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LDL CHOLESTEROL REDUCTION WITH BMS-962476, AN ADNECTIN INHIBITOR OF PCSK9: RESULTS OF A SINGLE ASCENDING DOSE STUDY

Poster Contributions
Hall C
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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 being 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 2 serious adverse events (SAE) considered unrelated to study-drug, none resulted in study discontinuation. 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.

Treatment	N	Route	Statin	Maximal Mean % LDL-C reduction (SD)	Day 2 Mean % PCSK9 reduction (SD)
Placebo	16	SC	No	2.3 (6.24)	-
0.01 mg/kg	6	SC	No	10.0 (11.68)	22.7(8.8)
0.03 mg/kg	6	SC	No	11.5 (7.98)	26.5(15.1)
0.1 mg/kg	6	SC	No	22.2(10.13)	70.0(17)
0.3 mg/kg	6	SC	No	29.5 (9.36)	91.9(4.7)
0.3 mg/kg	6	IV	No	26.6 (20.64)	99.0(0.2)
1 mg/kg	6	IV	No	47.0 (6.97)	99.0(0.5)
0.1 mg/kg	6	SC	Yes	37 (25.36)	75.9(22.2)
0.3 mg/kg	6	SC	Yes	48 (16.76)	91.9(3.7)