A1-1995

Safety and Pharmacokinetics of BMS-650032 Following Multiple Ascending Doses for 14 Days in Healthy Subjects

P.O. Box 5400
Princeton, NJ 08543-5400
609-818-6510 (work)
609-818-3220 (fax)
timothy.eley@bms.com

T. ELEY[1], C. PASQUINELLI[1], P. WENDELBURG[1], C. VILLEGAS[1] , B. HE[1], S. LIAO[1], H. JIANG[1], T. MARBURY[2], R. BERTZ[1], D. GRASELA[1]

[1]Bristol-Myers Squibb, Princeton, NJ, [2]Orlando Clinical Res. Ctr., Orlando, FL

INTRODUCTION

- The HCV NS3/4A protease is an essential enzyme for viral replication and has been validated as a target for anti-HCV therapy in clinical trials
- BMS-650032 is a potent and selective HCV NS3 protease inhibitor with *in vitro* picomolar potency vs. NS3/4A protease complexes in genotype 1a/1b
  - Replicon EC50: Genotype 1a (4 nM); Genotype 1b (1 nM)
  - *In vitro*: synergistic with IFN- α and other HCV inhibitors
- BMS-650032 was generally well tolerated at single doses up to 1200 mg in healthy subjects and 600 mg in HCV-infected subjects
- Antiviral activity observed following three days of dosing in HCV-infected subjects suggests that doses of 200-600 mg twice daily may be therapeutic[1]

OBJECTIVES

Primary Objective:

- To assess the safety and tolerability of multiple doses of BMS-650032 in the range of 10 to 600 mg twice daily in healthy subjects

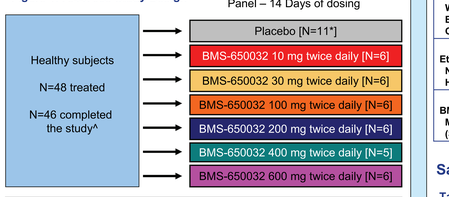
Secondary Objectives:

- To assess the effect of multiple oral doses of BMS-650032 on electrocardiographic (ECG) parameters including heart rate, PR, QRS, QT, QTc intervals
- To assess the pharmacokinetics of BMS-650032 following single and multiple oral doses, including accumulation index, time to steady-state, and diurnal variation in healthy subjects

METHODS

- Study AI447003 was a phase 1, double-blind, placebo-controlled, sequential, multiple ascending dose study [Figure 1]. Eight (8) healthy subjects were randomized within each of the 6 dose panels (6 active:2 placebo each dose)
- Clinic Furlough Day 17; Discharge Day 21

Figure 1: AI447003 Study Design



Key inclusion criteria
• Healthy women not of child-bearing potential and men
• 18–49 years of age
• BMI 18–32 kg/m^2

^Two subjects did not complete the study – one withdrew consent and one met an exclusion criterion revealed after dosing;

*Subjects completing the study per dose panel

METHODS (cont'd)

Study Assessments

- **Safety and Tolerability**
  - Physical examinations, vital signs, ECGs, and clinical labs were assessed periodically. Subjects were monitored for adverse events (AEs) throughout the study
  - AEs were summarized by preferred term, system organ class and dose
  - The effects of BMS-650032 on liver function tests (LFTs) were explored graphically and by summary statistics
- **Pharmacokinetics (PK)**
  - Blood samples for PK collected after AM dose on Day 1 and Day 14 and PM dose on Day 13 for 100 mg panel (PM data not shown)
  - BMS-650032 concentrations in plasma were obtained via a validated LC-MS/MS assay with LLOQ of 0.05 ng/mL and mean deviation from nominal concentration of ±8%
  - PK parameters were calculated by non-compartmental methods using Kinetica
  - PK parameters summarized by dose; time to steady state assessed graphically; dose-exposure relationship assessed via power and spline models

RESULTS

Demographics

Table 1. Demographics and Physical Measurements, Treated Subjects

Characteristics	Placebo (N=12)	BMS- 650032 Dose Twice Daily (N=6)					
		10 mg	50 mg	100 mg	200 mg	400 mg	600 mg
Age, years							
Mean (SD)	34.5 (8.95)	35.3 (3.20)	32.0 (6.51)	32.2 (10.82)	32.8 (12.02)	36.7 (7.97)	40.3 (4.46)
Gender, n (%)							
Male	11 (91.7)	4 (66.7)	4 (66.7)	5 (83.3)	5 (83.3)	4 (66.7)	4 (66.7)
Female	1 (8.3)	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)
Race, n (%)							
White	5 (41.7)	4 (66.7)	5 (83.3)	5 (83.3)	5 (83.3)	3 (50.0)	6 (100)
Black	7 (58.3)	1 (16.7)	1 (16.7)	0	1 (16.7)	3 (50.0)	0
Other	0	1 (16.7)	0	1 (16.7)	0	0	0
Ethnicity, n (%)							
Non-Hispanic	5 (41.7)	2 (33.3)	2 (33.3)	4 (66.7)	2 (33.3)	2 (33.3)	3 (50.0)
Hispanic	7 (58.3)	4 (66.7)	4 (66.7)	2 (33.3)	4 (66.7)	4 (66.7)	3 (50.0)
BMI kg/m^2							
Mean (SD)	27.85 (2.70)	28.30 (2.37)	28.02 (3.28)	24.67 (1.67)	27.15 (3.83)	24.92 (4.37)	24.80 (2.03)

