First Report of SVR12 for a NS5A Replication Complex Inhibitor, BMS-790052, in Combination With PegIFNα-2a and RBV: Phase IIA Trial in Treatment-Naive HCV Genotype 1 Subjects

Poster 1373

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BACKGROUND

- BMS-790052 is a potentially first-in-class, highly selective HCV NS5A Replication Complex Inhibitor with picomolar potency and broad genotypic coverage *in vitro*[1]
  - EC_{50} values of 50 and 9 pM against genotype (GT) 1a and 1b replicons
  - BMS-790052 inhibits HCV RNA replication through the NS5A protein, an essential component of the HCV replication complex[2]
- BMS-790052 has a pharmacokinetic profile supportive of once-daily dosing
- BMS-790052 plus pegylated interferon alfa-2a (pegIFNα-2a) and ribavirin (RBV) can achieve high rates of early HCV RNA suppression (RVR and eRVR) compared with placebo[3]
- This poster presents the first sustained virologic response (SVR) data obtained for a NS5A Replication Complex Inhibitor

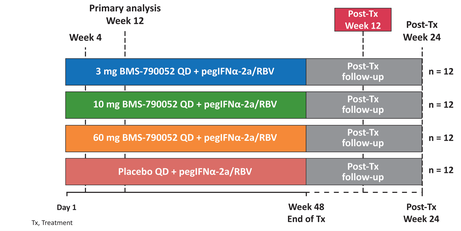
OBJECTIVES

- Assess the efficacy and safety of BMS-790052 in combination with pegIFNα-2a in treatment-naïve subjects infected with HCV GT1

METHODS

- Treatment-naive, non-cirrhotic subjects with HCV GT1 infection

Figure 1. AI444014 Study Design



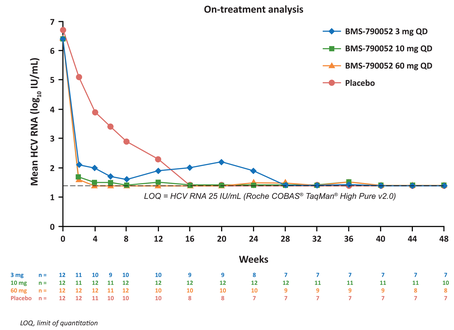
RESULTS

Table 1. Baseline Demographics and Disease Characteristics

	BMS-790052 3 mg QD (n = 12)	BMS-790052 10 mg QD (n = 12)	BMS-790052 60 mg QD (n = 12)	Placebo (n = 12)
Age, median years	52	50.5	51	49.5
Male, n (%)	9 (75)	8 (67)	7 (58)	8 (67)
Race, n (%)				
White/Other	9 (75)	10 (83)	10 (83)	10 (83)
Black/African-American	3 (25)	2 (17)	2 (17)	2 (17)
HCV GT, n (%)				
1a	8 (67)	8 (67)	9 (75)	7 (58)
1b	4 (33)	4 (33)	3 (25)	5 (42)
IL28B RS12979860 (n/N*):				
CC	3/8	5/11	1/8	4/9
CT	4/8	4/11	6/8	4/9
TT	1/8	2/11	1/8	1/9
HCV RNA, mean (SD) $\log_{10}$ IU/mL	6.3 (0.69)	6.4 (0.72)	6.5 (0.43)	6.7 (0.41)

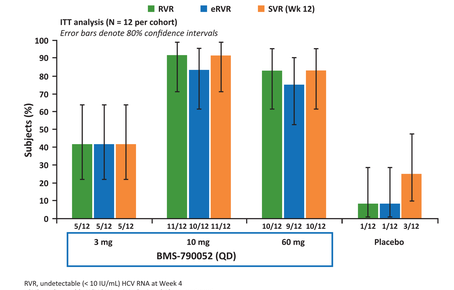
All patients received pegIFNα-2a/RBV
** Number of patients within specified cohort with available* IL28B *RS12979860 SNP genotype data*

Figure 2. On-Treatment HCV RNA Suppression



LOQ, limit of quantitation

Figure 3. Virologic Responses



RVR, undetectable (< 10 IU/mL) HCV RNA at Week 4
eRVR, undetectable HCV RNA at Weeks 4 and 12 on treatment
SVR (Wk 12), undetectable HCV RNA at Week 12 post-treatment
ITT, intent to treat

Figure 4. Virologic Responses by RS12979860 *IL28B* SNP Genotype

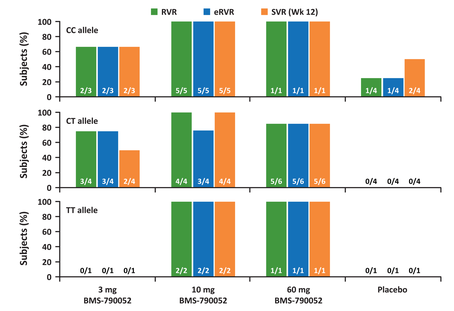
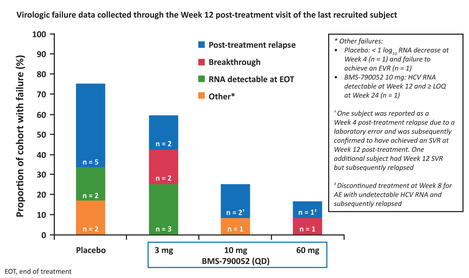


