of vital sign measurements, electrocardiograms, physical examinations and clinical laboratory tests. All patients who received treatment were included in the safety evaluation. Findings of potential significance were carefully reviewed for clinical importance by a physician from the BMS Department of Clinical Pharmacology.

In this study there were no Deaths and no other Serious Adverse Events (SAEs). Nine (9) subjects discontinued due to Adverse Events (AEs) while receiving BMS-201038, and no subjects discontinued due to AEs while receiving placebo, as summarized in the following table.

Subjects Discontinuing Due to AEs

Site-Subject Number	AE(s) Leading to Discontinuation BMS Decode (CRF Text)
001-003	ALAT increased (increased SGPT) ASAT increased (increased SGOT) Hepatomegaly (hepatomegaly)
002-036	Pain abdomen (pain lower abdomen) Diarrhea (diarrhea) Nausea (nausea) Fatigue (decreased energy) Malaise (body aches) Headache (HA)
003-005	Distention abdomen (bloating) Eructation (belching) Nausea (nausea)
003-012	Appetite decreased (decreased appetite) Diarrhea (diarrhea) Fatigue (fatigue) Weight loss (weight loss)
003-018	Cramp abdomen (abdominal cramping) Flatulence (flatus) Diarrhea (diarrhea)
003-029	Diarrhea (diarrhea) Vomiting (vomiting)
007-002	Diarrhea (diarrhea) Depletion volume (dehydration) Weakness (weakness) LFTs increased (elevated LFT's)

Subjects Discontinuing Due to AEs

Site-Subject Number	AE(s) Leading to Discontinuation BMS Decode (CRF Text)
007-034	Diarrhea (diarrhea)
008-026	Diarrhea (diarrhea) Nausea (nausea)

There were a total of 30 Adverse Events (AEs) in 16 of the 38 placebo-treated subjects, and 105 AEs in 35 of the 38 BMS-201038-treated subjects. All AEs are summarized by subject in Appendix 4. and AEs that counted appear in Appendix 5.

AEs of particular clinical interest were those in the gastrointestinal and hepatobiliary body systems. The following table lists counted gastrointestinal and hepatobiliary AEs by treatment group, body system and primary term.

Gastrointestinal and Hepatobiliary Counted Adverse Events, By Treatment Group and Primary Term

BODY SYSTEM PRIMARY TERM	Treatment Placebo (n = 38)	Treatment BMS-201038 (n = 38)
GASTROINTESTINAL		
Abdominal Pain	1	6
Decreased Appetite	0	4
Diarrhea	3	31
Distention Abdomen	0	5
Dyspepsia/Heartburn	0	3
Epigastric Pain	0	1
Eructation	0	1
Flatulence	0	5
Lesion Oral	3	0
Nausea/Vomiting	0	12
Oropharynx Bleeding	1	0
HEPATOBILIARY		
Increased ALAT	0	2
Increased ASAT	0	2
Hepatomegaly	0	1
Increased Liver Function Tests	0	3

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