LDL Cholesterol Reduction with BMS-962476, An Adnectin Inhibitor of PCSK9: Results Of A Single Ascending Dose Study

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Abstract

Background: BMS-962476 is an anti-human proprotein convertase subtilisin/kexin type 9 (PCSK9) Adnectin-based protein therapeutic formatted with 40 kDa branched polyethylene glycol developed to prevent PCSK9-LDL receptor binding and reduce LDL cholesterol (LDL-C). We report safety, tolerability and efficacy of single ascending subcutaneous (SC) or intravenous (IV) doses of BMS-962476 in healthy subjects on diet or statins and LDL-C >130 or >100 mg/dL, respectively (NCT01587365).
Methods: At each dose 8 subjects were randomized 3:1 to a single SC or IV dose of BMS-962476 or placebo (PBO). Treatment began in diet only subjects with 0.01 mg/kg SC and based on tolerability escalated sequentially to 0.03, 0.1 and 0.3 mg/kg SC, followed by 0.3 and 1.0 mg/kg IV. Subjects on statins received 0.1 and 0.3 mg/kg SC doses. Free PCSK9 and LDL-C were measured but remained blinded. Subjects were confined for 5 days post-dose and then followed as outpatients.
Results: Of 64 randomized subjects 60 completed the 43 day study. There were no deaths or discontinuations due to AEs. There were 2 serious adverse events (SAE) considered unrelated to study-drug. BMS-962476 was well tolerated and AEs were similar to PBO. Maximal dose-related reductions of LDL-C up to 48% occurred between day 4 and 14 (Table). Doses >0.3 mg/kg reduced free PCSK9 >90%.
Conclusion: BMS-962476, a novel and effective anti-PCSK9 therapeutic agent, rapidly reduces free PCSK9 and LDL-C, and in this first in human study was well tolerated and had no notable safety signals.

Background

- Proprotein convertase subtilisin/kexin type 9 (PCSK9), is a serine protease mainly synthesized in the liver that is secreted into the plasma where it plays a significant role in regulating hepatic LDL receptors and promoting their degradation and consequently plasma low-density lipoprotein (LDL) cholesterol levels.[1,2]
- Inhibitors to PCSK9 inhibitors, particularly monoclonal antibodies, have been extensively studied in phase 1 and 2 and appear to be effective, safe and well tolerated.[3-9] A phase 1 single ascending dose study with a siRNA has also been reported to be effective at reducing both PCSK9 in the plasma along with LDL-C reduction.[10]
- BMS-962476 is an anti-human proprotein convertase subtilisin/kexin type 9 (PCSK9) Adnectin-based protein therapeutic formatted with 40 kDa branched polyethylene glycol developed to prevent PCSK9-LDL receptor binding and reduce LDL cholesterol (LDL-C).
- We report a randomized, double-blind, placebo-controlled, ascending single-dose study to evaluate the safety, pharmacokinetics and pharmacodynamics of BMS-962476 in otherwise healthy subjects with elevated LDL-C on diet alone and in patients on background statin therapy.

Materials & Methods

- The trial was approved by the Institutional Review Board governing the clinical site. All patients reviewed and signed Informed Consent prior to any study procedures. The trial was registered (NCT01587365) and carried out between May 2012 and May 2013. Sixty-four subjects participated in this clinical trial, including 48 who received BMS-962476 and 16 who received placebo.
- Patients and Study Design: This was a randomized, double-blind, placebo-controlled, sequential panel, partially overlapping single ascending dose study in healthy adult subjects with LDL-c ≥130 and ≤190 mg/dL on diet only or on statin therapy with LDL-c ≥ 100 mg/dL. Eight diet-only subjects were assigned to each of up to 6 separate and sequential SC and IV dose panels and treated on Day 1 with single doses of BMS-962476 or placebo at escalating doses of 0.01, 0.03, 0.1, and 0.3 mg/kg SC, and 0.3 and 1.0 mg/kg IV, respectively.
- The 2 highest SC doses that were safe and well tolerated in diet-only subjects were then administered to 8 patients on statin therapy per panel. See the Study Schematic Figure 1.

