BMS-986094 (INX-08189) Plus Peginterferon Alfa-2a and Ribavirin Results in Treatment-Naïve HCV-Genotype 2/3 Patients Compared to Peginterferon Alfa-2a and Ribavirin: Week 12 Results

Bristol-Myers Squibb, Princeton, NJ

Background

- BMS-986094 (INX-08189)
  - phosphoramidate precursor of its active triphosphate
  - potent, pan-genotypic NS5B nucleotide inhibitor
- During 7 day dosing as monotherapy or combined with ribavirin (RBV), BMS-986094 was well-tolerated and exhibited dose-dependent antiviral activity in HCV genotype 1 patients without evidence of resistance[1]
- The following presentation includes the week 12 on treatment data for AI472-003, which evaluated BMS-986094 (doses ranging from 25 mg to 100 mg once daily) or placebo combined with pegylated interferon alfa (alfa) or ribavirin (RBV) for 12 weeks
  - BMS-986094 treated patients not achieving eRVR, and all placebo treated patients received an additional 12 weeks of alfa/RBV (24 weeks of therapy)

[1]Rodrigues-Torres *et al. AASLD* November 4-8, 2011, San Francisco, CA, Poster 354.

Methods

Objectives

- **Safety**
  - To evaluate the safety and tolerability of BMS-986094 given once daily in combination with peginterferon alfa-2a (alfa) and ribavirin (RBV) for 12 weeks in HCV infected genotype 2 and 3, treatment-naïve non-cirrhotic patients

- **Efficacy**
  - To assess the virologic (including rapid virologic response [RVR], extended rapid virologic response [eRVR], complete early virologic response [cEVR], SVR12, SVR24) response to BMS-986094 and placebo given once daily in combination with alfa/RBV for 12 weeks in chronically-infected genotype 2 and 3 HCV, treatment-naïve, non-cirrhotic patients
  - To assess whether the duration of alfa/RBV treatment can be reduced when dosed adjunctively with BMS-986094

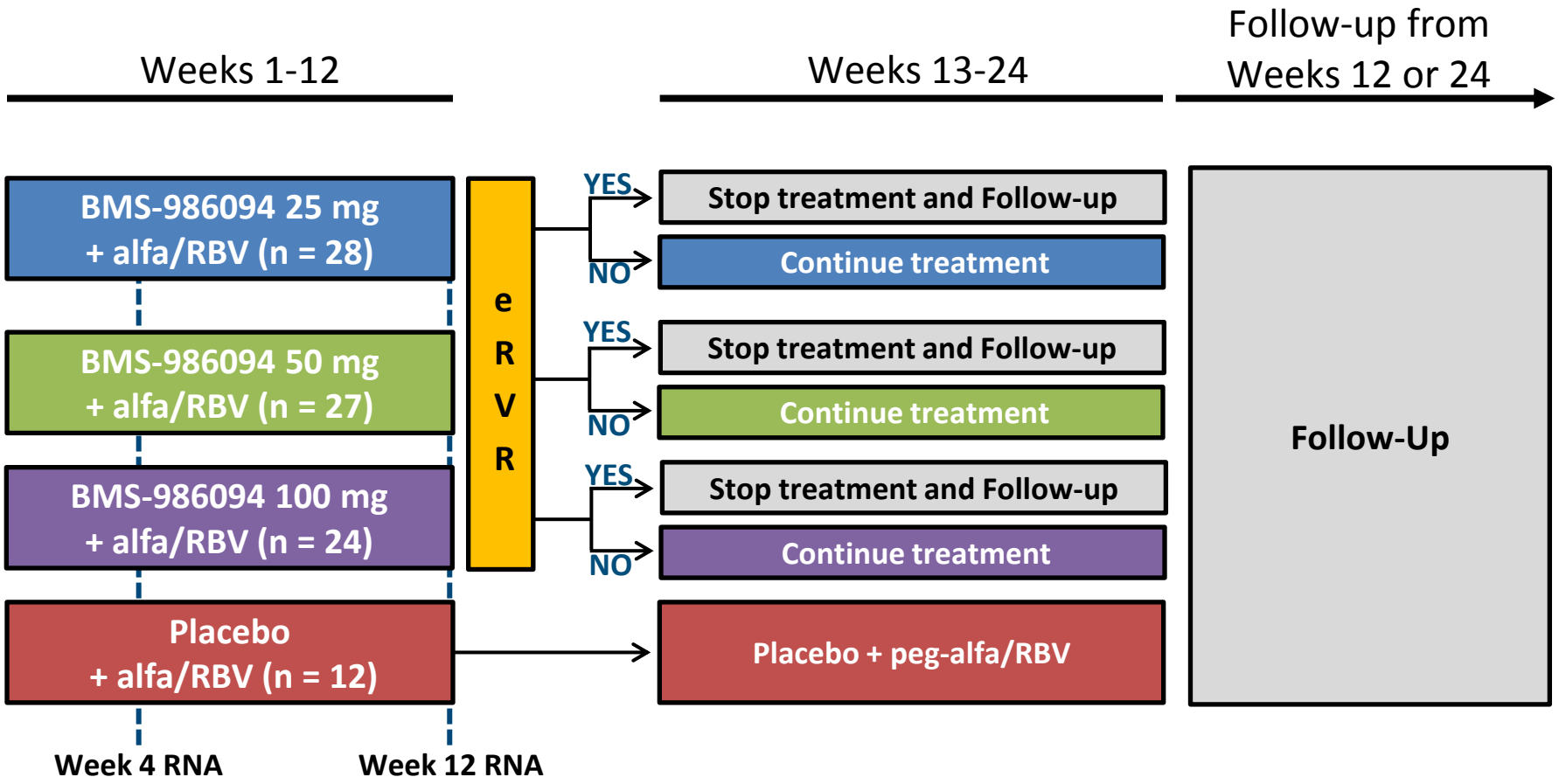
Methods (cont)

