BMS-824393 Is a Potent Hepatitis C Virus NS5A Inhibitor With Substantial Antiviral Activity When Given as Monotherapy in Subjects With Chronic G1 HCV Infection

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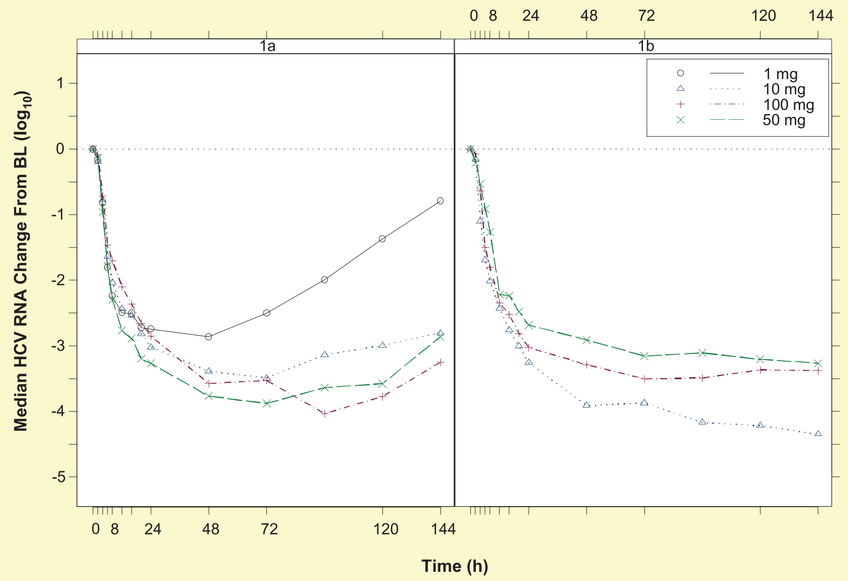
ABSTRACT

Background: NS5A plays a central role in hepatitis C virus (HCV) replication. BMS-824393 is a potent NS5A inhibitor with broad genotypic coverage, including picomolar in vitro potency against genotypes 1a and 1b. In a combined single and multiple ascending-dose study with healthy subjects, BMS-824393 was shown to be well-tolerated and had a pharmacokinetic profile supportive of once-daily dosing.

Methods: The objectives of this open-label, multiple ascending/descending-dose, monotherapy study were to evaluate the antiviral activity, safety, tolerability, and pharmacokinetics of BMS-824393 in treatment-naive subjects with genotype 1 chronic HCV. Men or women, 18 to 60 years of age with HCV RNA $\geq 10^5$ IU/mL with noncirrhotic compensated liver disease received either 1, 10, 50, or 100 mg of BMS-824393 for 3 days (10 subjects [7 G1a and 3 G1b] per dose group).

Results: Following oral administration, BMS-824393 was readily absorbed with largely dose-proportional exposures over the studied dose range. BMS-824393 exposures were comparable to those observed in healthy subjects. The mean terminal half-life of BMS-824393 ranged from 15 to 25 hours. The figure below shows the median decline in HCV RNA up to hour 144 for all doses after BMS-824393 administration at hours 0, 24, and 48. Median decline in G1a HCV RNA at hour 72 after 3 doses of 1, 10, 50, and 100 mg of BMS-824393 was 2.5 $\log_{10}$, 3.5 $\log_{10}$, 3.9 $\log_{10}$, and 3.5 $\log_{10}$, respectively. Median decline in G1b HCV RNA at hour 72 after 3 doses of 10, 50, and 100 mg of BMS-824393 was 3.9 $\log_{10}$, 3.2 $\log_{10}$, and 3.5 $\log_{10}$, respectively. All BMS-824393 multiple doses were well-tolerated. The only adverse events that occurred in more than 1 subject were headache and backache, both of which occurred in 2 subjects, were mild, and were deemed unrelated to BMS-824393 by the investigator.



