Coadministration of BMS-790052 and BMS-650032 Does Not Result in a Clinically Meaningful Pharmacokinetic Interaction in Healthy Subjects

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ABSTRACT

Background: NS5A plays a central role in viral replication of hepatitis C virus (HCV). BMS-790052 is a first-in-class and potent NS5A Inhibitor with broad genotypic coverage. BMS-650032 is a potent HCV NS3 inhibitor with in vitro activity against genotypes 1a and 1b. Proof-of-concept multiple-dose studies in HCV subjects for each compound demonstrated a robust decline in HCV RNA when administered as monotherapy. Combinations of 2 or more direct-acting antiviral (DAA) agents are expected to be part of future HCV therapy; therefore, assessment of a potential drug-drug interaction with these 2 compounds together is warranted prior to commencement of clinical trials in HCV patients.

Methods: The objective of this open-label, randomized, multiple-dose study was to assess the pharmacokinetics (PK), safety, and tolerability of BMS-790052 and BMS-650032 when coadministered in healthy subjects for 14 days. Subjects received either 60 mg BMS-790052 QD or 600 mg BMS-650032 Q12h for 7 days during a lead-in period, followed by coadministration of 30 mg BMS-790052 QD and 200 mg BMS-650032 Q12h for 14 days. Plasma concentrations were obtained via liquid chromatography-tandem mass spectroscopy. Geometric mean ratios (GMR) and 90% confidence intervals (CI) for BMS-790052 and BMS-650032 PK were estimated by general linear mixed effects models.

Results: BMS-790052 and BMS-650032 exposures following respective doses of 30 mg QD and 200 mg Q12h administered together were comparable to historical data for similar doses of each compound administered alone. The GMR (90% CI) for BMS-790052 and BMS-650032 $AUC_{(TAU)}$ were 1.156 (0.895,1.491) and 1.025 (0.734,1.433), respectively. Following dose normalization to 60 mg, BMS-790052 exposure ($AUC_{(TAU)}$) after coadministration of 30 mg QD with BMS-650032 200 mg Q12h for 14 days was similar to exposure observed following 7 days of BMS-790052 60 mg QD in the lead-in period, with a GMR (90% CI) of 1.202 (1.113,1.298). Following dose normalization to 600 mg Q12h, BMS-650032 exposure ($AUC_{(TAU)}$) after coadministration of 200 mg Q12h with BMS-790052 30 mg QD was similar to exposure observed in the lead-in period, with a GMR (90% CI) of 0.868 (0.726,1.038).

Conclusions: Coadministration of BMS-790052 and BMS-650032 in healthy subjects did not result in a clinically meaningful PK interaction; a clinically meaningful PK interaction is not anticipated when BMS-790052 and BMS-650032 are coadministered in HCV patients. Based on the results of this study, a clinical trial with BMS-790052 and BMS-650032, both with and without pegylated interferon/ribavirin, has commenced to assess the effect of dual NS5A plus NS3 inhibition in HCV therapy.

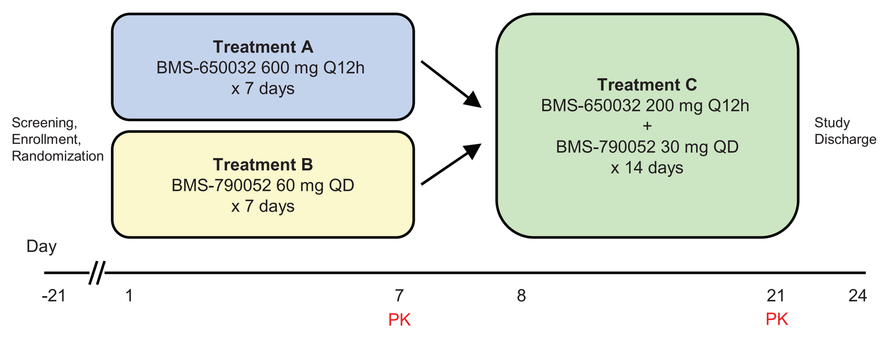
BACKGROUND AND OBJECTIVES

- Studies of potential drug-drug interaction between DAA agents are increasingly important, as future HCV therapy is expected to include DAA combination therapy
- BMS-790052, a first-in-class, potent HCV NS5A inhibitor, and BMS-650032, a highly active HCV NS3 inhibitor, have both shown significant antiviral activity as monotherapy or when combined with pegylated interferon/ribavirin in subjects with chronic HCV infection and are excellent candidates for use together in combination therapy
- The primary objective of this study was to assess the PK of BMS-790052 and BMS-650032 when coadministered, relative to administration of each alone
- The secondary objective was to assess the safety and tolerability of BMS-790052 and BMS-650032 when coadministered and administered alone