Figure 5. Summary of Virologic Failures



* *Other failures:*
- *Placebo: < 1 $\log_{10}$ RNA decrease at Week 4 (n = 1) and failure to achieve an EVR (n = 1)*
- *BMS-790052 10 mg: HCV RNA detectable at Week 12 and ≥ LOQ at Week 24 (n = 1)*

* *One subject was reported as a Week 4 post-treatment relapse due to a laboratory error and was subsequently confirmed to have achieved an SVR at Week 12 post-treatment. One additional subject had Week 12 SVR but subsequently relapsed*

† *Discontinued treatment at Week 8 for AE with undetectable HCV RNA and subsequently relapsed*

EOT, end of treatment
AE, adverse event
EVR, early virologic response

Virologic breakthrough on-treatment defined as a > 1 $\log_{10}$ increase in HCV RNA from nadir, or quantifiable levels of RNA following a drop to undetectability

Summary of Efficacy Results

- Higher rates of SVR at Week 12 post-treatment were achieved in all BMS-790052 dose groups compared with placebo (Figure 3)
  - BMS-790052 3 mg, 10 mg, and 60 mg SVR12 rates were 42% (5/12 subjects), 92% (11/12), and 83% (10/12), respectively, versus 25% (3/12) for placebo
  - Early HCV RNA response (RVR and eRVR) correlates well with Week 12 SVR for subjects treated with BMS-790052 plus pegIFNα-2a/RBV
- Virologic breakthrough and relapse were uncommon in the 10 mg and 60 mg dose groups
- In an exploratory analysis evaluating the *IL28B* RS12979860 SNP, 10 mg and 60 mg BMS-790052 plus pegIFNα-2a/RBV resulted in high rates of SVR at Week 12 regardless of the host genotype (CC, CT, or TT; Figure 4).
  - In this small, non-stratified study there were fewer CC allele genotypes in the 60 mg group
  - Additional evaluation in larger cohorts will be necessary for confirmation

Table 2. Summary of Key Safety Data

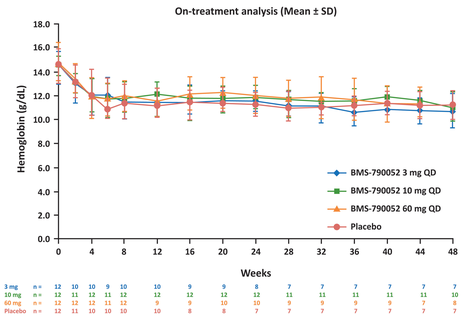
n (%)	BMS-790052 3 mg QD (n = 12)	BMS-790052 10 mg QD (n = 12)	BMS-790052 60 mg QD (n = 12)	Placebo (n = 12)
Grade 3-4 AEs	1 (8.3)	3 (25.0)	4 (33.3)	5 (41.7)
Discontinuations due to AEs	1 (8.3)	1 (8.3)	4 (33.3)*	2 (16.7)
SAEs	1 (8.3)	1 (8.3)	1 (8.3)	0
Deaths	0	0	0	0
Tx interruptions due to AEs				
BMS-790052 (>3 days)	1 (8.3)	1 (8.3)	2 (16.7)	0
RBV (>3 days)	1 (8.3)	1 (8.3)	1 (8.3)	0
PegIFNα-2a (> 14 days)	0	0	0	0
Dose reductions				
PegIFNα-2a	2 (16.7)	3 (25.0)	3 (25.0)	6 (50.0)
RBV	5 (41.7)	6 (50.0)	7 (58.3)	7 (58.3)
Filgrastim use	2 (16.7)	3 (25.0)	0	2 (16.7)
Erythropoietin use	1 (8.3)	3 (25.0)	3 (25.0)	2 (16.7)

** Four different events: anxiety, rash, alopecia, lymphopenia*
SAE, serious AE

Table 3. Adverse Events Occurring in at Least Four Patients (33.3%) in any Cohort

n (%)	BMS-790052 3 mg QD (n = 12)	BMS-790052 10 mg QD (n = 12)	BMS-790052 60 mg QD (n = 12)	Placebo (n = 12)
Fatigue	7 (58.3)	6 (50.0)	6 (50.0)	9 (75.0)
Headache	7 (58.3)	9 (75.0)	3 (25.0)	3 (25.0)
Insomnia	4 (33.3)	4 (33.3)	5 (41.7)	6 (50.0)
Nausea	5 (41.7)	4 (33.3)	4 (33.3)	6 (50.0)
Anemia	3 (25.0)	5 (41.7)	6 (50.0)	5 (41.7)
Influenza-like illness	6 (50.0)	3 (25.0)	2 (16.7)	4 (33.3)
Irritability	6 (50.0)	3 (25.0)	3 (25.0)	2 (16.7)
Pruritus	3 (25.0)	5 (41.7)	4 (33.3)	3 (25.0)
Alopecia	1 (8.3)	4 (33.3)	3 (25.0)	2 (16.7)
Asthenia	1 (8.3)	3 (25.0)	5 (41.7)	1 (8.3)
Neutropenia	3 (25.0)	4 (33.3)	2 (16.7)	5 (41.7)
Cough	2 (16.7)	5 (41.7)	1 (8.3)	3 (25.0)
Rash	4 (33.3)	4 (33.3)	2 (16.7)	3 (25.0)
Decreased appetite	3 (25.0)	2 (16.7)	4 (33.3)	3 (25.0)
Vomiting	2 (16.7)	1 (8.3)	4 (33.3)	0

