BMS-790052, a First-in-Class Potent Hepatitis C Virus NS5A Inhibitor, Demonstrates Multiple-Dose Proof-of-Concept in Subjects With Chronic GT1 HCV Infection

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ABSTRACT

Background: NS5A plays a central role in hepatitis C virus (HCV) replication. BMS-790052 is a first-in-class and potent NS5A inhibitor with broad genotypic coverage. In a multiple ascending-dose (MAD) study with healthy subjects, BMS-790052 was shown to be well-tolerated and had a pharmacokinetic (PK) profile supportive of once-daily dosing.

Methods: The objectives of this randomized, double-blind, placebo-controlled, MAD monotherapy study were to evaluate the antiviral activity, safety, tolerability, and PK of BMS-790052 in treatment-naive subjects infected with genotype 1 HCV. Men and women, 18 to 60 years of age with HCV RNA ≥10^5 IU/mL with noncirrhotic compensated liver disease, were eligible to participate in the study. Patients were randomized to receive 14 days of 1, 10, 30, 60, or 100 mg once-daily (QD) or 30 mg twice-daily (BID) of BMS-790052 or placebo (5 patients per dose; active:placebo = 4:1).

Results: Following oral administration, BMS-790052 was readily absorbed with largely dose-proportional exposures over the studied dose range. The mean terminal half-life of BMS-790052 was approximately 13 to 15 hours. Mean maximum declines in HCV RNA in genotype 1a- and 1b-infected subjects after multiple doses of 1, 10, 30, 60, and 100 mg QD and 30 mg BID BMS-790052 were as follows:

Table 1. Mean Maximum Decline in HCV RNA (log_{10})

Genotype	QD Dose Range (mg)					BID Dose (mg)
	1	10	30	60	100	30
1a (n)	2.4 (2)	3.0 (2)	3.3 (4)	3.8 (4)	3.6 (3)	2.6 (2)
1b (n)	3.3 (2)	4.3 (2)	N/A	N/A	4.5 (1)	5.7 (2)

N/A = not applicable.

The antiviral effect was not sustained for the entire 14 days of dosing and some subjects experienced viral rebound on or before day 7 of dosing. All BMS-790052 multiple doses were well-tolerated and had a safety profile similar to that of placebo. There were no serious adverse events or discontinuations due to adverse events. The only adverse event that occurred in >10% of subjects was headache, reported in 5 (20.8%) subjects receiving BMS-790052 and 2 (33.3%) placebo recipients.

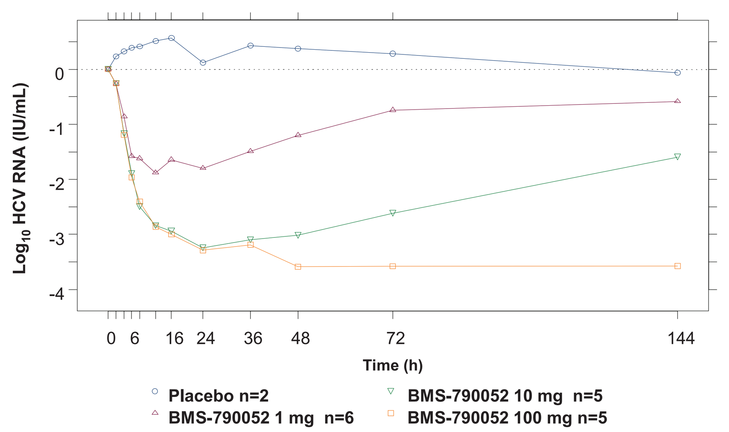
Conclusions: BMS-790052 is a potent NS5A inhibitor that produces a robust decline in HCV RNA following multiple doses in subjects chronically infected with either HCV genotype 1a or genotype 1b. A subsequent clinical study of BMS-790052 in treatment-naive genotype 1 HCV subjects demonstrated potent early antiviral activity against both genotypes 1a and 1b when combined with pegylated interferon/ribavirin. BMS-790052 was well-tolerated in multiple doses of up to 100 mg and has a PK profile that supports once-daily dosing. These results support the importance of inhibiting NS5A-mediated HCV replication in the treatment of HCV. Further studies are under way to confirm the role of NS5A inhibition in HCV therapy.

