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Multiple Ascending Dose Study of BMS-790052, an NS5A Replication Complex Inhibitor, in Patients Infected With Hepatitis C Virus Genotype 1

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Abbreviations

PK, pharmacokinetics

HCV, hepatitis C virus

PEG-IFN, pegylated interferon

RBV, ribavirin

DAA, direct-acting antiviral

AE, adverse event

NS5A, nonstructural protein 5A

ECG, electrocardiogram

C_{trough}, trough concentrations

C_{min}, minimum observed plasma concentration

C_{max}, maximum observed plasma concentration

T_{max}, time of maximum observed plasma concentration

AUC, area under the plasma concentration time curve

$AUC_{(TAU)}$, AUC over 12-hour dosing interval for 30 mg twice daily

$T_{1/2}$, half life

CLT/F, apparent total body clearance

CV, coefficient of variation

PCR, polymerase chain reaction

ISG, interferon-stimulated gene

QD, once daily

BID, twice daily

NA, not applicable

AI, accumulation index

CLT/F, apparent total body clearance

ABSTRACT: The antiviral activity, resistance profile, pharmacokinetics (PK), safety and tolerability of BMS-790052, an NS5A replication complex inhibitor, were evaluated in a double-blind, placebo-controlled, sequential panel, multiple ascending dose study. Thirty patients with chronic hepatitis C virus (HCV) genotype 1 infection were randomized to receive a 14-day course of BMS-790052 (1, 10, 30, 60 or 100 mg once daily or 30 mg twice daily) or placebo in a ratio of 4:1. ***Results:*** The mean maximum decline from baseline in HCV RNA ranged from 2.8 to 4.1 $\log_{10}$ IU/mL; the placebo group showed no evidence of antiviral activity. Most patients experienced viral rebound on or before day 7 of treatment with BMS-790052 monotherapy; viral rebound was associated with viral variants that had been previously implicated in resistance development in the *in vitro* replicon system. The PK profile was supportive of once-daily dosing with median peak plasma concentrations at 1-2 hours postdose and mean terminal half-life of 12-15 hours. Steady state was achieved following 3-4 days of daily dosing. BMS-790052 was well tolerated in all dose groups with adverse events occurring with a similar frequency in BMS-790052- and placebo-treated groups. There were no clinically relevant changes in vital signs, laboratory, or electrocardiogram parameters. ***Conclusion*:** BMS-7590052 is the first NS5A replication complex inhibitor with multiple dose proof-of-concept in clinic. At doses of 1-100 mg daily, BMS-790052 was well-tolerated, had a PK profile supportive of once-daily dosing, and produced a rapid and substantial decrease in HCV-RNA levels in patients chronically infected with HCV genotype 1.

The current treatment of chronic hepatitis C virus (HCV) infection, a regimen of pegylated interferon alpha (PEG-IFN)-2a or -2b, and ribavirin (RBV) remains unsatisfactory, particularly in the large number of patients with HCV genotype 1 infection whose sustained viral response rates are currently ~40% (1). However, treatment for HCV infection is rapidly evolving with the introduction of direct-acting antiviral (DAA) agents (2, 3). The combination of telaprevir, an HCV NS3 protease inhibitor, with PEG-IFN alpha-2a and RBV has been associated with sustained viral response rates of 61%-67% in patients with genotype 1 infection (2). Telaprevir is administered three times a day and has been associated with adverse events (AEs) such as rash and anemia (4). There continues to be an unmet medical need for additional DAA agents with different mechanisms of action and resistance patterns that are easy to administer, more effective, and well tolerated. Focusing on the critical importance of non-structural protein 5A (NS5A) for HCV replication, BMS-790052 was identified as a potent and highly selective inhibitor of HCV based on inhibitor binding and mapping, inhibitor-induced resistant substitutions, and crystal structure modeling. *In vitro* data have shown that BMS-790052 inhibits HCV genotype 1 replicons with a median 50% effective concentration of ≤50 pM, while BMS-790052-resistant variants remain fully sensitive to interferon alpha and small-molecule inhibitors of HCV protease and polymerase (5). NS5A is a multifunctional protein required for *in vivo* and *in vitro* HCV replication and has no known human homologs, making it an attractive target for therapeutic intervention (6).

BMS-790052 was previously found to be safe and well tolerated administered in healthy non-HCV-infected subjects at doses up to 200 mg as a single dose, and up to 60 mg once daily for 14 days. In a previous trial of patients chronically infected with HCV, administration of a single

100-mg dose of BMS-790052 was associated with a 3.3 $\log_{10}$ reduction in mean viral load measured 24 hours postdose. This response was sustained for an additional 120 hours in two patients infected with genotype 1b virus (6). Here we report the results of the first placebo-controlled, multiple ascending dose clinical study to evaluate the antiviral activity, resistance profile, pharmacokinetics (PK), safety, and tolerability of an HCV NS5A replication complex inhibitor, BMS-790052, in patients chronically infected with HCV genotype 1.