Nonclinical Background and Study Design Rationale

- One-month oral toxicity combination studies with BMS-790052 and BMS-650032 in rats and monkeys did not identify any clinical findings or unique toxicity; the toxicologic profile was similar to the findings observed in the single toxicity studies with no overlapping toxicity
- Toxicokinetic evaluation in monkeys demonstrated a ~2-fold increase in the exposure of BMS-790052 when coadministered with BMS-650032
- Toxicokinetic evaluation in monkeys demonstrated a ~2- to 15-fold increase in the exposure of BMS-650032 when coadministered with BMS-790052
- Based on these animal findings, which suggest a potential drug-drug interaction in vivo, the current study was designed with a lead-in phase at higher doses and a combination phase at lower doses

Study Design

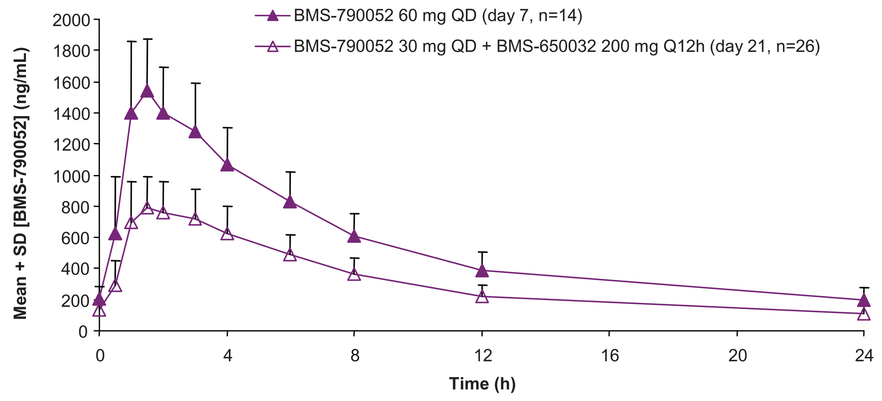


METHODS

- A total of 28 healthy male and female subjects were randomly assigned to initial treatment with BMS-790052 (n=14) or BMS-650032 (n=14)
- Morning doses of BMS-790052 and BMS-650032 were administered following an overnight fast; evening doses of BMS-650032 were administered after at least a 2-hour fast
- PK parameters for BMS-650032 and BMS-790052 were derived from plasma concentration vs time data by noncompartmental analysis using the program Kinetica
- Safety assessments were based on reported adverse events and the results of vital sign measurements, physical examinations, ECGs, and clinical laboratory tests

RESULTS

BMS-790052 Plasma Profiles



BMS-790052 Statistical Analysis

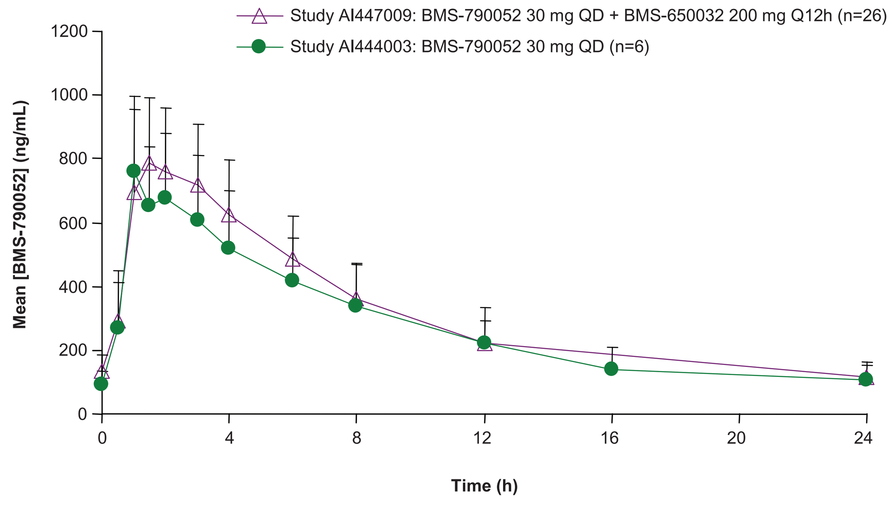
Dose-normalized statistical analysis: BMS-790052 30 mg QD coadministered with BMS-650032 200 mg Q12h (TRT C) relative to BMS-790052 60 mg QD (TRT B)

PK Parameter	TRT B BMS-790052 60 mg QD Geo Mean (CV)	TRT C BMS-790052 30 mg QD + BMS-650032 200 mg Q12h Geo Mean (CV) Normalized to 60-mg Dose	GMR (90% CI)
$AUC_{(TAU)}$	12074 (25)	14515 (28)	1.202 (1.113, 1.298)
C_{max}	1496 (24)	1599 (26)	1.069 (0.971, 1.176)
C_{min}	163 (39)	217 (35)	1.330 (1.221, 1.449)