- A multi-center in US only, double-blind, placebo (PBO)-controlled, phase 2 study
- Patients
  - HCV genotype 2 or 3 infection
  - Treatment naïve
  - Non-cirrhotic patients
- Treatment
  - BMS-986094 25 mg, 50 mg, 100mg or PBO once daily plus alfa/RBV for 12 weeks
  - Stratified by
    - Genotype 2 or 3
    - IL28B genetic variation (CC versus any T allele)
    - HCV RNA level (>10,000,000 IU/mL versus lower)

Methods (cont)

- Molecular diagnostics
  - HCV RNA assessed by Roche Cobas TaqMan®: Lower limit of quantification (LLOQ) 25 IU/mL
  - HCV genotype determined by TRUGENE 5'NC
- Efficacy data through Week 12
  - **RVR**: rapid virologic response, undetectable HCV RNA at week 4
  - **cEVR:** complete early virologic response, undetectable HCV RNA at week 12
  - **eRVR**: extended rapid virologic response, undetectable HCV RNA at weeks 4 and 12
- Safety data
  - Adverse events (AE)
  - Serious adverse events (SAEs)
  - Discontinuations due to AEs
  - Clinical laboratory abnormalities
  - Electrocardiogram (ECG): over read by central cardiologist
  - Vital signs and physical exams
- External safety review committee (SRC)
  - All subjects completed Week 12 visit on 6May2012; Week 12 database lock on 21May2012
  - SRC reviewed Week 12 data on 11June2012
  - No changes in study conduct were recommended