MATERIALS AND METHODS

Study Design

This study was a double-blind, placebo-controlled, sequential panel, multiple ascending dose study. Six dose regimens of BMS-790052 in HCV genotype 1-infected patients were evaluated (1 mg once daily, 10 mg once daily, 30 mg once or twice daily, 60 mg once daily, and 100 mg once daily) (ClinicalTrials.gov number, NCT00663208). Five patients in each panel were randomized to receive a 14-day course of orally administered BMS-790052 or placebo in a ratio of 4:1. Patients were admitted to one of eight clinical facilities in the United States between May 2008 and June 2009, and required to remain in-house from day −1 (screening day) to day 2, and from day 13 to day 15. Patients were permitted to be furloughed from the clinical facility from day 3 to day 12 and from day 16 to study discharge, which occurred at approximately day 182 for patients receiving active drug, following completion of additional blood sampling for analysis of HCV RNA and genomic substitutions. Patients treated with placebo were not required to return for follow-up visits beyond day 28. The majority of patients were treated as inpatients from day −1 to day 15. BMS-790052 or placebo was administered under fasting conditions. No intrapatient dose escalation was allowed. Dose escalation between panels occurred only after all safety data (through the final dose) from four patients receiving BMS-

790052 in the prior dose panel were reviewed and deemed safe by the Bristol-Myers Squibb medical monitor in consultation with the investigators. No concomitant medications (prescription, over-the-counter or herbal) were permitted to be administered during the study, unless they were prescribed by the investigator for treatment of specific clinical events or were approved by the medical monitor prior to dosing. The study was approved by the institutional review boards in all study centers and conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization, in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Informed written consent was obtained from all patients.

Patients were randomly assigned to receive BMS-790052 or placebo according to a computer-generated randomization scheme prepared by Bristol-Myers Squibb. An Interactive Voice Response System was used to assign a unique subject number and a blinded container number, which was provided to the blinded study staff who supervised and recorded the drug administration.

The sample size was based on the primary endpoint of the study, defined as the change in $\log_{10}$ HCV RNA from baseline to day 7. A mean decrease of at least 1.5 $\log_{10}$ HCV RNA within one dose panel would suggest that BMS-790052 was sufficiently active to proceed to late phase development. If BMS-790052 had no effect, administration of drug to four patients within a dose panel would yield a probability of 0.01 to observe a mean decrease in $\log_{10}$ HCV RNA of more than 1.5. If the true mean decrease was 2.0, the probability of observing a mean decrease in $\log_{10}$

HCV RNA of more than 1.5 would be 0.78. These calculations are based on the assumption that $\log_{10}$ HCV RNA is normally distributed, with a standard deviation for the change of 1.3.

Patients

Eligible patients for this study were men and women, ages 18-60 years inclusive, with a body mass index of 18-35 kg/m^2, who were chronically infected (longer than 6 months) with HCV genotype 1, and who were treatment-naive to interferon and RBV. Additional inclusion criteria were: plasma HCV RNA ≥100,000 IU/mL; documented FibroTest score of ≤0.72 and APRI ≤2, or the absence of cirrhosis based on liver biopsy within 12 months; women of childbearing potential were not to be nursing or pregnant and had to be willing to agree to use double barrier contraception for at least 1 month before dosing, during dosing, and at least 12 weeks after the last dose of study medication.

The main exclusion criteria were: patients with prior documented cirrhosis on liver biopsy; previous exposure to a NS5A replication co-factor inhibitor; coinfection with human immunodeficiency virus; coinfection with hepatitis B virus.

Safety Assessments

Blood and urine samples for clinical laboratory evaluations, single 12-lead electrocardiogram (ECG), and blood pressure measurements were collected at specified time points throughout the study. Safety assessments were based on reported AEs and the results of vital sign measurements, physical examinations, ECGs, and clinical laboratory tests. The incidences of AEs were tabulated and reviewed for their clinical relevance.

Pharmacokinetics

Serial blood samples for PK analysis were obtained on day 1 for 24 hours after the morning dose, and on day 14 for 72 hours after the last dose. PK samples for the once-daily dosing groups were collected on day 1 and day 14 predose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose. In addition, PK samples were collected 48 hours (day 15) and 72 hours (day 16) postdose. PK samples for the 30 mg twice-daily dosing group were collected using the same PK sampling schedule as the once-daily dosing groups, but a second dose was not administered on day 14. Blood samples for trough concentrations (C_{trough}), minimum observed plasma concentration (C_{min}), and steady-state assessment were obtained on days 2, 3, 4, 5, 7, 9, 11, and 13 prior to the morning dose. The PK parameters derived from the plasma concentration versus time data by noncompartmental methods were: maximum observed plasma concentration (C_{max}), C_{min}, time of maximum observed plasma concentration (T_{max}), area under the concentration curve (AUC) over 12-hour dosing interval for 30 mg twice daily ($AUC_{(TAU)}$), half-life ($T_{1/2}$), and apparent total body clearance (CLT/F). The $AUC_{(0-24)}$ for the 30 mg twice-daily dosing group was determined by multiplying the $AUC_{(0-12)}$ by 2. In addition, accumulation index, degree of fluctuation, and time to steady-state were assessed. Additional blood samples were collected on day 14 immediately prior to and 2 hours after the morning dose for *ex vivo* protein binding determination. Protein binding in human plasma was assessed in triplicate at both time points. Plasma samples for BMS-790052 were prepared by a liquid-liquid extraction procedure and assayed by Tandem Labs (West Trenton, NJ) using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) method during the period of known analyte stability. The lower limit of quantitation of the assay in human plasma was 0.0500 ng/mL. Chromatographic separation was achieved using a Genesis C8, 50 x 2.1 mm, 4 µm column (Grace Vydac, Hesperia, CA) with a gradient mobile phase of 10 mM ammonium acetate in water with 0.1%