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

- When BMS-790052 30 mg QD was normalized to a dose of 60 mg QD, BMS-790052 $AUC_{(TAU)}$, C_{max}, and C_{min} were similar to those observed with 60 mg QD alone

BMS-790052 Current Study (Study AI447009) vs Historical Data From Healthy Volunteers (Study AI444003)



RESULTS (cont'd)

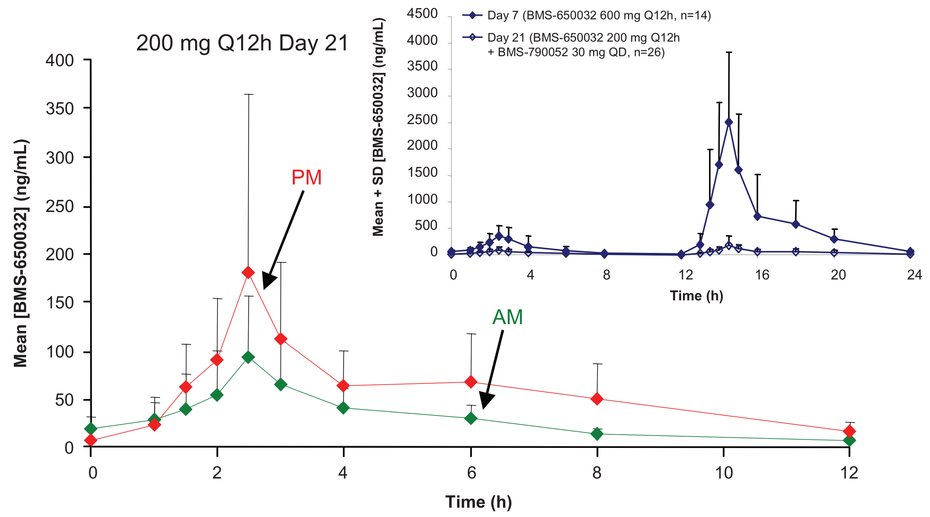
BMS-790052 Current Study (Study AI447009) vs Historical Data (Study AI444003)

Statistical analysis: BMS-790052 30 mg QD coadministered with BMS-650032 200 mg Q12h (TRT C) relative to BMS-790052 30 mg QD historical data

PK Parameter	Study AI447009 (BMS-790052 + BMS-650032)	Study AI444003 (BMS-790052 Alone)	GMR (90% CI)
$AUC_{(TAU)}$	7251 (28)	6275 (39)	1.156 (0.895, 1.491)
C_{max}	799 (26)	734 (30)	1.089 (0.864, 1.374)
C_{min}	108 (35)	92 (54)	1.172 (0.848, 1.620)

- Exposures of BMS-790052 30 mg QD when coadministered with BMS-650032 were comparable to historical data for BMS-790052 30 mg QD administered alone