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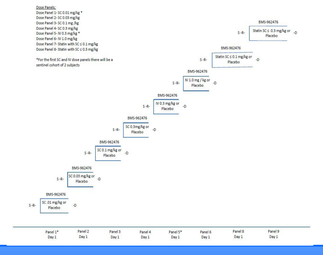
Figure 1. Study flow chart



❖ Main additional inclusion criteria were; Healthy male and female subjects (body mass index [BMI] = 18.0 to 35.0 kg/m^2, aged 18 to 65 years) as determined by medical history, physical examination, ECGs, vital signs, and clinical laboratory evaluations were eligible to participate in dose panels 1 to 6.
❖ Male and female patients (BMI = 18.0 to 37.0 kg/m^2, aged 18 to 75 years) on stable statin therapy and LDL-c ≥ 100 mg/dL and triglycerides ≤200 mg/dL were eligible to participate in dose panels 7 and 8. Women were not of childbearing potential. All women had to have had a negative pregnancy test within approximately 24 hours prior to dosing with study drug.

Objectives

Primary safety and tolerability objectives;
- Numbers of subjects with serious adverse events (SAEs), deaths or discontinuations due to adverse events (AEs),
- AEs of injection site reactions, or potentially clinically significant changes in vital signs and electrocardiogram (ECG) parameters.

Secondary objectives were as follows:
- To assess the PD effects of single SC or IV doses of BMS-962476 on plasma unbound (free) PCSK9 concentrations and serum LDL-C
- To assess the effects of BMS-962476 on total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), very low density lipoprotein-cholesterol (VLDL-C), and triglycerides
- To assess the effects of BMS-962476 on total apolipoprotein B and A-1 serum concentrations
- To assess the effects of BMS-962476 on total plasma PCSK9 concentrations
- To assess single dose PK and dose proportionality of BMS-962476 following SC or IV administration
- To assess the absolute bioavailability of a single SC dose of 0.3 mg/kg of free and total BMS-962476
- To assess the frequency of anti-BMS-962476 antibodies (immunogenicity) following single SC and IV doses of BMS-962476

Exploratory objectives were as follows:
- To assess the effects of BMS-962476 on other lipid and cardiovascular risk biomarkers including but not limited to lipoprotein a (Lp[a]) and high sensitivity C-reactive protein (hs-CRP), as appropriate
- To compare the PD effects of BMS-962476 in normal healthy subjects and in patients with statin therapy

Statistical Considerations

Safety Analyses:
- All recorded AEs were listed and tabulated by system organ class, preferred term, and treatment. Injection site reactions were evaluated as AEs. Vital signs, any significant physical examination findings, and clinical laboratory test results were listed and summarized by treatment. Electrocardiogram readings were evaluated by the investigator and abnormalities, if present, were listed.

Pharmacodynamic Analyses:
- Summary statistics were tabulated by treatment (dose and route of administration) for plasma unbound (free) and total PCSK9 concentrations; fasting serum total cholesterol, LDL, HDL, and VLDL cholesterol; triglycerides; total apolipoprotein B and A-1, and the corresponding changes from baseline. Each parameter and corresponding changes were plotted versus time by treatment (dose and route of administration).

Results

BASELINE PARAMETERS:
A total of 153 subjects were screened, 64 subjects were eligible, randomized and received study drug, and 60 subjects completed all required study visits. The baseline demographics are shown below in Table 1.

Disposition	SC 0.01 mg/kg N = 6	SC 0.03 mg/kg N = 6	SC 0.1 mg/kg N = 6	SC 0.3 mg/kg N = 6	IV 0.1 mg/kg N = 6	IV 0.3 mg/kg N = 6	Statin + SC 0.1 mg/kg N = 6	Statin + SC 0.3 mg/kg N = 6	SC PBO N = 8	IV PBO N = 4	Statin + SC PBO N = 4	Total SC N = 24	Total IV N = 12	Total Statin + SC N = 12	Total N = 64
Subjects randomized	6	6	6	6	6	6	6	6	8	4	4	24	12	12	64
Subjects completing the study, n (%)	6 (100.0)	6 (100.0)	6 (100.0)	5 (83.3)	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	7 (87.5)	3 (75.0)	4 (100.0)	23 (95.8)	11 (91.7)	12 (100.0)	60 (93.8)
Subjects not completing the study, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (25.0)	0 (0.0)	1 (4.2)	1 (8.3)	0 (0.0)	4 (6.3)
Reason for not completing the study, n (%)															
Subject withdrew consent	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (4.2)	1 (8.3)	0 (0.0)	3 (4.7)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

Abbreviations: IV = intravenous (given over 20 mins); n = number of non-missing observations; N = number of subjects; SC = subcutaneous; TRT = treatment; PBO = placebo
Percentage based on all treated subjects. Placebo groups are pooled across the SC only, SC + Statin, and IV dose panels, respectively.