formic acid/0.1% formic acid in acetonitrile. Mass spectrometry data were acquired using an API 4000 mass spectrometer (MDS Sciex®, Thornhill, Ontario, Canada) operated in a positive electrospray ionization mode. The selected reaction monitoring transitions (±0.3 amu) were 370.4 > 130.2 for BMS-790052 and 375.4 > 130.2 for BMS-790052-13C. The intra-assay precision for BMS-790052 was within 12.1% coefficient of variation (CV) and the inter-assay precision was within 11.9% CV. Protein binding samples were also prepared and analyzed by the validated procedure described above.

Viral Kinetics

HCV RNA levels were determined using the Cobas® TaqMan® HCV Test, v2.0 (Roche, Pleasanton, CA; lower limit of quantification, 25 IU/mL; lower limit of detection, 10 IU/mL) at screening, days −1, 1 (2, 4, 6, 8, 12, 16, and 20 hours post-first dose), 2, 3, 4, 5, 7, 9, 11, 14, 15, 16, 17, 21, and 28. Thereafter, blood samples for HCV RNA levels were collected at approximately days 42, 98, and 182. Viral rebound was defined as an HCV RNA increase by at least 0.5 $\log_{10}$ following HCV RNA nadir.

Viral resistance was evaluated by genotypic and phenotypic analysis. In brief, viral RNA was isolated from patient serum with a QIAamp MiniElute Viral Vacuum Kit (QIAGEN, Inc., Valencia, CA). First strand cDNA was synthesized from random hexamer primers with a SuperScript III First-Strand Synthesis System for reverse transcription-polymerase chain reaction (PCR) (Invitrogen Corporation, Carslbad, CA). The NS5A coding region was amplified with genotype-specific primers. A second PCR with the same primers, or a nested PCR with internal primers, was performed when required to obtain sufficient NS5A cDNA for sequence analysis. Sequences covering both strands were obtained for purified PCR products and compared to

control replicon sequences (H77c and Con1 for genotype 1a and 1b, respectively). Sequence traces were examined at the known resistance sites for possible variations. Total RNA was isolated from serum samples taken at the following time points: days −1, 1 (4, 8, and 12 hours post-first dose), 2, 3, 4, 7, and 14 (5).

Additional blood samples were collected for analyses of host response (interferon-stimulated genes [ISGs]). ISG expression (2'5'-oligoadenylate synthetase 1, myxovirus resistance 1, and Viperin) was assessed by quantitative PCR using blood samples collected on days −1, 1 (4 and 8 hours postmorning dose), 2, 3, 7 and 14.

Statistical Analysis

Antiviral activity was assessed by the magnitude of change in plasma HCV RNA levels from baseline. The change from baseline in $\log_{10}$ HCV RNA was summarized by study day, time, and dose. The primary endpoint of the study was defined as the change in $\log_{10}$ HCV RNA from baseline to day 7. Each individual's maximum decrease from baseline in $\log_{10}$ HCV RNA, as well as the day of maximum observed decrease, was summarized by dose. Antiviral activity endpoints were also summarized by HCV subtype (1a, 1b). Associations between selected baseline characteristics (ie, HCV subtype, baseline $\log_{10}$ HCV RNA, race, body mass index, FibroTest result) and antiviral activity were explored graphically.

The multiple-dose PK of BMS-790052, including plasma protein binding and free fraction, was described by summary statistics for the PK parameters by dose and study day. Point estimates and 90% confidence intervals were constructed for accumulation indices, using general linear models fitted to log-transformed data with study day (days 1 and 14) as a fixed effect, and

measurements within each patient as repeated measurements. Point estimates and 90% confidence intervals for differences at the log-scale were exponentiated to obtain estimates and confidence intervals for ratios of geometric means on the original scale. To assess the dependency on dose, scatter plots of C_{max}, $AUC_{(TAU)}$, and C_{min} versus dose were provided by day. Time to steady state was evaluated by summary statistics of C_{trough} by study day and dose, and by plotting geometric mean C_{trough} versus study day by dose.

The ISG gene expression levels were first normalized by the housekeeping gene hypoxanthine phosphoribosyltransferase 1. When multiple measurements were available for the same patient, time point, and gene, the median of the available ISG expression was used. Statistical analyses were based on the normalized gene expression levels. The gene expression levels (percentage of baseline) were summarized by gene, dose, and visit. No additional analyses relating the gene expression to BMS-790052 exposure or decline in HCV RNA were performed since there were no clear differences observed in the meantime profile between placebo and BMS-790052-treated groups.