Conclusions: BMS-824393 is BMS' second NS5A inhibitor that produces a rapid and robust decline in HCV RNA following multiple doses in patients chronically infected with HCV genotype 1a or 1b. BMS-824393 was well-tolerated following multiple doses of up to 100 mg and has a pharmacokinetic 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 planned to confirm the role of NS5A inhibition in future HCV therapy.

BACKGROUND AND OBJECTIVES

- NS5A is a multifunctional protein that plays a central role in replication of HCV, making it an attractive target for therapeutic intervention
- BMS-824393, a second NS5A inhibitor in development by BMS, is a potent and highly selective inhibitor of HCV NS5A, with in vitro picomolar potency against genotypes 1a and 1b
- BMS-824393 was well-tolerated in single and multiple doses in healthy subjects
- BMS-824393 has demonstrated a pharmacokinetic profile supportive of once-daily dosing
- **The objectives of the current study were to evaluate the antiviral activity, pharmacokinetics, safety, and tolerability of BMS- 824393 in subjects chronically infected with HCV genotype 1**

METHODS

- Study Design
  - Open-label, multiple-dose monotherapy study
  - Ten subjects in each dose group were to receive either 1,10, 50, or 100 mg of BMS-824393 for 3 days
  - Between 5 and 7 subjects in each dose group were to have genotype subtype 1a
- 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
- 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 Abbott RealTime HCV RNA Test, LOD = 12 IU/mL
- Pharmacokinetic parameters were derived from the plasma concentration vs time data
  - BMS-824393 in human plasma was assayed using a validated LC-MS/MS method during the period of known analyte stabilities
  - Plasma concentration vs time data were analyzed by noncompartmental methods using the Kinetica® program

Aspartate Aminotransferase-to-Platelet Ratio Index; LOD = limit of detection; LC-MS/MS = liquid chromatography-tandem mass spectroscope.

- 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 multiple-dose pharmacokinetics of BMS-824393 was described by summary statistics for the pharmacokinetic parameters by treatment and study day

RESULTS

Table 1. Demographics and Baseline Characteristics

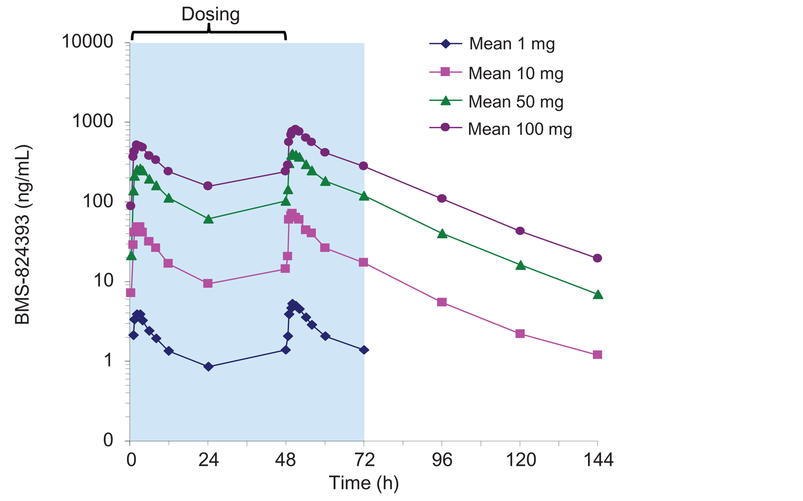
	1 mg (n=7)	10 mg (n=10)	50 mg (n=10)	100 mg (n=10)	Total (N=37)
Male, n (%)	4 (57)	6 (60)	8 (80)	8 (80)	26 (70)
Age (y), mean (range)	42 (25-54)	44 (24-59)	51 (34-58)	49 (28-59)	47 (24-59)
Race: white, n (%)	6 (86)	9 (90)	8 (80)	7 (70)	30 (81)
BMI (kg/m^2), mean (range)	27 (24-31)	27 (23-33)	26 (21-33)	26 (22-29)	27 (21-33)
HCV treatment naive, n (%)	7 (100)	10 (100)	10 (100)	10 (100)	37 (100)
HCV RNA at screening (IU/mL x 10^5), mean (range)	46.3 (6.01-72.4)	6.25 (2.28-16.6)	19.8 (1.09-62.2)	49.4 (4.00-189.0)	29.2 (1.09-189.0)
HCV genotype subtype 1a, n(%)	7 (100)	7 (70)	7 (70)	7 (70)	28 (76)

Baseline demographic characteristics were generally comparable across dose groups.
Dosing at 1 mg was stopped after 7 subjects due to observed inferior antiviral effect.

