Poster Number LB12

BMS-790052 is a First-in-class Potent Hepatitis C Virus (HCV) NS5A Inhibitor for Patients with Chronic HCV Infection: Results from a Proof-of-concept Study

Richard E Nettles[1], Caly Chien[1], Ellen Chung[1], Anna Persson[1], Min Gao[1], Makonen Belema[1], Nicholas Meanwell[1], Michael DeMicco[2], Thomas Marbury[3], Ronald Goldwater[4], Patrick G Northup[5], John Coumbis[1], Walter K Kraft[6], Michael Charlton[7], Juan Carlos Lopez-Talavera[1], Dennis M Grasela[1]

[1]Bristol-Myers Squibb, Research and Development, Princeton, NJ; [2]Advanced Clinical Research Institute, Anaheim, CA; [3]Orlando Clinical Research Center, Orlando, FL; [4]PAREXEL International, Baltimore, MD; [5]University of Virginia, Charlottesville, VA; [6]Thomas Jefferson University, Philadelphia, PA; [7]Mayo Clinic, Rochester, MN

Background

- NS5A is an essential component of the hepatitis C virus (HCV) replication complex
- BMS-790052 is a first-in-class, highly selective, oral HCV NS5A inhibitor
- BMS-790052 has broad genotype coverage and exhibits picomolar *in vitro* potency against genotypes 1a and 1b

Table 1: BMS-790052 EC_{50} for HCV Genotypes 1–5

Replicon or virus	EC_{50} (pM)
1a	50
1b	9
2a (JFH)	63
2a (JFH virus)	12
3a*	127
4a*	12
5a*	33
BVDV replicon†	>10^7
A panel of 10 RNA and DNA viruses	>10^7

*Data derived from chimeric replicons; †Bovine viral diarrhea virus

- BMS-790052 has additive to synergistic effects in combination with interferon and other HCV inhibitors *in vitro*
- In a single ascending dose study in healthy non-HCV infected patients (Protocol AI444-001), BMS-790052:
  - was safe and well tolerated
  - had a pharmacokinetic (PK) profile suggesting the possibility of once-daily dosing

Methods

Study Design

- Double-blind, placebo-controlled, single ascending dose study
- Patients were randomized to receive 1, 10 or 100 mg of BMS-790052 or placebo
  - Six patients per dose (active:placebo=5:1)
- Enrollment criteria
  - Male or female
  - 18 to 49 years of age
  - HCV genotype 1
  - Treatment naïve or experienced
  - Body mass index (BMI) of 18–35 kg/m^2
  - HCV RNA ≥10^5 IU/mL at screening
  - Documented FibroTest™ score of ≤0.59 and AST to platelet ratio index (APRI) ≤2
  - Non-cirrhotic compensated liver disease

Study Objectives

- Primary
  - To assess the safety and tolerability of a single oral dose of 1, 10 and 100 mg of BMS-790052 in patients with chronic genotype 1 HCV infection
- Secondary
  - To assess the single-dose PK of BMS-790052
  - To assess the effect of a single dose of BMS-790052 on plasma HCV RNA dynamics

Study Assessments

- Safety and tolerability
  - Assessed by physical examination, vital sign measurements, ECGs, clinical laboratory tests and adverse event (AE) reporting
- Bioanalytical methods
  - LC/MS/MS (tandem mass spectrometry)
  - LLOQ=0.05 ng/mL for BMS-790052
  - QC deviations within +/- 15% for BMS-790052
- PK analysis
  - PK parameters were calculated by non-compartmental analysis using Kinetica™
- HCV RNA was measured with the Roche COBAS® TaqMan® HCV Test, v2.0
  - LLOQ=25 IU/mL
- Statistical analysis
  - PK parameters and changes in HCV RNA from baseline (in $\log_{10}$ IU/mL) were calculated and summarized by dose (baseline HCV RNA defined as $\log_{10}$ IU/mL prior to dosing)

Results

Study Population

Table 2: Demographics and Baseline Characteristics

	1 mg (n=6)	10 mg (n=5)	100 mg (n=5)	Placebo (n=2)	Total (n=18)
Male, n (%)	5 (83)	2 (40)	1 (20)	2 (100)	10 (56)
Age (years), mean (range)	41 (31–48)	42 (23–49)	41 (32–45)	28 (22–34)	41 (23–49)
Race: white, n (%)	5 (83)	5 (100)	2 (40)	2 (100)	12 (75)
BMI (kg/m^2), mean (range)	27 (21–33)	26 (24–28)	30 (26–34)	23 (21–25)	27 (21–34)
HCV Treatment Naïve, n (%)	4 (67)	4 (80)	4 (80)	2 (100)	14 (78)
HCV RNA at Screening (IU/mL x10^5), mean (range)	49.5 (1.29–170)	94.5 (1.16–307)	81.0 (3.40–376)	11.1 (8.59–13.6)	66.5 (1.16–376)
HCV Genotype Subtype 1a, n (%)	6 (100)	3 (60)	2 (40)	2 (100)	13 (72)

- Eighteen patients were randomized into the study
  - One patient randomized to the placebo arm received active drug (1 mg) due to a dosing error
  - One patient in the 10 mg cohort withdrew from the study 8 hours after study drug administration due to personal, non-drug related reasons

Safety

- There were no serious adverse events (SAEs) or AE-related study discontinuations
- There were 15 AEs in total
  - Headache was the most common AE (n=4)
    - Incidence was not dose-related
  - No other AE occurred in more than one patient
  - All AEs were mild except for one event of moderate headache that began prior to receipt of BMS-790052 and deemed as unrelated by the Principal Investigator
- No clinically relevant impact on vital signs, physical examinations, ECGs or laboratory tests
- Single doses of 1, 10 and 100 mg of BMS-790052 were generally safe, well tolerated and had a safety profile similar to that of placebo