BACKGROUND AND OBJECTIVES

- NS5A is a multifunctional protein required for in vivo and in vitro hepatitis C virus (HCV) replication; it has no known human homologues, making it an attractive target for therapeutic intervention[1]
- BMS-790052 is a first-in-class, potent, and highly selective inhibitor of HCV NS5A, with in vitro picomolar potency
- BMS-790052 was generally well-tolerated in single doses of up to 100 mg in patients with chronic HCV genotype 1
- A multiple ascending-dose (MAD) study of BMS-790052 in healthy subjects demonstrated a pharmacokinetic (PK) profile that supports once-daily dosing
- BMS-790052 produced a robust decline in HCV RNA following a single dose in subjects chronically infected with HCV genotype 1
- **The objectives of the current MAD study were to evaluate the antiviral activity, PK, safety, and tolerability of BMS-790052 in subjects chronically infected with HCV genotype 1**

1. Gao M, et al. *Nature*. 2010;465:96-100.

Figure 1. Mean Change in HCV RNA From Baseline Following Single Doses of BMS-790052 or Placebo



Gao M, et al. *Nature*. 2010;465:96-100.

METHODS – STUDY DESIGN

- Double-blind, placebo-controlled, sequential-panel, MAD study
- Five subjects in each panel were randomized to receive a 14-day course of orally administered BMS-790052 or placebo in a ratio of 4:1
- Subjects were randomized to receive 1,10, 30, 60, or 100 mg BMS-790052 QD, or 30 mg BID, or placebo
- Enrollment Criteria
  - Men and women, ages 18 to 60 years inclusive, chronically infected with HCV genotype 1
  - Body mass index (BMI) of 18 kg/m^2 to 35 kg/m^2
  - HCV RNA viral load ≥100,000 IU/mL at screening
  - Documented FibroTest score of ≤0.72 and APRI ≤2, or the absence of cirrhosis based on liver biopsy within last 12 months

APRI = Aspartate Aminotransferase-to-Platelet Ratio Index.

- Study Assessments
  - Safety assessments were based on reported adverse events and the results of vital sign measurements, physical examinations, ECGs, and clinical laboratory tests
  - Antiviral activity was assessed by the magnitude of change in plasma HCV RNA levels from baseline
    - HCV RNA was measured with the Roche COBAS® TaqMan® HCV Test, v2.0, LLOQ = 25 IU/mL
    - Viral rebound was defined as HCV RNA increase by at least 0.5 log_{10} following HCV RNA nadir
- PK parameters were derived from the plasma concentration vs time data
    - BMS-790052 in human plasma was assayed using a validated LC-MS/MS method during the period of known analyte stability

LLOQ = lower limit of quantitation; LC-MS/MS = liquid chromatography-tandem mass spectroscopy.

- Statistical Analysis
  - The magnitude of the change in log_{10} HCV RNA levels was assessed by summarizing changes from baseline by time, study day, and treatment; the primary assessment of the antiviral activity was based on the change from baseline to day 7
  - The multiple-dose PK of BMS-790052 was described by summary statistics for the PK parameters by treatment and study day
  - Plasma concentration vs time data were analyzed by noncompartmental methods using the program Kinetica®

RESULTS

- Patient Disposition and Study Population
  - 30 subjects were enrolled and received study medication
  - 29 subjects completed the study through day 28
  - One subject was lost to follow-up posttreatment on day 28 after receiving all doses of BMS-790052 10 mg QD

Table 2. Demographics and Baseline Characteristics

	QD Dose Range (mg)						BID Dose (mg)
	Placebo n=6	1 n=4	10 n=4	30 n=4	60 n=4	100 n=4	30 n=4
Age (y) Mean (range)	48 (43-54)	39 (29-48)	46 (29-59)	47 (43-52)	39 (29-47)	44 (34-49)	45 (38-53)
Male, n (%)	5 (83)	3 (75)	3 (75)	4 (100)	3 (75)	3 (75)	4 (100)
Race: white, n (%)	6 (100)	4 (100)	2 (50)	4 (100)	2 (50)	3 (75)	4 (100)
BMI (kg/m^2) Mean (range)	28.4 (19.3-34.9)	29.4 (23.5-34.9)	29.9 (27.6-32.5)	30.9 (26.3-35.0)	29.2 (25.0-33.3)	26.7 (22.8-30.1)	28.1 (25.4-31.4)
Baseline HCV RNA (IU/mL x 10^5), Mean (range)	53.5 (8.30-138)	3.62 (.058-10.6)	8.47 (3.22-19.6)	64.0 (12.6-140)	129 (18.4-244)	79.4 (3.54-199)	95.1 (43.5-195)
HCV genotype 1a, n (%)	1 (17)	2 (50)	2 (50)	4 (100)	4 (100)	3 (75)	2 (50)