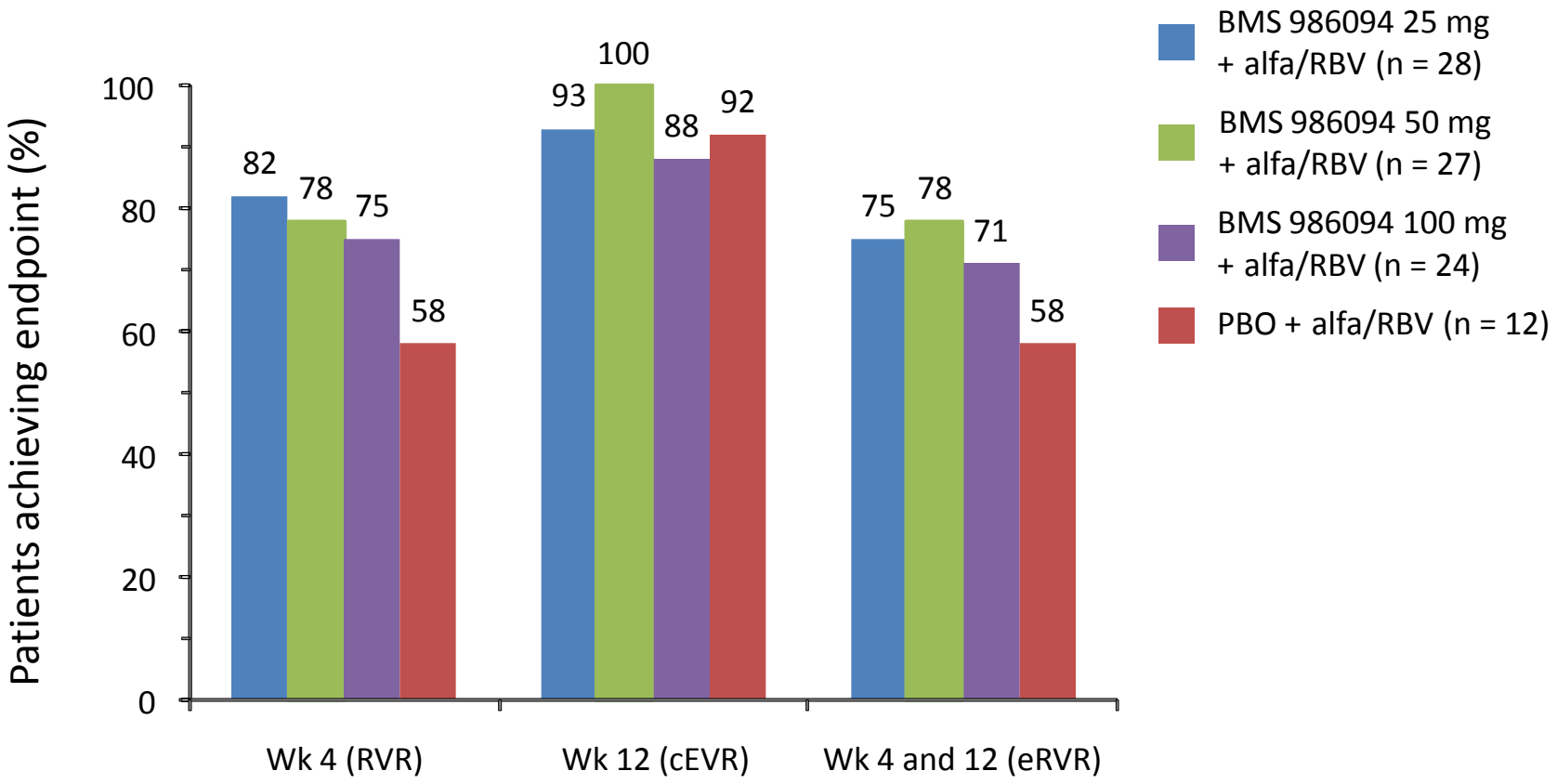
Study Design



Baseline Demographic and Disease Characteristics

Characteristic	BMS-986094 25 mg + alfa/RBV (n = 28)	BMS-986094 50 mg + alfa/RBV (n = 27)	BMS-986094 100 mg + alfa/RBV (n = 24)	Placebo + alfa/RBV (n = 12)
Median age, years (range)	50 (33-60)	50 (24-62)	46 (22-61)	51 (41-64)
Male gender, n (%)	15 (53.6)	16 (59.3)	13 (54.2)	10 (83.3)
Mean BMI, kg/m^2 (SD)	27.5 (4.69)	28.1 (4.70)	26.7 (4.07)	27.2 (3.07)
Race, n (%)				
White	23 (82.1)	26 (96.3)	21 (87.5)	12 (100)
American Indian	3 (10.7)	0	2 (8.3)	0
Asian	2 (7.1)	1 (3.7)	0	0
Other/Mexican	0	0	1 (4.2)	0
Mean baseline HCV RNA, $\log_{10}$ IU/mL	6.1	6.0	5.6	6.1
HCV genotype, n (%)				
3	15 (53.6)	14 (51.9)	13 (54.2)	7 (58.3)
2	13 (46.4)	12 (44.4)	11 (45.8)	5 (41.7)
Missing	0	1 (3.7)	0	0
***IL28B* genotype (rs12979860), n (%)**				
CC	12 (42.9)	11 (40.7)	10 (41.7)	6 (50.0)
CT	13 (46.4)	11 (40.7)	14 (58.3)	5 (41.7)
TT	3 (10.7)	4 (14.8)	0	1 (8.3)
Missing	0	1 (3.7)	0	0

Virologic Response



- **RVR**: rapid virologic response, undetectable HCV RNA at week 4
- **cEVR:** complete early virologic response, undetectable HCV RNA at week 12
- **eRVR**: extended rapid virologic response, undetectable HCV RNA at weeks 4 and 12

Key Safety Parameters Through Week 12

Event, n (%)	BMS-986094 25 mg + alfa/RBV (n = 28)	BMS-986094 50 mg + alfa/RBV (n = 27)	BMS-986094 100 mg + alfa/RBV (n = 24)	Placebo + alfa/RBV (n = 12)
Deaths	0	0	0	0
Patients with at least 1 serious AE	1 (3.6)	1 (3.7)	1 (4.2)	3 (25.0)
Ventricular extrasystoles	0	0	0	1 (8.3)
Abdominal pain	1 (3.6)	0	0	0
Chest pain	0	0	1 (4.2)*	0
Pneumonia	1 (3.6)	0	0	0
Thermal burn	0	0	0	1 (8.3)
Transient ischemic attack	0	1 (3.7)	0	1 (8.3)
COPD	1 (3.6)	0	0	0
Patients with at least 1 AE leading to discontinuation	1 (3.6)	0	1 (4.2)	1 (8.3)
Hypoacusis	0	0	1 (4.2)	0
Influenza like illness	1 (3.6)	0	0	0
Depression	0	0	0	1 (8.3)

* Grade 2 serious AE (due to hospitalization) considered not related to all study drugs (onset Week 10: 26Mar2012; resolved 30Mar2012). SAE form reported patient was admitted to ER for atypical chest pain. Both MI and infection were ruled out. Patient treated with Flexeril and Percocet and discharged

Grade 3/4 AEs Through Week 12

Event, n (%)	BMS-986094 25 mg + alfa/RBV (n = 28)	BMS-986094 50 mg + alfa/RBV (n = 27)	BMS-986094 100 mg + alfa/RBV (n = 24)	Placebo + alfa/RBV (n = 12)
Patients with at least 1 Grade 3 or higher AE	1 (3.6)	5 (18.5)	3 (12.5)	4 (33.3)
Neutropenia	1 (3.6)	5 (18.5)	1 (4.2)	0
Anemia	0	0	0	1 (8.3)
Ventricular extrasystoles	0	0	0	1 (8.3)
Vomiting	0	0	1 (4.2)	0
Thermal burn	0	0	0	1 (8.3)
Respiratory fume inhalation disorder	0	0	0	1 (8.3)
Transient ischemic attack	0	0	0	1 (8.3)
Migraine	0	0	1 (4.2)	0
Headache	0	0	0	1 (8.3)
Wrist surgery	0	0	1 (4.2)	0

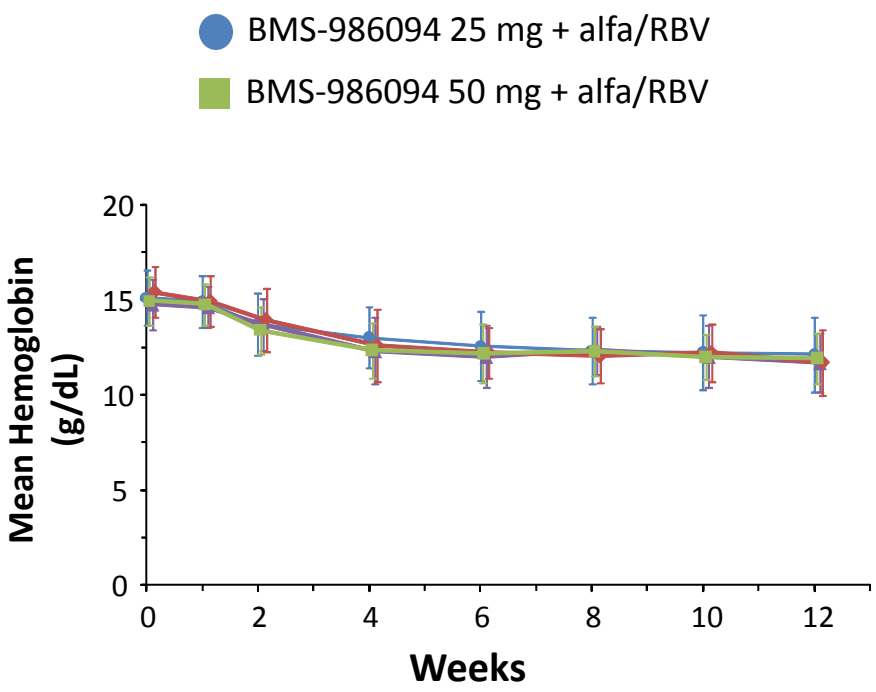
Adverse Events of Any Grade Occurring in ≥15% of Patients Through Week 12