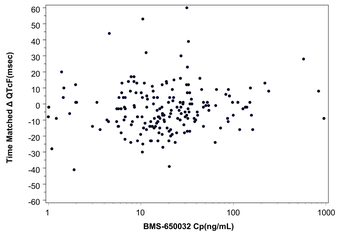
Safety

Table 2. Adverse Events Experienced by ≥2 subjects in any dose panel

Adverse Event	Placebo N=12	BMS- 650032 Dose Twice Daily (N=6)					
		10 mg	50 mg	100 mg	200 mg	400 mg	600 mg
Headache, n (%)	3 (25)	2 (33.3)	2 (33.3)	2 (33.3)	0	2 (33.3)	1 (16.7)
Increased urinary frequency, n (%)	0	4 (66.7)	1 (16.7)	0	2 (33.3)	0	0
Dizziness, n (%)	0	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (16.7)	1 (16.7)

RESULTS (cont'd)

Figure 2. Time Matched ΔQTcF Intervals versus BMS-650032 Plasma Concentrations for Day 14



No apparent association between concentration and ΔQTcF
8 subjects total (2 placebo) with max ΔQTcF 30–60 msec,
Maximum observed ΔQTcF = 60 msec at 200 mg twice daily
No subjects with max ΔQTcF >60 msec
No clinically-significant ECG effects were observed.

Figure 3. Mean Change from Baseline in AST versus Study Day

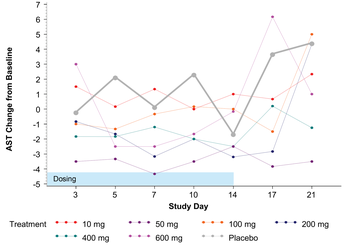
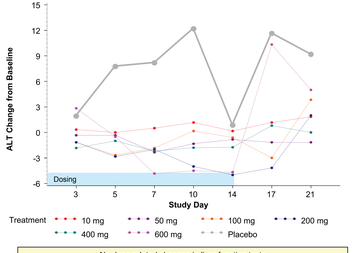


Figure 4. Mean Change from Baseline in ALT versus Study Day



No dose-related changes in liver function tests

Overall Safety Summary

- Administration of BMS-650032 for 14 days was generally well tolerated by healthy subjects at all doses
- There were no deaths, serious adverse events, or discontinuations due to AEs
- There were no dose-dependent trends in AEs or laboratory marked abnormalities
- Most AEs were mild to moderate in intensity; 1 AE was severe (toothache) and all AEs resolved prior to study completion
- One subject receiving placebo experienced elevations in AST and ALT, which were reported as AEs
- There was no clinically relevant change in vital signs or ECG parameters

Pharmacokinetics

Figure 5A: Mean Plasma Concentration-Time Profiles for BMS-650032 Following Administration of First Dose to Fasted Healthy Subjects (Day 1)

Figure 5B: Mean Plasma Concentration-Time Profiles for BMS-650032 Following Twice Daily Administration to Fasted Healthy Subjects (Day 14)