- Safety
  - There were no deaths, serious adverse events, or treatment discontinuations due to adverse events
  - Adverse events that occurred in more than 1 subject are displayed in the following table
  - Treatment-emergent adverse events were reported at a similar frequency following administration of BMS-790052 and placebo, and no dose-related trends were apparent following administration of BMS-790052 at doses of 1 mg to 100 mg
  - One placebo recipient reported a sinus headache of severe intensity; all other adverse events were mild or moderate in intensity
  - The most frequent treatment-emergent adverse event was headache (20.8% of subjects receiving BMS-790052 and 33.3% of placebo recipients)
  - There were no clinically relevant changes in laboratory findings, vital signs, physical examinations, or ECGs

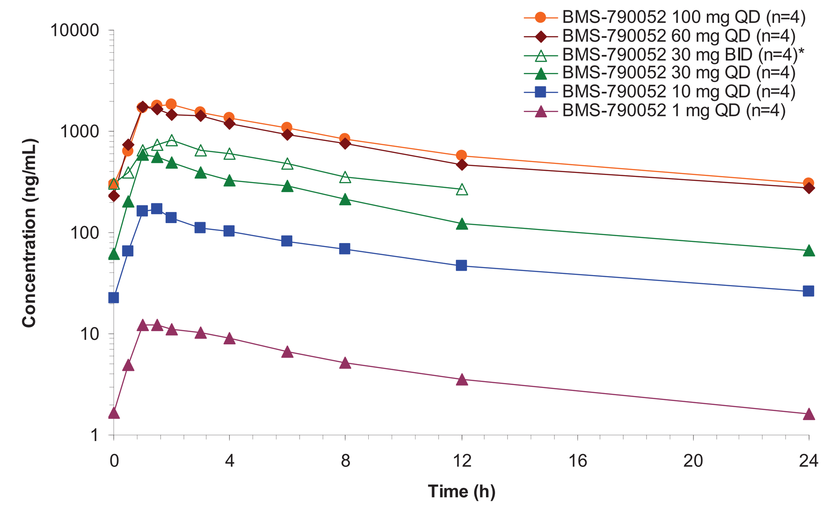
RESULTS (cont'd)

Table 3. Adverse Events That Occurred in More Than One Subject

Adverse Events That Occurred in >1 Subject n (%)	QD Dose Range (mg)					BID Dose (mg)	Placebo
	1 n=4	10 n=4	30 n=4	60 n=4	100 n=4	30 n=4	n=6
Headache	0	1 (25)	0	2 (50)	1 (25)	1 (25)	2 (33)
Back pain	0	1 (25)	0	1 (25)	0	0	0
Diarrhea	0	1 (25)	0	0	1 (25)	0	0
Fatigue	1 (25)	1 (25)	0	0	0	0	0
Insomnia	1 (25)	0	0	1 (25)	0	0	0
Abdominal pain	0	0	0	0	1 (25)	0	1 (17)

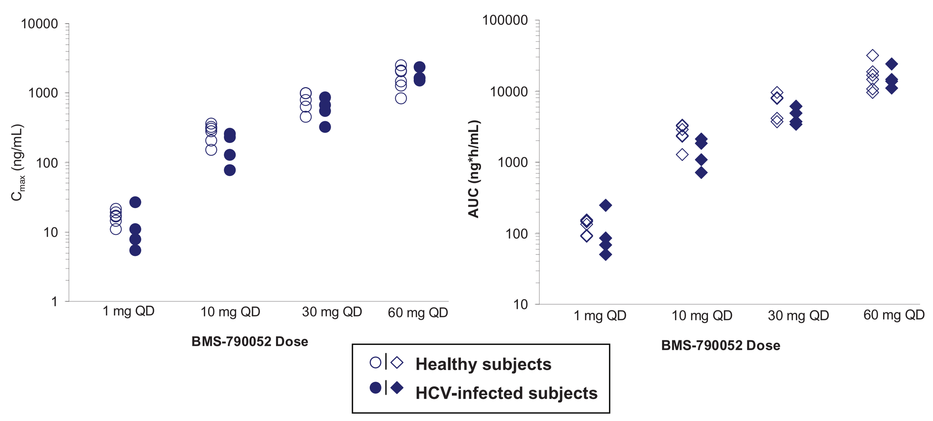
- PK
  - BMS-790052 was readily absorbed, with peak plasma concentrations achieved approximately 1 to 2 hours postdose
  - Steady state was achieved by day 4, consistent with a terminal half-life of approximately 13 to 15 hours
  - BMS-790052 has demonstrated protein binding-adjusted 90% effective concentration (PB-adjusted EC_{90}) values in replicon for HCV genotype 1a and 1b of 0.283 ng/mL and 0.0362 ng/mL, respectively. At all doses studied and beginning on day 1, all subjects had BMS-790052 minimum observed concentration (C_{min}) values above the PB-adjusted EC_{90} values for both genotypes
  - After administration of 10 mg to 100 mg QD, BMS-790052 C_{min} values were greater than the 10-fold protein binding– adjusted EC_{90} value for genotype 1a (2.83 ng/mL)