Event, n (%)	BMS-986094 25 mg + alfa/RBV (n = 28)	BMS-986094 50 mg + alfa/RBV (n = 27)	BMS-986094 100 mg + alfa/RBV (n = 24)	Placebo + alfa/RBV (n = 12)
Patients with at least 1 AE	27 (96.4)	27 (100)	23 (95.8)	12 (100)
Fatigue	13 (46.4)	13 (48.1)	11 (45.8)	7 (58.3)
Nausea	8 (28.6)	6 (22.2)	10 (41.7)	4 (33.3)
Myalgia	8 (28.6)	10 (37.0)	8 (33.3)	2 (16.7)
Headache	9 (32.1)	8 (29.6)	7 (29.2)	6 (50.0)
Rash	7 (25.0)	5 (18.5)	7 (29.2)	0
Irritability	6 (21.4)	3 (11.1)	7 (29.2)	2 (16.7)
Insomnia	11 (39.3)	7 (25.9)	6 (25.0)	5 (41.7)
Anemia	4 (14.3)	3 (11.1)	5 (20.8)	2 (16.7)
Vomiting	2 (7.1)	3 (11.1)	5 (20.8)	2 (16.7)
Chills	1 (3.6)	5 (18.5)	5 (20.8)	2 (16.7)
Pruritus	3 (10.7)	3 (11.1)	5 (20.8)	4 (33.3)
Dyspepsia	2 (7.1)	1 (3.7)	4 (16.7)	0
Diarrhea	5 (17.9)	6 (22.2)	4 (16.7)	1 (8.3)

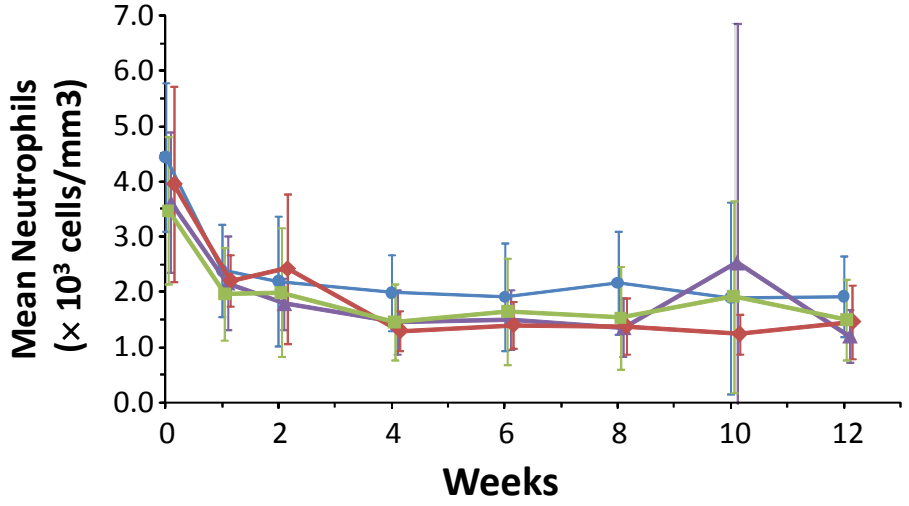
Adverse Events of Any Grade Occurring in ≥15% of Patients Through Week 12 (cont)

Event, n (%)	BMS-986094 25 mg + alfa/RBV (n = 28)	BMS-986094 50 mg + alfa/RBV (n = 27)	BMS-986094 100 mg + alfa/RBV (n = 24)	Placebo + alfa/RBV (n = 12)
Pyrexia	6 (21.4)	4 (14.8)	4 (16.7)	2 (16.7)
Muscle spasms	3 (10.7)	4 (14.8)	4 (16.7)	2 (16.7)
Dyspnea	3 (10.7)	3 (11.1)	4 (16.7)	2 (16.7)
Neutropenia	4 (14.3)	7 (25.9)	3 (12.5)	1 (8.3)
Dizziness	7 (25.0)	4 (14.8)	3 (12.5)	2 (16.7)
Back pain	1 (3.6)	0	1 (4.2)	2 (16.7)
Depression	8 (28.6)	3 (11.1)	1 (4.2)	2 (16.7)
Anxiety	5 (17.9)	2 (7.4)	1 (4.2)	4 (33.3)
Dry skin	1 (3.6)	5 (18.5)	1 (4.2)	4 (33.3)
Alopecia	1 (3.6)	4 (14.8)	1 (4.2)	2 (16.7)
Dry eye	0	0	0	2 (16.7)
Abdominal pain upper	1 (3.6)	0	0	2 (16.7)
Influenza-like illness	9 (32.1)	6 (22.2)	0	0
Disturbance in attention	0	0	0	2 (16.7)

