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). BMS-790052 is a first-in-class and potent NS5A Inhibitor with broad genotypic coverage. Treatment A (BMS-790052 30 mg QD) demonstrated a robust decline in HCV RNA when administered as monotherapy. 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

One-month oral toxicity combination studies with BMS-790052 and BMS-650032 in rats and monkeys did not identify any oral findings that could predict a potential drug-drug interaction in support of the current study. Toxicokinetic evaluation in monkeys demonstrated a ~2-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 pharmacokinetic phase at higher doses and a combination phase at lower doses.

Stud Design

RESULTS

PK Parameter

T140 (subject A)

1080 ± 250 mg Q12h

90% CI

GMR (90% CI)

AUC0-t/ Cmax (ng/mL)

1209 ± 250 mg Q12h

1209 ± 250 mg Q12h

1.202 (1.113, 1.298)

Cmin (ng/mL)

1080 ± 250 mg Q12h

1080 ± 250 mg Q12h

0.895 (0.726, 1.038)

Cmax (ng/mL)

1209 ± 250 mg Q12h

1209 ± 250 mg Q12h

1.072 (1.044, 1.099)

GMR: BMS-790052 30 mg + BMS-650032 200 mg Q12h vs. BMS-790052 30 mg QD

BMS-790052 Statistical Analysis (cont’d)

Dose-normalized statistical analysis

Dose-optimized cohort analysis

Study AI447009: BMS-650032 200 mg Q12h + BMS-790052 30 mg QD (n=26)

Safety

Adverse events were based on reported adverse events and the results of vital sign and laboratory evaluations. Safety assessments were based on reported adverse events and the results of vital sign measurements, physical examinations, ECGs, and clinical laboratory tests.

DISCUSSION

The PK interaction observed in the nonclinical species was not observed in normal healthy human volunteers.

Do not safety issues emerged from the evaluation of the clinical laboratory, vital sign, ECG, or physiological examination data.

BMS-650032 200 mg Q12h

BMS-790052 30 mg QD + BMS-650032 200 mg Q12h (day 21, n=26)

Cmax (ng/mL)

Cmin (ng/mL)

AUC0-120h (ng*h/mL)

Roughly similar, no significant AEs were noted during the lead-in period. 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. PK parameters were derived from blood plasma concentration–time data by noncompartmental analysis using the program Kinetica. The objective of this open-label, randomized, multiple-dose study was to assess the safety and tolerability of BMS-790052 and BMS-650032 when coadministered and administered alone.

BMS-790052 Statistical Analysis

BMS-790052 Plasma Profiles

BMS-650032 Plasma Profiles

Dosage-optimized statistical analysis

BMS-790052 200 mg Q12h + BMS-650032 200 mg Q12h (T2) relative to BMS-790052 200 mg Q12h

BMS-650032 200 mg Q12h

BMS-790052 30 mg QD + BMS-650032 200 mg Q12h (day 21, n=26)

BMS-790052 30 mg QD + BMS-650032 200 mg Q12h (day 21, n=26)

BMS-650032 Statistical Analysis (cont’d)

Dose-normalized statistical analysis

Dose-optimized cohort analysis

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-expansion phase will be observed for BMS-650032 exposure, which may be due to the temporal relationship of food and BMS-650032 administration.

DISCLOSURES


Wilford Hall-Methodist Research.

AASLD, The Liver Meeting in Boston, MA, October 29 – November 2, 2010