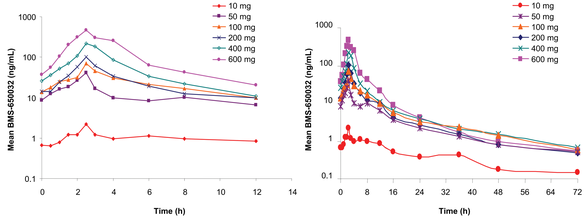


Table 3. Summary Statistics – Pharmacokinetic Parameters by dose

PK Parameters	BMS-650032 Dose Twice Daily											
	10 mg N=6		50 mg N=6		100 mg N=6		200 mg N=6		400 mg N=6	400 mg N=5	600 mg N=6	
Study Day	**Day 1**	**Day 14**	**Day 1**	**Day 14**	**Day 1**	**Day 14**	**Day 1**	**Day 14**	**Day 1**	**Day 14**	**Day 1**	**Day 14**
Cmax (ng/mL)– Geometric Mean (CV%)	0.4 (56)	2.0 (51)	11.8 (106)	38.6 (55)	12.7 (78)	59.7 (75)	33 (122)	88 (62)	97 (55)	228 (51)	211 (56)	489 (77)
AUCtau (ng*h/mL)– Geometric Mean (CV%)	2.3 (35)	9.4 (42)	28.5 (74)	108.5 (49)	50.5 (51)	258 (40)	97.7 (101)	300 (39)	378 (43)	596 (39)	628 (39)	1257 (57)
C12 (ng/mL)– Geometric Mean (CV%)	0.16 (57)	0.71 (71)	1.1 (67)	6.1 (44)	2.6 (47)	9.5 (25)	4.3 (50)	8.4 (60)	15.2 (48)	10.1 (42)	19.6 (89)	16.7 (76)
AI for AUC(TAU)– Geometric Mean (CV%)– (Min, Max)		4.1 (41) (2.6, 6.9)		3.8 (24) (2.7, 5.3)		5.1 (73) (2.3, 14.1)		3.1 (68) (0.8, 8.5)		1.8 (40) (1.4, 3.2)		2.0 (43) (0.6, 3.3)

Median Tmax all panels (Day 14): 2.5 h

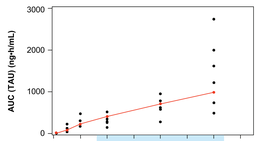
Mean T-HALF (Day 14) range: 17.4–23.4 h

Mean CLT/F (Day 14) range: 388–1060 L/h

There were no notable diurnal differences observed for Cmax and AUC(TAU) at 100 mg twice daily. C12 appeared higher in the morning (data not shown).

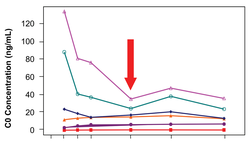
RESULTS (cont'd)

Figure 6: Scatter Plot and Fitted Regression Line (Spline) of BMS-650032 AUC(TAU) on Day 14 vs. Dose



Exposure to BMS-650032 increases disproportionately with increasing dose up to 200 mg twice daily and less dramatically at doses above 200 mg twice daily.

Figure 7: Geometric Mean Pre-dose AM troughs (C0) versus study day to assess steady state



Steady State achieved by Day 7 at all doses

DISCUSSION

- No signals for skin rash, pruritis, anemia, or dysgeusia as reported with other HCV NS3 protease inhibitors[2,3]
- Increased urinary frequency in 7 Subjects
  - Mild to moderate (all but one considered related)
  - Resolved spontaneously in 4 subjects while still on treatment and in 3 subjects at 1, 2 and 6 days after treatment cessation
  - Based on urinalysis and serum creatinine measurements, there was no evidence of altered kidney function
  - Not observed in the higher dose (400 and 600 mg) groups
  - Not observed to date in any other studies with BMS-650032
- BMS-650032 AUC(TAU) and Cmax increased more than dose-proportionally from 10 mg to 600 mg twice daily
  - Exposure increased with increasing dose and such increases appeared higher for doses <200 mg than for those ≥200 mg.
- Implication of metabolic auto-induction
  - Accumulation Index for AUC(TAU) ranged from 1.7 to 5.1 and appeared to be relatively lower at higher doses
  - C12 values on Day 14 similar to Day 1 or slightly lower at 400 mg and 600 mg twice daily
  - Pre-dose (AM) trough pattern at higher doses supports auto-induction at doses ≥200 mg twice daily
  - Despite auto-induction, steady state appears to be achieved by Day 7 at all doses
- Low plasma exposures and high oral clearance (CLT/F) suggest importance of preferential liver distribution for antiviral effect (animal L:P ranged from 40- to 359-fold)
  - High oral clearance with half-life of ~20 hours supports extensive tissue distribution
  - Once daily administration may be feasible with extensive liver distribution and is being investigated in Phase 2A at a 600 mg dose with Pegylated interferon and ribavirin

CONCLUSIONS

- Multiple oral doses of BMS-650032 in the range of 10 to 600 mg twice daily for 14 days were safe and well tolerated in healthy subjects.
- High oral clearance may be consistent with preferential hepatic distribution.
- Based on the favorable safety and tolerability profile shown in this trial and the antiviral activity presented elsewhere,[1] further development of BMS-650032 in combination with pegylated interferon/ribavirin or other direct acting antivirals is warranted.

REFERENCES

1. Pasquinelli C, Eley T, Villegas C, et al. Safety, Tolerability, Pharmacokinetics and Antiviral Activity following Single- and Multiple-Dose Administration of BMS-650032, a Novel HCV NS3 Inhibitor, in Subjects with Chronic Genotype 1 HCV Infection. AASLD 2009, Boston, MA.
2. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med.* 2009 Apr 30;360(18):1827-38.
3. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet.* 2010 Aug 6. [Epub ahead of print]

ACKNOWLEDGMENT

Anna Persson, Yaoshi Wu & Shu-Pang Huang for additional statistical support.