Hematologic: Hemoglobin or Neutrophils Through Week 12

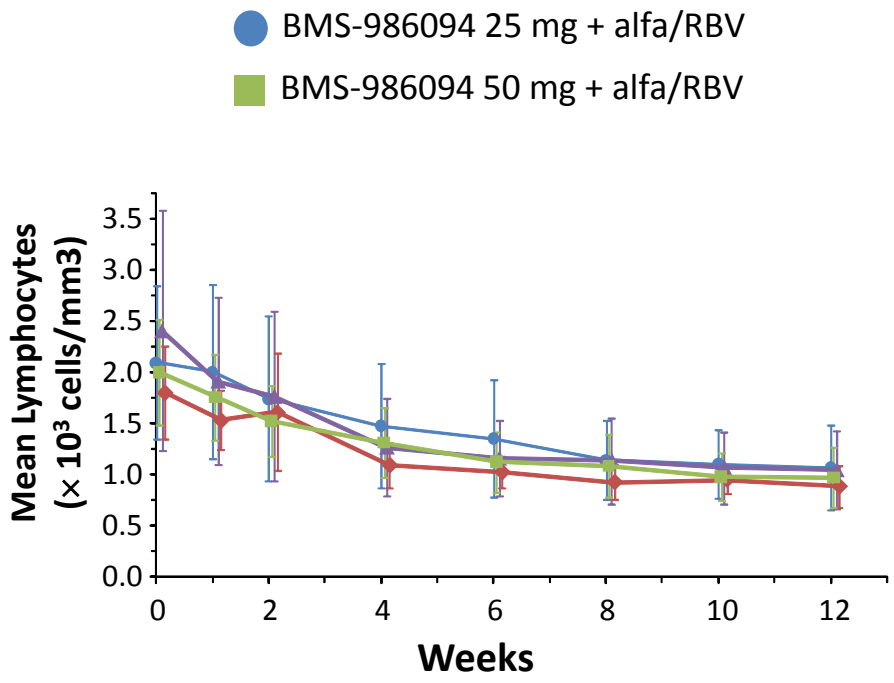


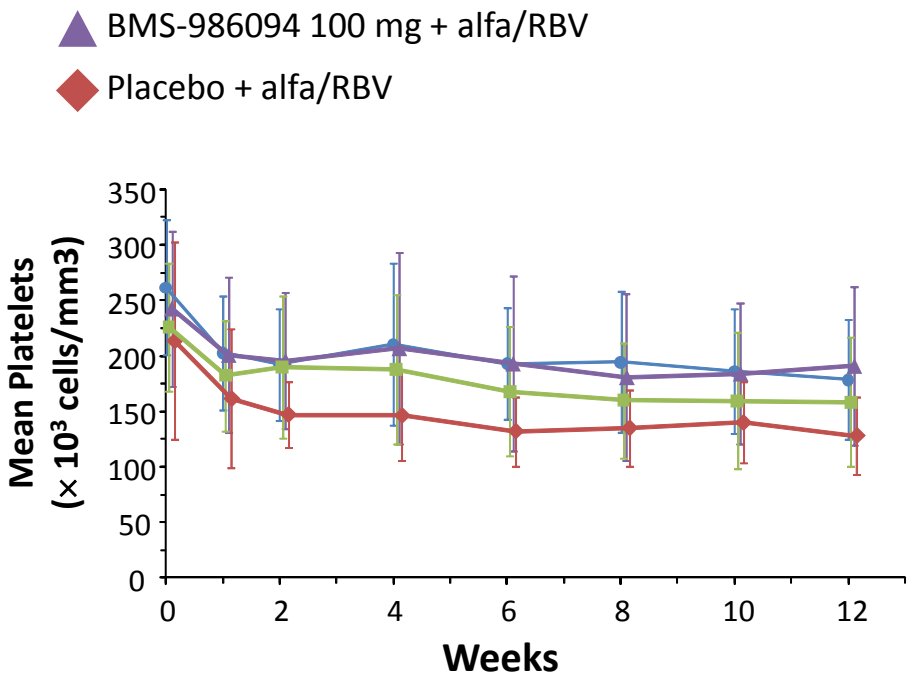
BMS-986094							
25 mg n = 28	28	26	26	27	25	26	27
50 mg n = 27	26	27	28	27	26	27	27
100 mg n = 24	24	21	22	22	21	21	21
Placebo n = 11	12	10	10	11	11	10	11



BMS-986094							
25 mg n = 28	28	24	23	25	23	23	26
50 mg n = 27	25	25	26	27	23	27	24
100 mg n = 24	23	21	22	22	21	21	21
Placebo n = 10	11	9	9	9	10	10	10

Hematologic: Lymphocytes or Platelets Through Week 12





BMS-986094							
25 mg n = 28	28	24	23	25	23	23	26
50 mg n = 27	25	25	26	27	23	27	24
100 mg n = 24	23	21	22	22	21	21	21
Placebo n = 10	11	9	9	9	10	10	10

BMS-986094							
25 mg n = 28	28	24	23	23	23	22	26
50 mg n = 27	25	24	25	25	23	27	24
100 mg n = 24	22	20	22	21	20	20	21
Placebo n = 10	11	9	9	9	10	10	10