All recorded AEs were listed and tabulated by system organ class, preferred term, and treatment. Vital signs, ECG parameters, and clinical laboratory tests were listed and summarized by dose. Any significant physical exam findings and clinical laboratory results were listed. ECG readings were evaluated by the investigators and all identified abnormalities were documented. The effects of BMS-790052 on ECG parameters (heart rate, pulse rate, QRS, QT and QTc) and blood pressure were explored graphically and by summary statistics. Absolute levels, as well as changes from baseline (last observation prior to dosing on day 1), were summarized and plotted

versus time by dose and study day. Associations between ECG parameters or blood pressure and BMS-790052 concentrations were explored graphically.

All statistical analyses were carried out using SAS/STAT® Version 8.2 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics

Thirty patients were enrolled and received study medication and 29 patients completed the study through day 28 (one patient was lost to follow-up posttreatment on day 28 after receiving all doses of BMS-790052 10 mg once daily). Twenty patients completed the long-term follow-up to approximately day 182. Baseline and demographic characteristics were comparable across all treatment groups (Table 1) with the exception of the observed baseline HCV RNA, which was numerically lower in patients receiving BMS-790052 1 mg and 10 mg compared with other groups. However, all dosed patients belonged to the protocol-specified study population with plasma HCV RNA ≥100,000 IU/mL at screening.

Effect of BMS-790052 on HCV RNA

Individual changes from baseline in $\log_{10}$ HCV RNA are shown in Figure 1. The mean change in $\log_{10}$ HCV RNA from baseline to day 2, the mean change in $\log_{10}$ HCV RNA from baseline to day 7, the mean maximal decrease from baseline in $\log_{10}$ HCV RNA, and the day of maximum decrease are presented in Table 2. Although this is a very small sample size, patients infected with HCV genotype 1b generally demonstrated greater antiviral responses than patients with HCV genotype 1a; across all treatment groups undetectable HCV RNA levels (<25 IU/mL) at

day 14 were found in 4 of 7 patients with genotype 1b versus 0 of 17 patients with genotype 1a infection. HCV genotype was the only baseline characteristic that appeared to affect the magnitude of antiviral activity of BMS-790052 (baseline $\log_{10}$ HCV RNA, race, body mass index, and FibroTest explored). Many patients experienced viral rebound on or before day 7 of dosing. In general, antiviral effect was not observed in placebo recipients with the exception of a rapid and transient decline in HCV RNA in two patients, one of whom was likely administered a single dose of BMS-790052 in error.

Host Response to BMS-750052 (ISGs)

Expression of individual ISGs, including 2'5'-oligoadenylate synthetase 1, myxovirus resistance 1, and Viperin, were monitored to measure host response as a function of antiviral responses and drug exposures. There was no clear difference in the meantime profile of individual ISG expression levels (percent of baseline), normalized by the hypoxanthine phosphoribosyltransferase 1 gene between the placebo-treated and the BMS-790052-treated dose groups at baseline or on day 1 (4 and 8 hours postmorning dose), 2, 3, 7, or 14 (data not shown).

Resistance Profile

Population sequencing revealed amino acid substitutions in NS5A at baseline and at rebound that had been previously implicated in resistance development in the *in vitro* replicon system (5). Major resistance substitutions were observed at residues M28, Q30, L31, and Y93 for genotype 1a, and at L31 and Y93 for genotype 1b. Additional variants, including those with linkage between two resistance substitutions, were also detected. These variants conferred different levels of resistance to BMS-790052 in the replicon system. A more detailed description of the observed viral variants will be presented elsewhere.

Pharmacokinetics

BMS-790052 exposure in plasma was assessed on days 1 and 14 (Table 3). The concentration-time profiles for BMS-790052 on day 14 of dosing are shown in Figure 2. BMS-790052 was readily absorbed following daily oral doses of 1-100 mg, with median peak plasma concentrations 1-2 hours postdose and a mean terminal $T_{1/2}$ of 12-15 hours. BMS-790052 exposures after 14 days of dosing (C_{max}, C_{min}, and $AUC_{(TAU)}$) increased in a largely dose-dependent manner from 1 to 100 mg once daily; however, exposures overlapped between 60 and 100 mg once daily. Steady state was achieved following 3-4 days of daily dosing. Accumulation indices after 14 days of daily dosing of BMS-790052 are in agreement with the $T_{1/2}$ of BMS-790052 administered as a once-daily regimen. BMS-790052 was approximately 99% bound to human plasma proteins, with protein binding appearing to be independent of dose over the dose range studied.

After 14 days of dosing of 1-100 mg BMS-790052, all patients had BMS-790052 C_{min} values above the replicon 90% median effective concentration values of 0.283 and 0.0362 ng/mL for genotype 1a and 1b, respectively. Furthermore, BMS-790052 C_{min} values exceeded the protein binding-adjusted EC_{90} values after just a single dose (day 1). BMS-790052 C_{min} values were numerically greater than the 10-fold protein binding adjusted EC_{90} for genotype 1a (2.83 ng/mL) after administration of 10-100 mg BMS-790052 once daily.

Safety and Tolerability

There were no deaths, serious AEs or treatment discontinuations due to AEs. Treatment-emergent AEs were reported at a similar frequency following administration of BMS-790052 (16

of 24 [66.7%]) and placebo (4 of 6 [66.7%]) and no dose-related trends were apparent following administration of BMS-790052 at doses of 1-100 mg. One placebo recipient reported a sinus headache of severe intensity; all other AEs were mild or moderate in intensity.