Figure 2. Mean Plasma Concentration-Time Profiles for BMS-790052 on Day 14 of Dosing



*Profile displayed for AM dose only (0-12 hours).

Figure 3. Scatterplots of BMS-790052 Day 14 C_{max} and $AUC_{(TAU)}$ vs Dose in Normal Healthy Volunteers and HCV-Infected Subjects



C_{max} = maximum observed concentration; AUC = area under the concentration vs time curve.

RESULTS (cont'd)

- HCV RNA Suppression
  - Patients infected with HCV genotype 1b generally demonstrated greater antiviral responses than patients with HCV genotype 1a; across all cohorts, below limits of quantification HCV RNA levels (<25 IU/mL) at day 15 were found in 4 of 7 patients with genotype 1b vs none of 17 patients with genotype 1a infection
  - Although there was evidence of HCV antiviral activity after 7 days of administration of BMS-790052, this drug effect was not sustained for the entire 14 days of dosing; many patients experienced viral rebound on or before day 7 of dosing

Table 4. Mean Maximum Decline in HCV RNA (log_{10})

Genotype	QD Dose Range (mg)					BID Dose (mg)
	1	10	30	60	100	30
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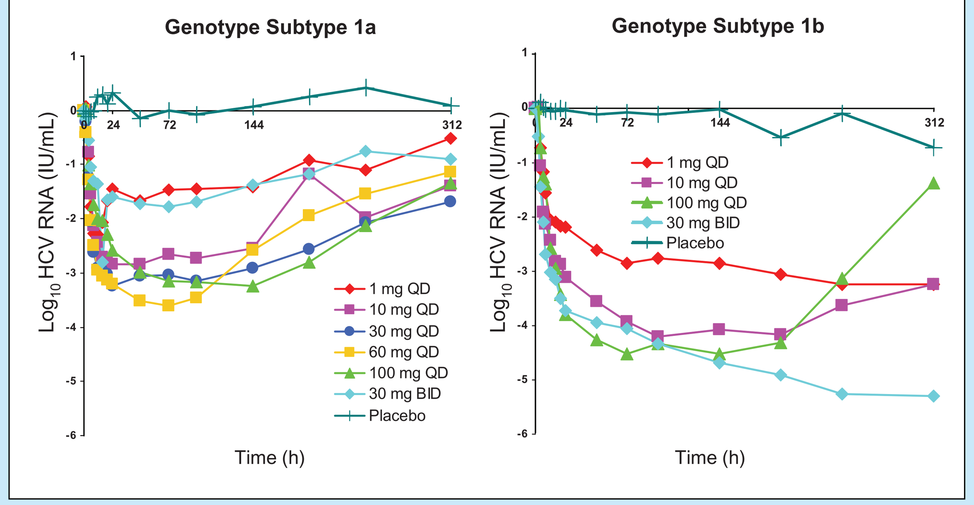
N/A = not available.

Figure 4. Mean Decline in HCV RNA



CONCLUSIONS

- BMS-790052, a first-in-class NS5A inhibitor, produces a robust decline in HCV RNA following multiple doses in subjects chronically infected with either HCV genotype 1a or genotype 1b
- BMS-790052 is well-tolerated over 14 days of multiple doses of up to 100 mg
- The PK profile of BMS-790052 supports once-daily dosing
- These results confirm the value of inhibiting NS5A-mediated HCV replication in the treatment of HCV. Further studies are under way to define the role of NS5A inhibition in combination with other direct-acting antiviral drugs and pegylated interferon/ribavirin

DISCLOSURES

- Nettles RE, Sevinksy H, Chung E, Burt D, Xiao H, Persson A, Bifano M, and Grasela DM are employees of Bristol-Myers Squibb
- Marbury T: No disclosures to report
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- DeMicco M: No disclosures to report
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