Figure 6. Hemoglobin Levels by Visit



N = number of subjects with measurement at specified time point

Table 4. Grade 3 or 4 AEs Through 48 Weeks

n (%)	BMS-790052 3 mg QD (n = 12)	BMS-790052 10 mg QD (n = 12)	BMS-790052 60 mg QD (n = 12)	Placebo (n = 12)
Total subjects with at least one event	1 (8.3)	3 (25.0)	4 (33.3)	5 (41.7)
Blood/lymphatic system	1 (8.3)	0	2 (16.7)	1 (8.3)
Lymphopenia	–		*1 (8.3)*	–
Neutropenia	–		*1 (8.3)*	*1 (8.3)*
Anemia	*1 (8.3)*		–	–
Respiratory/thoracic/mediastinal	1 (8.3)	0	2 (16.7)	0
Gastrointestinal	0	0	1 (8.3)	2 (16.7)
Infections & infestations	0	0	1 (8.3)	0
Psychiatric	0	0	1 (8.3)	1 (8.3)
Skin & subcutaneous tissue	0	0	1 (8.3)	0
Dermatitis exfoliative			*1 (8.3)*	
General/administration site	1 (8.3)	2 (16.7)	0	1 (8.3)
Hepatobiliary	0	0	0	1 (8.3)
Nervous system	0	1 (8.3)	0	1 (8.3)

Table 5. Grade 3 or 4 Laboratory Abnormalities Through 48 Weeks

n (%)	BMS-790052 3 mg QD (n = 11)*	BMS-790052 10 mg QD (n = 12)	BMS-790052 60 mg QD (n = 12)	Placebo (n = 12)
Hemoglobin	1 (9.1)	0	1 (8.3)	0
Absolute lymphocyte count	1 (9.1)	3 (25.0)	3 (25.0)	3 (25.0)
Absolute neutrophil count	2 (18.2)	4 (33.3)	3 (25.0)	4 (33.3)
Platelets	0	0	0	1 (8.3)
Alanine aminotransferase (ALT)	0	1 (8.3)	0	3 (25.0)
Total bilirubin	0	0	1 (8.3)	0

** Laboratory data unavailable for one subject. Denominator for percentages in this cohort is therefore 11 subjects. Events graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (2004 revision) (http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf)*

Summary of Safety Results

- In general, overall AEs, SAEs, and AE-related discontinuations were consistent with the safety profile of pegIFNα-2a/RBV background therapy
- Four subjects discontinued due to AEs in the 60 mg BMS-790052 group. However, no evidence of a safety signal was observed (Table 2)
  - All subjects had undetectable HCV RNA at discontinuation for: (1) anxiety (Week 8); (2) rash (Week 12); (3) alopecia (Week 24); and (4) lymphopenia (Week 40); the latter three subjects achieved SVR at Week 12 post-treatment
- No new on-treatment SAEs were reported beyond study week 24
- The BMS-790052 dosing groups were comparable to the placebo group for both dose reductions or interruptions of any study medication and in the use of filgrastim (C-GSF) or erythropoietin (Epogen)
- No incremental toxicity was associated with the addition of BMS-790052 to pegIFNα-2a/RBV for events of special interest, including:
  - hematologic events: anemia, neutropenia, lymphopenia or thrombocytopenia
  - dermatologic events: only one subject discontinued due to rash
  - hepatic events: ALT improved over time in all cohorts, with no evidence of hepatotoxicity

CONCLUSIONS

- Antiviral activity
  - BMS-790052 is a potent HCV Replication Complex Inhibator and can achieve high rates of SVR at Week 12 post-treatment in HCV GT1-infected patients when 10 mg (92%) or 60 mg (83%) BMS-790052 is combined with pegIFNα-2a/RBV
- Safety
  - BMS-790052 plus pegIFNα-2a/RBV was generally well tolerated with a safety profile consistent with that of pegIFNα-2a/RBV alone
- Future studies
  - The AI444014 Week 12 SVR results support further development of BMS-790052 combined with pegIFNα-2a/RBV, other HCV direct-acting antiviral agents, or interferon-lambda

REFERENCES

1. Gao M, *et al. Nature* 2010;465:96-100.
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3. Pol S, *et al. J Hepatol* 2010;52(suppl 1):S462.

Disclosure

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