The most frequent treatment-emergent AE was headache (20.8% of BMS-790052-treated patients and 33.3% of placebo-treated patients); headache did not appear to be dose-related and all events were considered by the investigator to be unrelated to study drug. Adverse events that occurred in more than one patient are shown in Table 4.

There were no clinically relevant changes in clinical laboratory values, vital signs, physical examinations, or ECGs.

DISCUSSION

The results of this study indicate that BMS-790052 is a potent NS5A replication complex inhibitor that produces a substantial decline in HCV RNA in patients chronically infected with either HCV genotype 1a or genotype 1b. BMS-790052 was shown to be generally well tolerated, and had a PK profile supportive of once-daily dosing.

The potent antiviral effect of BMS-790052 observed in a previous study was confirmed in the present study (6). In this study, HCV-RNA levels decreased by ~3 logs after a single dose in all BMS-790052-treated groups, other than the 1 mg group. This is consistent with single ascending dose results (6), and demonstrates that the *in vitro* picomolar potency of BMS-790052 translates *in vivo* to substantial antiviral activity. In addition, although the sample size was small, it appears that patients infected with HCV genotype 1b virus responded better than patients infected with

HCV genotype 1a virus, with a more marked and sustained viral RNA decline. This is consistent with both the difference in the intrinsic potency of BMS-790052 for genotype1a and 1b replicons (50 pM versus 9 pM), and the higher level of resistance observed *in vitro* for genotype 1a variants (6). The early suppression of HCV replication with BMS-790052 monotherapy is comparable with, and in some cases exceeds, that observed for other DAA agents (7, 8).

Using the standard model of HCV infection and treatment (9), treatment with BMS-790052 in a prior monotherapy study (6) was associated with improved estimation of HCV RNA clearance rate, shorter delay in viral clearance, and shorter HCV RNA $T_{1/2}$ as compared with PEG-IFN + RBV therapy and telaprevir therapy (10). In the current study, exposure to BMS-790052 again resulted in a rapid decline in HCV RNA in most patients. This early suppression of HCV replication with BMS-790052 monotherapy was commonly followed by viral rebound, as typically observed for short courses of DAA agents when administered as monotherapy (7, 11). In the current study, viral rebound generally occurred on or before day 7 of dosing and was associated with the emergence of previously described viral variants linked with high levels of viral resistance in the replicon system (5). A more detailed description of observed viral variants will be presented elsewhere. Importantly, preliminary data suggest that the combination of BMS-790052 with PEG-IFN + RBV therapy or other DAA agents will be effective at markedly reducing viral rebound (12, 13).

While the development of DAA agents to treat HCV has focused in part on inhibitors of the viral enzymes NS3 protease and NS5B RNA-dependent RNA polymerase (2), BMS-790052 was developed as a small molecule inhibitor targeting the HCV NS5A protein (6). The precise role of NS5A in HCV replication has not been defined; however, observations of inhibition of viral

replication in both *in vitro* replicon systems and single and multiple dose clinical trials confirm the essential role of NS5A in HCV replication. NS5A is a multifunctional viral protein that functions not only as an essential component of the HCV replication complex, but also as a modulator of cellular signaling pathways (14). The observed antiviral effects provide a rationale for the use of BMS-790052 in interferon-based combination therapy. A working model that may explain the potency of BMS-790052 is that its antiviral effect is amplified by the NS5A interactions with viral and cellular proteins. We have observed that BMS-790052 inhibits multiple stages of viral replication, such as the formation of replication complexes and active RNA replication (manuscript submitted). Furthermore, BMS-790052 exhibits additive or synergistic effects in replicon system studies with NS5B, NS3, and non-nucleoside NS5B inhibitors (6).

The PK profile of BMS-790052 supports once-daily dosing, with plasma concentrations throughout the 14-day dosing period above the protein binding-adjusted EC_{90} concentrations required for effective inhibition of HCV replication in the replicon systems. The exposure response observed in the current study suggests that the ranges evaluated in this study support a proposed therapeutic dose of 3-60 mg.

BMS-790052 was generally well tolerated over the study period for all doses evaluated. Adverse events occurred with a similar frequency in BMS-790052- and placebo-treated groups. All AEs were considered by the investigators to be unrelated to the medication.

In conclusion, the results of this study suggest that the novel NS5A replication complex inhibitor BMS-790052 can be administered orally once daily at doses of 10-100 mg daily and is well

tolerated. BMS-790052 produces a substantial decline in HCV RNA levels following multiple doses in patients chronically infected with either HCV genotype 1a or genotype 1b. These results confirm the importance of inhibiting NS5A-mediated HCV replication and the potential of BMS-790052 as part of combination therapy in the treatment of HCV. Additional clinical trials are ongoing to further confirm the safety and efficacy of BMS-790052 in patients with chronic HCV infection.