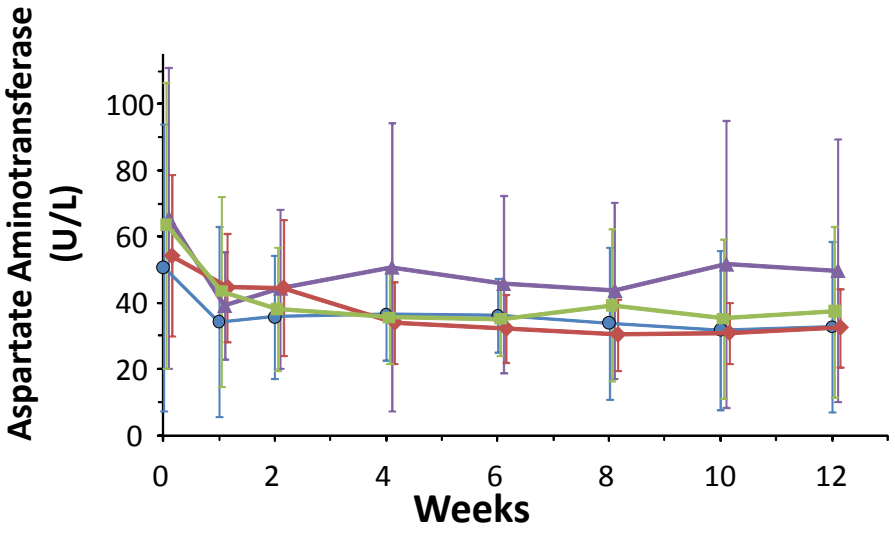
Hepatic: AST or ALT Through Week 12

BMS-986094 25 mg + alfa/RBV

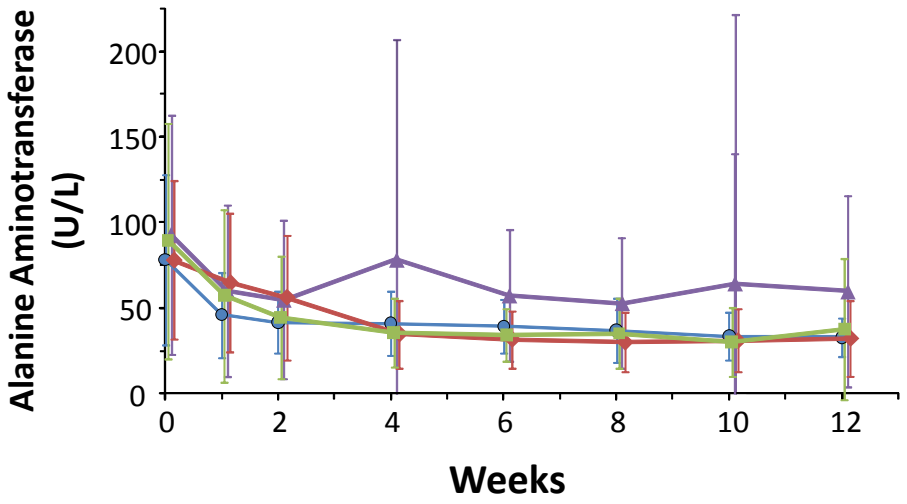
BMS-986094 50 mg + alfa/RBV

BMS-986094 100 mg + alfa/RBV

Placebo + alfa/RBV



BMS-986094							
25 mg n = 28	28	27	27	27	26	26	27
50 mg n = 27	26	27	28	27	27	27	26
100 mg n = 24	24	23	22	22	22	21	21
Placebo n = 11	12	10	11	11	11	10	11



BMS-986094							
25 mg n = 28	28	27	27	27	26	26	27
50 mg n = 27	26	27	28	27	27	27	26
100 mg n = 24	24	23	22	22	22	21	21
Placebo n = 11	12	10	11	11	11	10	11

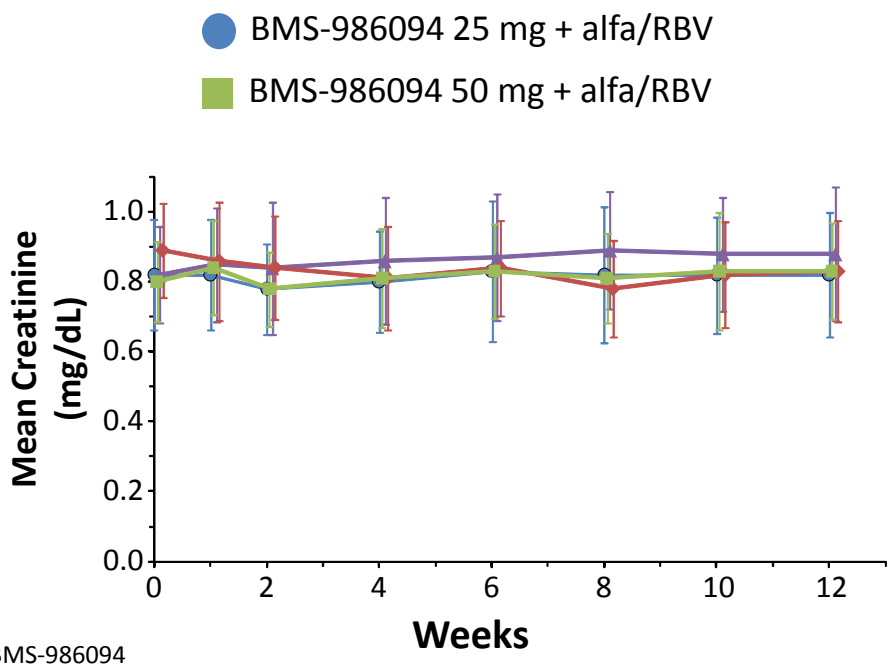
Grade 3/4 Hematologic and Hepatic Laboratory Abnormalities Through Week 12

Event, n	BMS-986094 25 mg + alfa/RBV (n = 28)		BMS-986094 50 mg + alfa/RBV (n = 27)		BMS-986094 100 mg + alfa/RBV (n = 24)		Placebo + alfa/RBV (n = 12)	
Hematologic Laboratory Abnormalities								
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	4	1	6	2	4	1	4	0
Lymphopenia	2	0	0	0	0	1	1	0
Anemia	8	-	6	-	7	-	7	-
Hepatic Laboratory Abnormalities								
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Increased total bilirubin	0	-	1	-	0	-	0	-
Elevated ALT	0	-	0	-	1	-	0	-