Pharmacokinetics

Figure 1: Mean (SD) Plasma Concentration vs. Time Profiles of BMS-790052

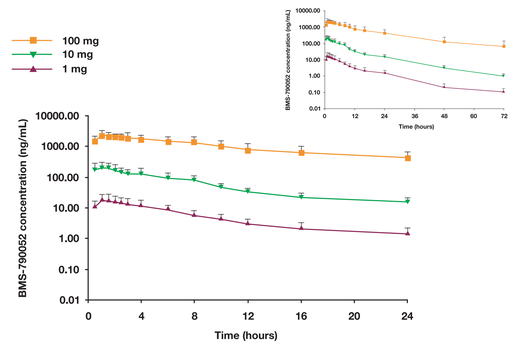
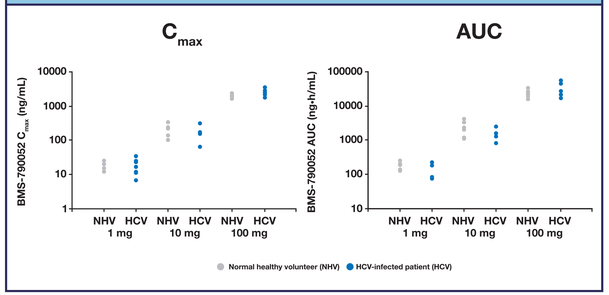


Figure 2: Scatterplots of BMS-790052 C_{max} and AUC vs. Dose in Normal Healthy Volunteers (Study AI444-001) and HCV-infected Patients



- Following oral administration in HCV-infected patients, BMS-790052:
  - was readily absorbed
  - exhibited more than dose-proportional increases in exposures over the dose range of 1 to 100 mg
  - produced exposures comparable to those observed in a previous study in healthy volunteers (Protocol AI444-001)
  - had C24 above the protein binding-adjusted (PBA) EC_{90} derived in replicon for both genotypes 1a and 1b at doses ≥1 mg

Table 3: Summary of Pharmacokinetic Parameters of BMS-790052 in HCV-infected Patients

Dose	1 mg	10 mg	100 mg
C_{max} (ng/mL), geometric mean (CV%)	15.7 (56)	178 (52)	2417 (27)
AUC (ng-h/mL), geometric mean (CV%)	129 (49)	1,431 (45)	29,256 (53)
T_{max} (hours), median (min, max)	1.0 (0.5, 3)	1.0 (1, 1.5)	1.5 (1, 3)
$t_{½}$ (hours), mean (SD)	9.7 (2.7)	12.1 (2.0)	14.0 (6.4)

HCV RNA Suppression

Figure 3: Mean Change in HCV RNA from Baseline Following a Single Dose of BMS-790052 or Placebo

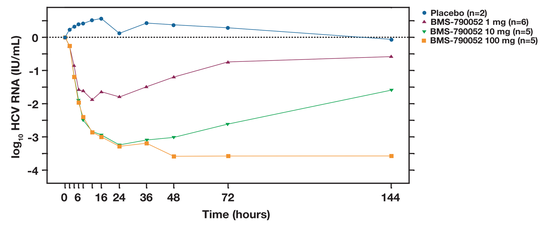
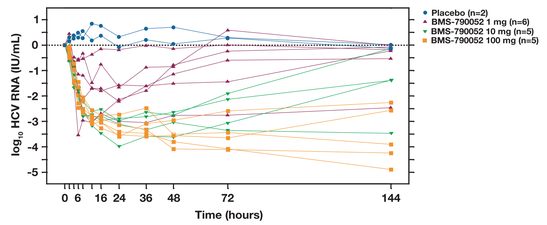


Figure 4: Individual Change in HCV RNA from Baseline Following a Single Dose of BMS-790052 or Placebo



- Mean decline in HCV RNA 24 hours after a single dose of BMS-790052 was:
  - 1.8 $\log_{10}$ IU/mL (range 0.18–3.0 $\log_{10}$) for 1 mg
  - 3.2 $\log_{10}$ IU/mL (range 2.9–4.0 $\log_{10}$) for 10 mg
  - 3.3 $\log_{10}$ IU/mL (range 2.7–3.6 $\log_{10}$) for 100 mg
- The 100 mg dose of BMS-790052 resulted in a mean decline in HCV RNA of 3.6 $\log_{10}$ IU/mL (range 3.0–4.1 $\log_{10}$ IU/mL) observed at 48 hours after dosing, which was maintained at 144 hours
- All active drug recipients had at least a 0.5 $\log_{10}$ decrease from baseline HCV RNA
- Eight of 16 (50%) active drug recipients achieved at least a 3 $\log_{10}$ IU/mL decrease in HCV RNA
- One active drug recipient achieved HCV RNA <LLOQ

Conclusions

- BMS-790052 is a potent NS5A inhibitor that:
  - was safe and well tolerated in single doses up to 100 mg
  - has a PK profile that potentially supports once-daily dosing
  - produced a robust decline in HCV RNA following a single dose in patients chronically infected with HCV genotype 1

Multiple ascending dose trials are ongoing

Disclosures

Richard E Nettles, Caly Chien, Ellen Chung, Anna Persson, Min Gao, Makonen Belema, Nicholas Meanwell, John Coumbis, Juan Carlos Lopez-Talavera and Dennis M Grasela are all employees of Bristol-Myers Squibb

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