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Figure Legends

Figure 1. Individual Change From Baseline in Log_{10} HCV RNA by Dose and HCV Genotype Subtype. BID, twice daily; HCV, hepatitis C virus; QD, once daily. HCV RNA was set to 25 or 10 IU/mL if observed value was less than lower limit of quantification (25 IU/mL) or lower limit of detection (10 IU/mL) respectively, when deriving changes from baseline. Dashed and solid lines indicate patients with HCV genotype 1a and 1b, respectively.

Figure 2. Mean Plasma Concentration-Time Profiles for BMS-790052 on Day 14 of Dosing. BID, twice daily; EC_{90}, 90% median effective concentration; QD, once daily.
* Profile displayed for morning dose only (0-12 hours).

Table 1. Baseline Characteristics of Patients

	Once Daily					Twice Daily	Placebo
	1 mg n = 4	10 mg n = 4	30 mg n = 4	60 mg n = 4	100 mg n = 4	30 mg n = 4	n = 6
Mean age, y (range)	39 (29-48)	46 (29-59)	47 (43-52)	39 (29-47)	44 (34-49)	45 (38-53)	48 (43-54)
Male, n (%)	3 (75)	3 (75)	4 (100)	3 (75)	3 (75)	4 (100)	5 (83)
Race, n (%)							
White	4 (100)	2 (50)	4 (100)	2 (50)	3 (75)	4 (100)	6 (100)
African American	0	2 (50)	0	1 (25)	1 (25)	0	0
Other	0	0	0	1 (25)	0	0	0
Mean BMI, kg/m^2 (range)	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)	28.4 (19.3-34.9)
Mean baseline HCV RNA, IU/mL × 10^5	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)	53.5 (8.30-138)
HCV genotype 1a, n (%)	2 (50)	2 (50)	4 (100)	4 (100)	3 (75)	2 (50)	1 (17)
Genotypic drug resistance mutation at baseline, n (%)	0	0	0	1 (25)	1 (25)	1 (25)	0

BMI, body mass index; HCV, hepatitis C virus.

Table 2. Summary Measures for Antiviral Activity

Endpoint	Genotype	Once Daily					Twice Daily	Placebo
		1 mg	10 mg	30 mg	60 mg	100 mg	30 mg	
Mean change from baseline* to day 2 in HCV RNA (range), log_{10} IU/mL	1a or 1b	-1.82 (-2.36; -1.24) [n = 4]	-2.97 (-3.27; -2.76) [n = 4]	-3.24 (-3.35; -3.10) [n = 4]	-3.20 (-3.83; -2.01) [n = 4]	-2.88 (-3.79; -1.10) [n = 4]	-2.66 (-4.25; -0.06) [n = 4]	0.02 (-0.26; 0.33) [n = 6]
	1a	-1.45 (-1.66; -1.24) [n = 2]	-2.84 (-2.92; -2.76) [n = 2]	-3.24 (-3.35; -3.10) [n = 4]	-3.20 (-3.83; -2.01) [n = 4]	-2.58 (-3.48; -1.10) [n = 3]	-1.60 (-3.14; -0.06) [n = 2]	0.33 [n = 1]
	1b	-2.19 (-2.36; -2.02) [n = 2]	-3.11 (-3.27; -2.94) [n = 2]	NA	NA	-3.79 [n = 1]	-3.72 (-4.25; -3.20) [n = 2]	-0.04 (-0.26; 0.23) [n = 5]
Mean change from baseline* to day 7 in HCV RNA (range), log_{10} IU/mL	1a or 1b	-2.13 (-3.34; -0.91) [n = 4]	-3.31 (-4.44; -1.87) [n = 4]	-2.91 (-3.33; -2.02) [n = 4]	-2.58 (-4.13; -0.88) [n = 4]	-3.18 (-4.53; -2.56) [n = 4]	-3.03 (-5.17; -0.54) [n = 4]	0.00 (-0.10; 0.17) [n = 5]
	1a	-1.41 (-1.92; -0.91) [n = 2]	-2.54 (-3.22; -1.87) [n = 2]	-2.91 (-3.33; -2.02) [n = 4]	-2.58 (-4.13; -0.88) [n = 4]	-3.23 (-3.79; -2.56) [n = 3]	-1.38 (-2.22; -0.54)) [n = 2]	0.06 [n = 1]
	1b	-2.85 (-3.34; -2.36) [n = 2]	-4.08 (-4.44; -3.72) [n = 2]	NA	NA	-4.53 [n = 1]	-4.69 (-5.17; -4.21) [n = 2]	-0.01 (-0.10; 0.17) [n = 4]
Mean maximum decrease from baseline in HCV RNA (range), log_{10} IU/mL	1a or 1b	-2.81 (-3.74; -2.04) [n = 4]	-3.63 (-4.44; -2.76) [n = 4]	-3.31 (-3.35; -3.24) [n = 4]	-3.75 (-4.72; -2.91) [n = 4]	-3.84 (-4.53; -3.49) [n = 4]	-4.10 (-5.82; -1.75) [n = 4]	-1.32 (-4.00; 0.00) [n = 6]
	1a	-2.37 (-2.70; -2.04) [n = 2]	-2.99 (-3.22; -2.76) [n = 2]	-3.31 (-3.35; -3.24) [n = 4]	-3.75 (-4.72; -2.91) [n = 4]	-3.62 (-3.81; -3.49) [n = 3]	-2.55 (-3.36; -1.75) [n = 2]	-0.15 [n = 1]
	1b	-3.25 (-3.74; -2.76) [n = 2]	-4.27 (-4.44; -4.11) [n = 2]	NA	NA	-4.53 [n = 1]	-5.65 (-5.82; -5.48) [n = 2]	-1.56 (-4.00; 0.00) [n = 5]
Day of maximum decrease in log_{10} HCV RNA, median (range)	1a or 1b	3.0 (1; 11) [n = 4]	6.0 (2; 7) [n = 4]	2.5 (2; 7) [n = 4]	3.5 (2; 5) [n = 4]	6.0 (3; 15) [n = 4]	12.5 (4; 16) [n = 4]	12.0 (2; 17) [n = 6]
	1a	1.0 (1; 1) [n = 2]	4.5 (2; 7) [n = 2]	2.5 (2; 7) [n = 4]	3.5 (2; 5) [n = 4]	5.0 (3; 15) [n = 3]	9.0 (4; 14) [n = 2]	3.0 [n =1]
	1b	8.0	6.0	NA	NA	7.0	13.5	15.0