BMS-650032 Plasma Profiles

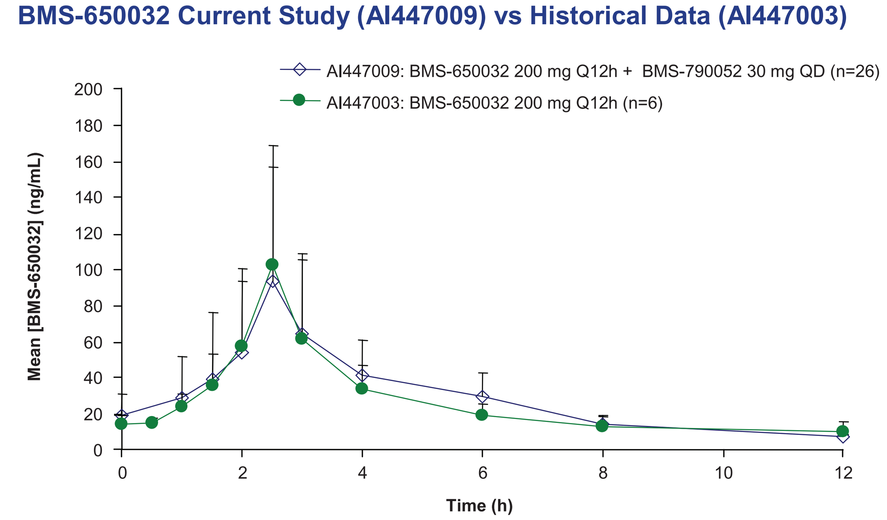


BMS-650032 Statistical Analysis Dose-Normalized

PK Parameter	TRT A BMS-650032 600 mg Q12h Geo Mean (CV)	TRT C BMS-790052 30 mg QD + BMS-650032 200 mg Q12h Geo Mean (CV) Normalized to 600-mg Dose	GMR (90% CI)
$AUC_{(TAU)}$ – AM	1063 (58)	923 (44)	0.868 (0.726, 1.038)
C_{max} – AM	420 (48)	247 (64)	0.581 (0.446, 0.758)
C_{min} – AM	10.9 (55)	19.3 (28)	1.756 (1.420, 2.171)
$AUC_{(TAU)}$ – PM	6104 (49)	1800 (43)	0.29 (0.23, 0.39)
C_{max} – PM	2257 (51)	428 (93)	0.19 (0.12, 0.29)
C_{min} – PM	55.7 (50)	45.5 (50)	0.82 (0.63, 1.07)

- When the 200 mg Q12h exposures were normalized to a dose of 600 mg Q12h, BMS-650032 $AUC_{(TAU)}$-AM was similar to 600 mg Q12h alone; $AUC_{(TAU)}$-PM was ~70% lower, C_{max}-AM and PM were both lower, C_{min}-AM was higher, and C_{min}-PM was comparable to 600 mg Q12h administered alone

BMS-650032 Current Study (AI447009) vs Historical Data (AI447003)



RESULTS (cont'd)

BMS-650032 Current Study (AI447009) vs Historical Data (AI447003)

PK Parameter	BMS-650032 200 mg Q12h: AI447009 (BMS-790052 + BMS-650032) Geo Mean (CV)	BMS-650032 200 mg Q12h: AI447003 (BMS-790052 Alone) Geo Mean (CV)	GMR (90% CI)
$AUC_{(TAU)}$ – AM	308 (44)	300 (39)	1.025 (0.734, 1.433)
C_{max} – AM	82 (64)	88 (62)	0.935 (0.573, 1.526)
C_{12}	6.44 (28)	8.44 (60)	0.763 (0.579, 1.006)

- Exposures of BMS-650032 200 mg Q12h when coadministered with BMS-790052 30 mg were comparable to historical data for BMS-650032 200 mg Q12h administered alone

Safety

- Administration of 7 days of treatment with BMS-650032 600 mg Q12h (Treatment A) or BMS-790052 60 mg QD (Treatment B), followed by 14 days of combination treatment with BMS-650032 200 mg Q12h + BMS-790052 30 mg QD (Treatment C), was well-tolerated by the healthy subjects in this study
- There were no deaths
- One (1) serious adverse event was reported. One (1) subject discontinued the study as per the protocol stopping rules due to an increase in AST; the adverse event (AE) was accompanied by an AE of increase in blood creatine kinase, which was considered serious. These laboratory changes were not associated with myalgia or any musculoskeletal AEs, and were consistent with exercise-related changes. The AE resolved following discontinuation of study drug
- Most AEs were mild in intensity, and no AE was assessed as severe or very severe in intensity
- Gastrointestinal AEs were the most common treatment-related AEs with all treatments, and all related AEs were mild in intensity
- No safety issues emerged from the evaluation of the clinical laboratory, vital sign, ECG, or physical examination data

AST = aspartate aminotransferase.

DISCUSSION

- The PK interaction observed in the nonclinical species was not observed in normal healthy subjects
- Exposures to BMS-650032 appear greater after the PM dose relative to the AM dose. This increase in exposure appears to be dose dependent
  - $AUC_{(TAU)}$ ↑ ~6-fold after PM dose of 600 mg Q12h
  - $AUC_{(TAU)}$ ↑ ~2-fold after PM dose of 200 mg Q12h
  - In a previous phase 1 study, no diurnal variation observed with 100 mg Q12h
- Diurnal variation observed was likely due to food effect
  - PM dose administered 2 hours after a standard meal
  - Data from a food-effect study suggest a high-fat meal increases AUC of BMS-650032 600-mg tablet ~12-fold
- The multiple-ascending-dose and proof-of-concept studies for BMS-650032 were dosed in the same manner; therefore, the increased PM exposures have been factored into the dose selection and safety evaluation

CONCLUSIONS

- Coadministration of BMS-790052 30 mg QD and BMS-650032 200 mg Q12h for 14 days did not result in a clinically meaningful PK interaction
- Coadministration of BMS-790052 30 mg QD and BMS-650032 200 mg Q12h for 14 days was well-tolerated in this study
- A dose-dependent AM/PM difference was observed for BMS-650032 exposure, which may be due to the temporal relationship of food and BMS-650032 administration

DISCLOSURES

- Bifano M, Sevinsky H, Bedford B, Coumbis J, Eley T, Huang SP, Grasela DM, and Bertz R are employees of Bristol-Myers Squibb
- Medlock M: No disclosures to report

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