Table 2. Baseline Demographics

Parameter	SC 0.01 mg/kg N = 6	SC 0.03 mg/kg N = 6	SC 0.1 mg/kg N = 6	SC 0.3 mg/kg N = 6	IV 0.1 mg/kg N = 6	IV 0.3 mg/kg N = 6	Statin + SC 0.1 mg/kg N = 6	Statin + SC 0.3 mg/kg N = 6	SC PBO N = 8	IV PBO N = 4	Statin + SC PBO N = 4	Total SC N = 24	Total IV N = 12	Total Statin + SC N = 12	Total N = 64
Age (years)															
Mean (SD)	49.5 (3.83)	45.8 (11.05)	58.0 (6.87)	46.3 (10.78)	51.0 (8.15)	46.8 (12.58)	53.8 (10.38)	58.8 (8.21)	48.6 (8.33)	46.5 (8.19)	53.3 (12.69)	49.9 (9.49)	48.9 (10.33)	56.3 (9.30)	50.8 (9.70)
Age, n (%)															
< 65	6 (100.0)	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	5 (83.3)	8 (100.0)	4 (100.0)	3 (75.0)	23 (95.8)	12 (100.0)	11 (91.7)	61 (95.3)
≥ 65	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (25.0)	1 (4.2)	0 (0.0)	1 (8.3)	3 (4.7)
Gender, n (%)															
Male	5 (83.3)	4 (66.7)	2 (33.3)	3 (50.0)	2 (33.3)	6 (100.0)	5 (83.3)	2 (33.3)	6 (75.0)	3 (75.0)	1 (25.0)	14 (58.3)	8 (66.7)	7 (58.3)	39 (60.9)
Female	1 (16.7)	2 (33.3)	4 (66.7)	3 (50.0)	4 (66.7)	0 (0.0)	1 (16.7)	4 (66.7)	2 (25.0)	1 (25.0)	3 (75.0)	10 (41.7)	4 (33.3)	5 (41.7)	25 (39.1)
Race, n (%)															
White	2 (33.3)	1 (16.7)	4 (66.7)	4 (66.7)	2 (33.3)	1 (16.7)	5 (83.3)	5 (83.3)	4 (50.0)	2 (50.0)	3 (75.0)	11 (45.8)	3 (25.0)	10 (83.3)	33 (51.6)
Black/ African American	4 (66.7)	5 (83.3)	2 (33.3)	2 (33.3)	4 (66.7)	5 (83.3)	1 (16.7)	1 (16.7)	4 (50.0)	2 (50.0)	1 (25.0)	13 (54.2)	9 (75.0)	2 (16.7)	31 (48.4)
BMI (kg/m^2) mean (SD)	29.17 (3.822)	28.52 (4.459)	29.78 (3.664)	30.33 (2.708)	27.40 (3.835)	30.53 (3.148)	29.07 (5.487)	28.08 (4.483)	28.98 (3.901)	28.90 (2.069)	27.35 (2.290)	29.45 (3.534)	28.97 (3.724)	28.58 (4.804)	28.97 (3.666)

Figure 2. Percent Change from baseline in PCSK9

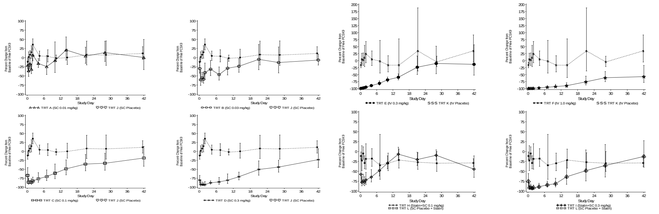
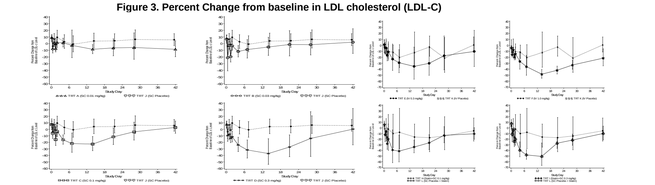


Figure 3. Percent Change from baseline in LDL cholesterol (LDL-C)