		(5; 11) [n = 2]	(5; 7) [n = 2]			[n = 1]	(11; 16) [n = 2]	(2; 17) [n = 5]

HCV, hepatitis C virus; NA, not applicable.

* HCV RNA was set to 25 or 10 IU/mL if observed value was less than lower limit of quantification (25 IU/mL) or lower limit of detection (10 IU/mL) respectively, when deriving changes from baseline.

Table 3. Pharmacokinetic Parameters

	Once Daily										Twice Daily	
	1 mg n = 4		10 mg n = 4		30 mg n = 4		60 mg n = 4		100 mg n = 4		30 mg n = 4	
Study day	1	14	1	14	1	14	1	14	1	14	1	14
Geometric mean C_{max}, ng/mL (CV)	15.73 (48)	10.43 (76)	159.67 (41)	154.20 (49)	483.37 (25)	555.88 (38)	1409.20 (13)	1726.38 (21)	1960.73 (21)	1853.93 (26)	563.57 (26)	831.79 (37)
Geometric mean $C_{min,}$ ng/mL (CV)	1.21 (105)	1.23 (95)	15.14 (49)	23.67 (53)	41.11 (34)	61.64 (42)	129.82 (25)	254.60 (42)	174.64 (21)	287.85 (37)	171.33 (53)	206.94 (74)
Median T_{max} (min-max), h	2.0 (1.0-3.0)	1.25 (1.0-2.0)	1.0 (1.0-2.0)	1.25 (1.0-1.5)	1.0 (0.5-1.0)	1.0 (1.0-1.5)	1.5 (1.5-3.0)	1.0 (1.0-2.0)	1.5 (1.0-1.5)	1.75 (1.0-2.0)	2.5 (1.5-3.0)	1.75 (1.0-2.0)
Geometric mean $AUC_{(TAU)}$, ng • h/mL (CV)	111.8 (54)	92.0 (80)	1113.6 (38)	1332.1 (46)	3582.6 (19)	4391.3 (27)	10691.5 (20)	15120.9 (35)	15136.1 (19)	17592.8 (15)	3307.2* (36)	5431.6* (35)
Mean $T_{1/2}$ (SD), h	NA	11.68 (2.21)	NA	14.31 (3.85)	NA	12.99 (2.04)	NA	12.81 (1.23)	NA	15.19 (3.41)	NA	13.04 (3.65)
Geometric mean CLT/F, mL/min (CV)	NA	181.12 (52)	NA	125.12 (52)	NA	113.86 (25)	NA	66.13 (29)	NA	94.74 (15)	NA	92.05 (35)
Geometric mean AI	NA	0.823	NA	1.196	NA	1.245	NA	1.414	NA	1.162	NA	1.642

$AUC_{(TAU)}$ (CV)		(29)		(16)		(20)		(17)		(25)		(16)
Geometric mean AI C_{max} (CV)	NA	0.663 (57)	NA	0.966 (26)	NA	1.150 (28)	NA	1.225 (10)	NA	0.946 (42)	NA	1.476 (32)

AI, accumulation index; AUC, area under the curve; CLT/F, apparent total body clearance; C_{max}, maximum observed plasma concentration; C_{min}, minimum observed plasma concentration; CV, coefficient of variation; NA, not applicable; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, time of maximum observed plasma concentration.

* $AUC_{(TAU)}$ = AUC over 12-hour dosing interval for 30 mg twice daily.