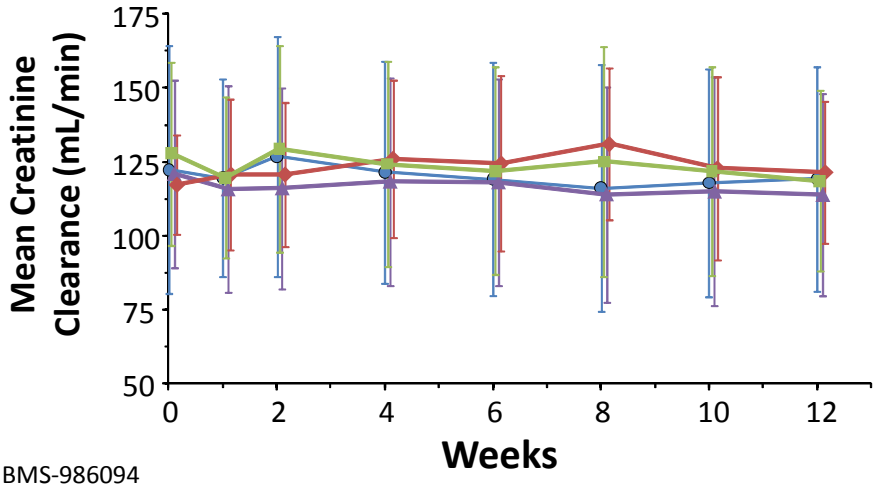
Neutropenia: grade 3, 500-749/mm^3; grade 4, < 500/mm^3
Lymphopenia: grade 3, 350-499/mm^3; grade 4, < 350/mm^3
Anemia: grade 3, hemoglobin 7-8.9 g/dL; grade 4, < 7.0 g/dL
Thrombocytopenia: grade 3, 25,000-49,999/mm^3; grade 4, < 25,000/mm^3

ALT elevations: grade 3, 5.1-10 x ULN; grade 4, > 10 x ULN
Bilirubin elevations: grade 3, 2.6-5 x ULN; grade 4, > 5 x ULN

Renal: Creatinine and Creatinine Clearance Through Week 12 (Mean)

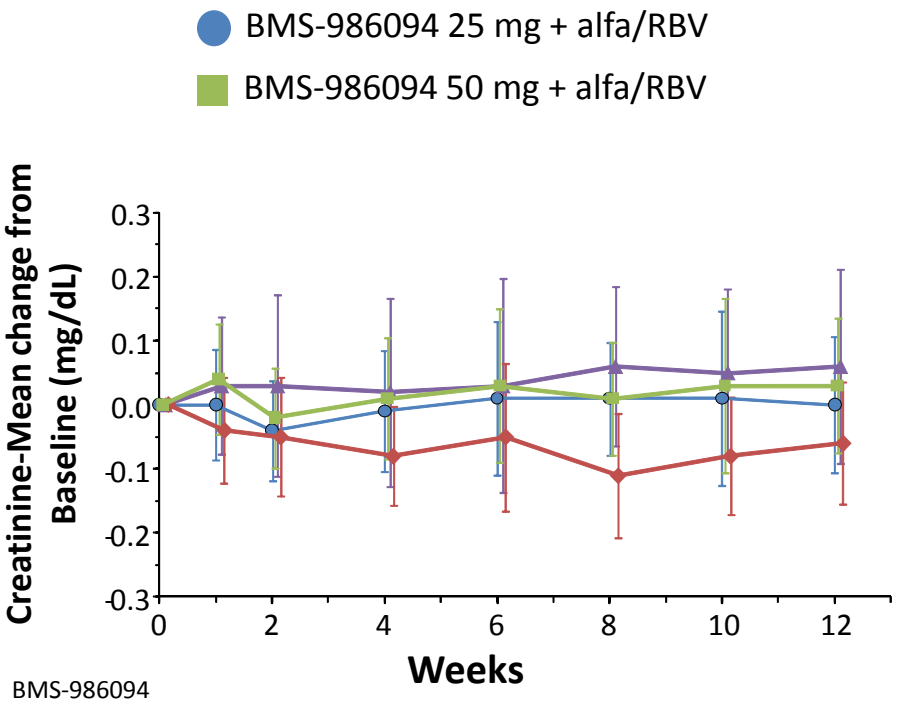


BMS-986094							
25 mg n = 28	28	27	27	27	26	26	27
50 mg n = 27	26	27	28	27	27	27	26
100 mg n = 24	24	23	22	22	22	21	21
Placebo n = 11	12	10	11	11	11	10	11