RESULTS (cont'd)

- Safety
  - All doses were generally well-tolerated
  - No BMS-824393–related deaths, serious adverse events, or discontinuations due to adverse events
  - No clinically relevant effect on ECGs, laboratory tests, vital signs, or physical examinations
  - There were 17 adverse events in 11 of 37 subjects (30%)
    - The majority of adverse events were mild
    - Only headache (2 of 37, 5%), atypical chest pain (2 of 37, 5%) and back pain (2 of 37, 5%) occurred in more than 1 subject
      - One of the back pain and both of the atypical chest pain events occurred more than 60 days after the last dose of BMS-824393 during the preplanned, prolonged follow-up period
- Pharmacokinetics
  - Following oral administration, BMS-824393 was readily absorbed
  - The mean terminal half-life ranged from 15 to 25 hours
  - BMS-824393 produced exposures comparable to those observed in a previous study in healthy volunteers (AI451001)

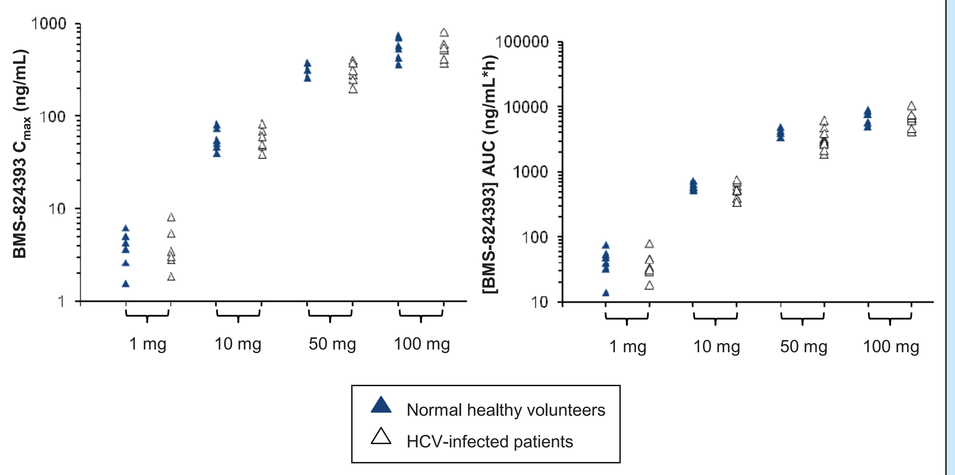
Figure 1. Mean Plasma Concentration-Time Profiles of BMS-824393 After 3 Days QD Oral Administration



Mean plasma concentration-time profiles of BMS-824393 after multiple oral administration of 1, 10, 50, and 100 mg BMS-824393 (QD for 3 days) in HCV-infected patients (lower limit of quantitation = 0.5 ng/mL).

Presented data are based on an unlocked database.

Figure 2. Scatterplots of BMS-824393 C_{max} and $AUC_{(TAU)}$ vs Dose in Normal Healthy Volunteers and HCV-Infected Patients



Comparison of BMS-824393 day 1 C_{max} values between normal healthy volunteers and HCV-infected patients from the multiple-dose studies (previous study AI451001 and current study AI451002, respectively).