Table 4. Adverse Events Occurring in More Than One Patient

Adverse Event	Once Daily					Twice Daily	BMS-790052 Any Dose	Placebo
	1 mg n = 4	10 mg n = 4	30 mg n = 4	60 mg n = 4	100 mg n = 4	30 mg n = 4	n = 24	n = 6
Headache, n (%)	0	1 (25)	0	2 (50)	1 (25)	1 (25)	5 (21)	2 (33)
Back pain, n (%)	0	1 (25)	0	1 (25)	0	0	2 (8)	0
Diarrhea, n (%)	0	1 (25)	0	0	1 (25)	0	2 (8)	0
Fatigue, n (%)	1 (25)	1 (25)	0	0	0	0	2 (8)	0
Insomnia, n (%)	1 (25)	0	0	1 (25)	0	0	2 (8)	0
Abdominal pain, n (%)	0	0	0	0	1 (25)	0	1 (4)	1 (17)

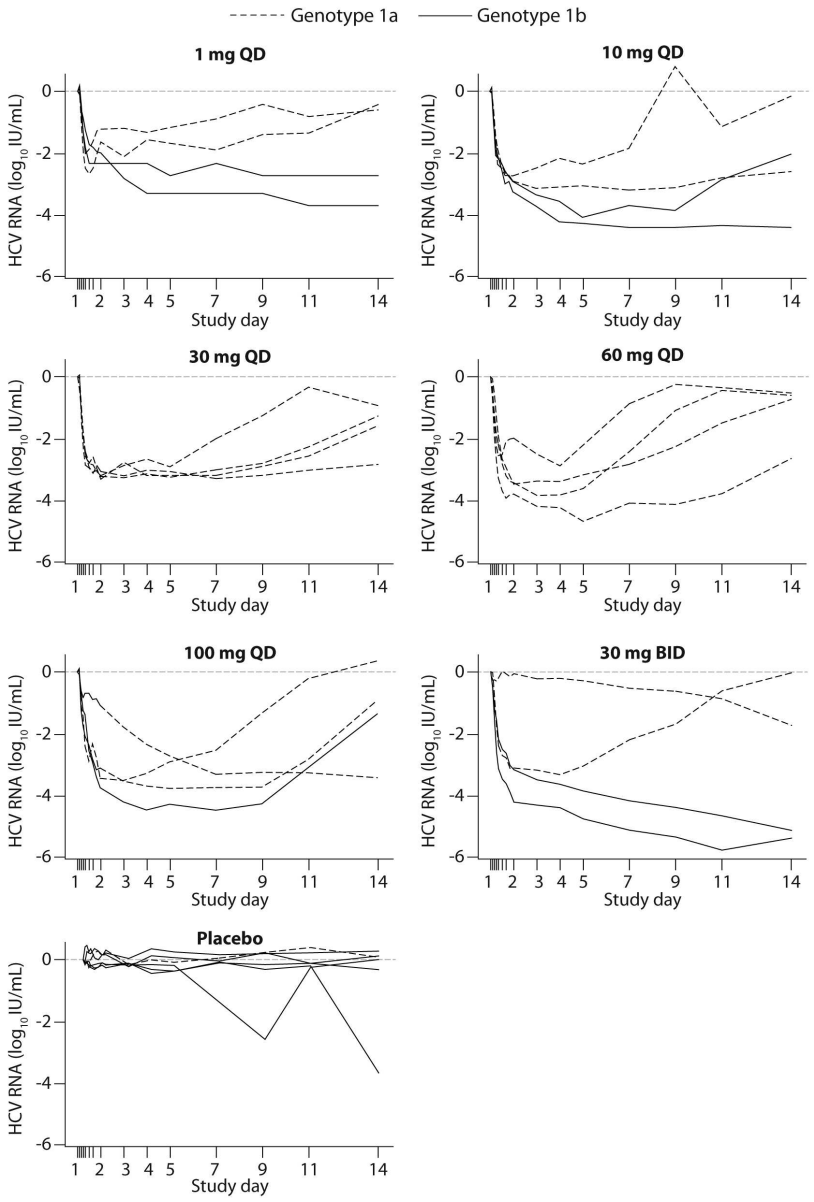

Figure 1
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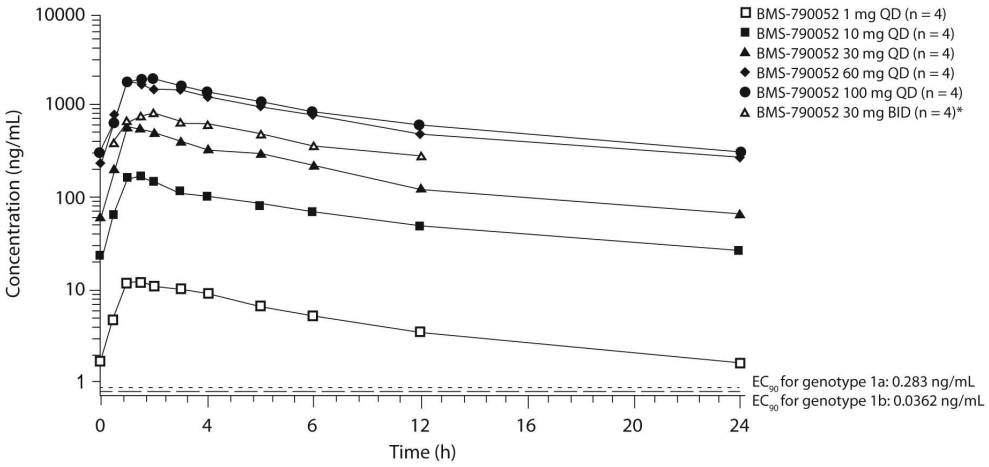

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CONSORT 2010 Flow Diagram