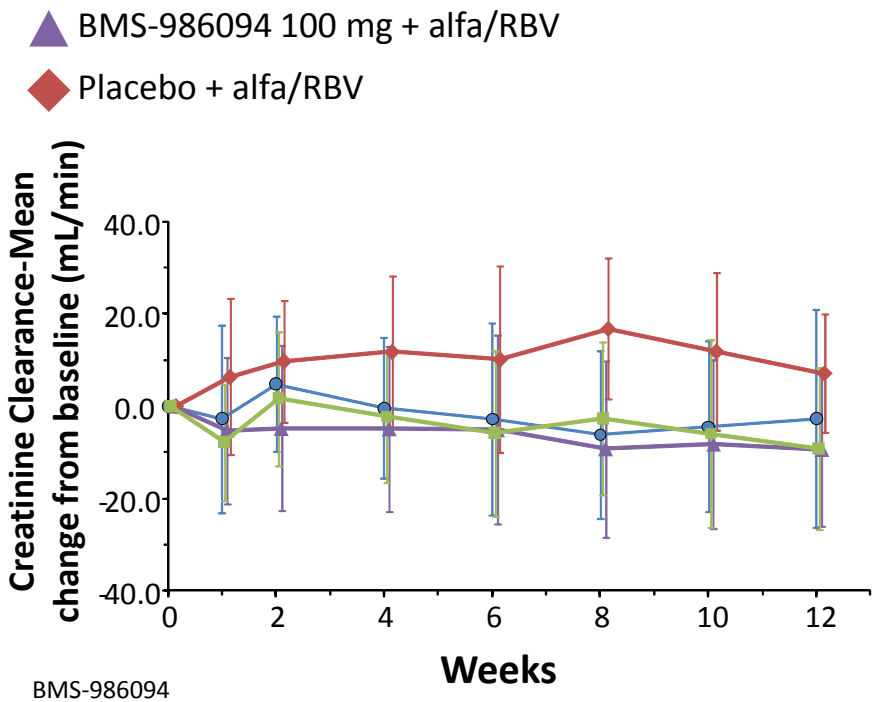


BMS-986094							
25 mg n = 28	28	27	27	27	26	26	27
50 mg n = 27	26	27	28	27	27	27	26
100 mg n = 24	24	23	22	22	22	21	21
Placebo n = 11	12	10	11	11	11	10	11

Renal: Creatinine and Creatinine Clearance Through Week 12 (Change from Baseline)



BMS-986094							
25 mg n =	28	27	27	27	26	26	27
50 mg n =	26	27	28	27	27	27	26
100 mg n =	24	23	22	22	22	21	21
Placebo n =	12	10	11	11	11	10	11



BMS-986094							
25 mg n =	28	27	27	27	26	26	27
50 mg n =	26	27	28	27	27	27	26
100 mg n =	24	23	22	22	22	21	21
Placebo n =	12	10	11	11	11	10	11

Cardiac and Renal: All Emergent Events Through Week 12

Event, n (%)	BMS-986094 25 mg + alfa/RBV (n = 28)	BMS-986094 50 mg + alfa/RBV (n = 27)	BMS-986094 100 mg + alfa/RBV (n = 24)	Placebo + alfa/RBV (n = 12)
Cardiac				
Ventricular extrasystoles	0	0	0	1 (8.3)
Chest pain	0	0	1 (4.2)[3]	0
Electrocardiogram abnormal	0	1 (3.7)[1]	0	0
Electrocardiogram Q wave	0	1 (3.7)[2]	0	0
Renal				
Pollakiuria (frequent urination)	0	1 (3.7)	0	0
Nephrolithiasis	1 (3.6)	0	0	0
Dysuria	1 (3.6)	0	1 (4.2)	0

[1] Grade 1 non-serious ECG change possibly related to all study drugs [onset Week 12 (end of treatment): 16Feb2012; end: 22Mar2012]; cardiologist over-read as "non-specific T wave abnormality; abnormal, clinically insignificant"

[2] Grade 1 non-serious ECG change (Q wave in lead III only) possibly related to study drug and (onset post treatment Week 12: 27Feb2012; end: 26Mar2012); cardiologist over read as normal ECG

[3] Grade 2 serious AE (due to hospitalization) considered not related to all study drugs (onset Week 10: 26Mar2012; resolved 30Mar2012) SAE form reported patient was admitted to ER for atypical chest pain; both MI and infection were ruled out; patient treated with Flexeril and percocet and discharged

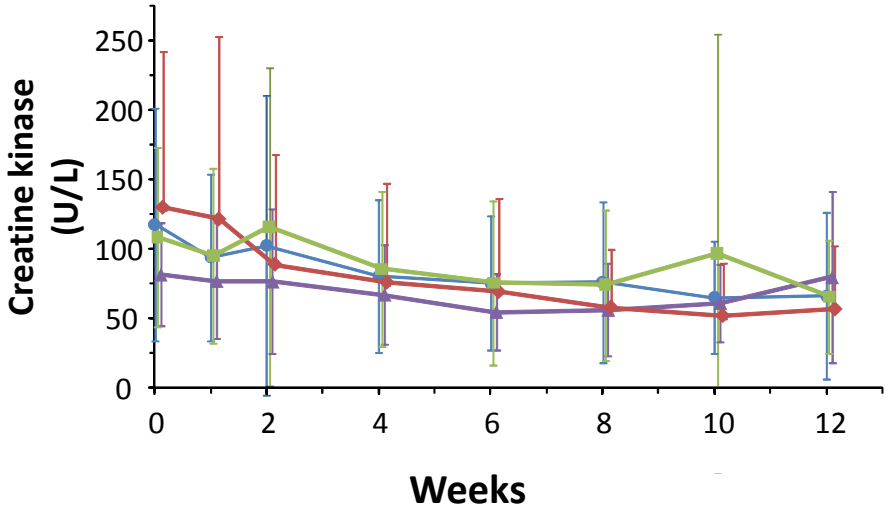
Creatinine Kinase Through Week 12

BMS-986094 25 mg + alfa/RBV

BMS-986094 100 mg + alfa/RBV

BMS-986094 50 mg + alfa/RBV

Placebo + alfa/RBV



BMS-986094							
25 mg n = 28	28	27	27	27	26	26	27
50 mg n = 27	26	27	27	27	27	27	26
100 mg n = 24	24	23	22	22	22	21	21
Placebo n = 11	12	10	11	11	11	10	11

Conclusions

- A higher proportion of patients treated with BMS-986094 achieved RVR and eRVR compared to alfa/RBV alone
- BMS-986094 appeared well tolerated with an AE profile comparable to control in 12 week combination data with peginterferon alfa-2a and RBV
- Part B of AI472-003 evaluated BMS-986094 (doses 50 mg to 200 mg once daily) combined with daclatasvir and/or RBV (AI472-003 Part B)
- Cardiac and renal safety events were noted in Part B of this study prompting cessation of all dosing of BMS-986094 on August 1, 2012 and termination of the program on August 23, 2012