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

RESULTS (cont'd)

Table 2. Summary of Day 3 Pharmacokinetics of BMS-824393 in HCV Patients After 3 Days of QD Oral Administration

Dose	1 mg	10 mg	50 mg	100 mg
C_{max} (ng/mL), geometric mean (CV %)	5.0 (51)	71 (34)	410 (22)	830 (32)
$AUC_{(TAU)}$ (ng/mL*h), geometric mean (CV %)	56 (50)	760 (37)	5040 (27)	10800 (30)
C24 (ng/mL), geometric mean (CV %)	1.3 (50)	15 (51)	108 (49)	260 (42)
T_{max} (h), median (min, max)	2 (1, 4)	2 (1.5, 4)	2 (1, 4)	2.5 (1.5, 4)
Half-life (h), mean (SD)	17 (5.5)	17 (2.3)	17 (2.3)	18 (2.3)

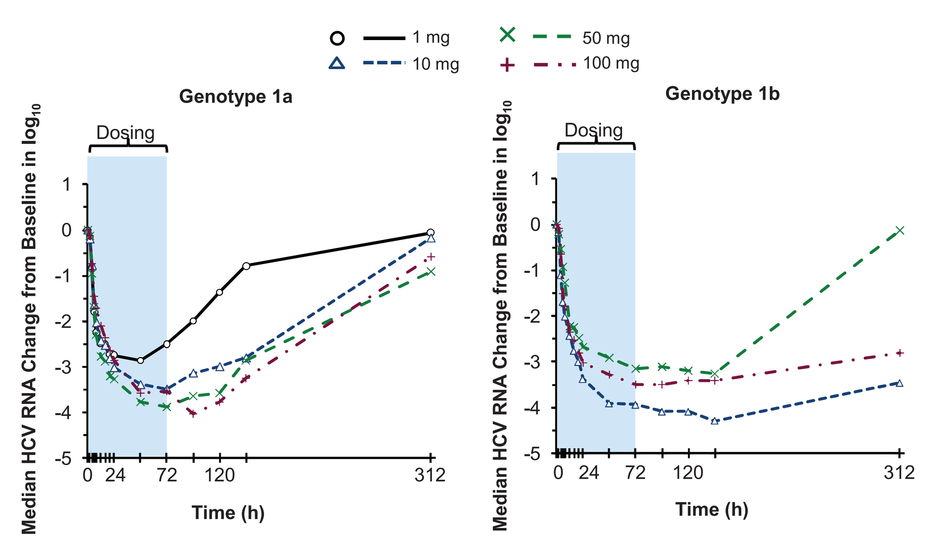
T_{max} = time to maximum concentration; SD = standard deviation.

Table 3. Median Decline in HCV RNA ($\log_{10}$) at Hour 72 After 3 Days of QD Oral Administration of BMS-824393

Genotype (n)	QD Dose Range (mg)			
	1	10	50	100
1a (7)	2.5	3.5	3.9	3.5
1b (3)	Not dosed	3.9	3.2	3.5

Data presented are based on an unlocked dataset.

Figure 3. Median Decline in HCV RNA



CONCLUSIONS

- BMS-824393, like BMS-790052, produces a rapid and robust decline in HCV RNA following 3 days of QD oral dosing in subjects chronically infected with either HCV genotype 1a or genotype 1b
- BMS-824393 is generally well-tolerated over 3 days of multiple doses of up to 100 mg
- The pharmacokinetic profile of BMS-824393 supports once-daily dosing
- These results provide further confirmation of the value of inhibiting NS5A-mediated HCV replication in the treatment of HCV. Additional studies are under way to further define the role of NS5A inhibition with BMS-824393 in the treatment of HCV infection

DISCLOSURES

- Nettles RE, Wang X, Quadri S, Wu Y, Gao M, Belema M, Persson A, and Grasela DM are employees of Bristol-Myers Squibb
- Lawitz EJ: *Grant/research support*: Abbott Laboratories, Achillion Pharmaceuticals, Inc., Anadys Pharmaceuticals, Inc., Bristol-Myers Squibb, Gilead Sciences, Inc., GlaxoSmithKline, GlobeImmune, Inc., Idenix Pharmaceuticals, Idera Pharmaceuticals Inc., Inhibitex, Inc., Medarex Inc., Medtronic, Inc., Merck & Co., Inc., Novartis AG, Pharmasset, Inc., Presidio Pharmaceuticals, Inc., Roche, Schering-Plough, ViroChem Pharma, Inc., and ZymoGenetics Inc.
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