EFFICACY - PCSK9 AND LIPID RESULTS
- Plasma free PCSK9 concentrations observed following SC doses of BMS-962476 and SC + statin treatments compared to placebo except with the 0.01 mg/kg SC dose. The decrease in free PCSK9 concentrations appeared to be greater with increasing dose of BMS 962476 (Figure 2) with a greater effect observed in subjects on diet alone compared to that in patients taking statins (Figure 2). Decreases were >90% of baseline with the 0.1 and 0.3 mg/kg doses in diet only and 0.3 mg/kg statin treated patients.
- There was a decrease from baseline in LDL-C levels observed following SC doses of BMS-962476 and SC + statin treatments compared with placebo except with the lowest 0.01 mg/kg SC dose. In general the decreases in LDL-C increased as dose increased with a greater effect observed in patients taking statins. However, the duration of the effect appeared greater in subjects on diet alone. Decreases in LDL-c were also observed for both of the IV doses compared to placebo.
- There was a decrease from baseline in total apolipoprotein B levels observed following SC doses of BMS 962476 and SC + statin treatments compared to placebo except with the 0.01 mg/kg SC dose. The decrease appeared to be greater as dose increased with a greater effect observed in diet-only subjects compared to that in patients taking statins. Decreases in apolipoprotein B were also observed for both of the IV doses compared to placebo. Total apolipoprotein A-1 levels followed a similar pattern to that of subjects receiving placebo.

SAFETY
- There were no deaths or discontinuations due to AEs.
- Two subjects experienced serious adverse events (SAEs) that were considered not related to study drug; 1 subject experienced a severe cerebrovascular accident 28 days following administration of Treatment A (0.01 mg/kg BMS 962476, SC) and 1 subject experienced a moderate episode of noncardiac chest pain 4 days following administration of 0.3 mg/kg BMS-962476, IV.
- A total of 31 (48.4%) of 64 subjects reported at least 1 AE; 7 (10.9%) of 64 subjects reported AEs that were considered related to study drug and 27 subjects (42.2%) reported AEs considered not related to study drug.
- The majority of AEs considered to be related to study drug involved injection site reactions (erythema, edema, and swelling).
- The most common AEs reported (by more than 1 subject) were headache, back pain, cough, dermatitis contact, injection site erythema, diarrhea, injection site edema, injection site reaction, musculoskeletal chest pain, and oropharyngeal pain; all other AEs were reported by 1 subject only.
- None of the AEs were considered clinically significant.
- There were no other clinically remarkable vital sign measurements, physical examination findings, or physical measurement findings nor clinically remarkable trends from baseline to discharge in vital sign measurements, physical examination findings, or physical measurement assessments.
- There were no clinically remarkable trends observed in laboratory findings.
- There were no AEs based on electrocardiogram (ECG) findings nor were there any findings that were assessed as clinically significant by the investigator.

Disclosure

E. Stein has received consulting fees from Amgen, Regeneron/Sanofi, Roche/Genentech and BMS related to PCSK9 inhibitor development

Summary

- Overall, BMS-962476 was safe and well tolerated following single SC and IV dosing in healthy subjects and in patients with hypercholesterolemia on statin therapy.
- In patients on statin background therapy BMS-962476 a single SC dose of 0.3 mg/kg reduced free PCSK9 >90% and LDL-C 48% from baseline.
- There was a dose related decrease from baseline in plasma free PCSK9 and total PCSK9 concentrations observed following SC, SC + statin, and IV doses of BMS-962476 compared to those with placebo with a greater effect observed in diet only subjects compared to patients taking statins.
- There was a dose-related decrease from baseline in LDL-c levels observed following the SC, SC + statin, and IV doses of BMS-962476 compared to those with placebo with a greater LDL-c-lowering effect observed in patients taking statins compared to healthy subjects. However, the duration of the effect appeared to be greater in healthy subjects.
- There was a decrease from baseline in total apolipoprotein B levels that paralleled reductions in LDL-C observed following SC, SC + statin, and IV doses of BMS-962476 compared to those with placebo.
- Cmax, AUC(0-T), and AUC(INF) of total and free BMS-962476 all increased with increasing dose of BMS-962476 in a dose-proportional manner for the SC administration.
- There did not appear to be an effect of total BMS-962476 plasma concentrations on the change from baseline QTcF.
- No subject had a positive antibody response.
- BMS-962476, an antiPCSK9 adnectin shows promise as an alternative to monoclonal antibodies to reduce circulating PCSK9 and LDL cholesterol.

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