Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient: NS5A Replication Co-factor Inhibitor (BMS-790052)		

SYNOPSIS

Final Clinical Study Report for Study AI444014

TITLE OF STUDY: A Phase 2a Study of BMS-790052 in Combination with Peginterferon Alfa-2a (Pegasys®) and Ribavirin (Copegus®) in Treatment Naive Subjects with Chronic Hepatitis C Virus Genotype 1 Infection

INVESTIGATORS/STUDY CENTERS: Fourteen (14) investigators in France and the United States

PUBLICATIONS:

STUDY PERIOD: Study Initiation Date: 23-Jun-2009 **CLINICAL PHASE:** 2a

Study Completion Date: The last patient/last visit has not yet occurred. The data cut-off for this report of the primary endpoints is 18-Dec 2009.

OBJECTIVES:

Primary

- Safety, as measured by the frequency of serious adverse events (SAEs), discontinuations due to adverse events (AEs), and Grade 3 - 4 laboratory abnormalities and,
- Antiviral activity as determined by the proportion of subjects with extended rapid virologic response (eRVR) defined as HCV RNA < 10 IU/mL at both Weeks 4 and 12.

Secondary

- Proportion of subjects with rapid virologic response (RVR), defined as HCV RNA < 10 IU/mL at Week 4;
- Proportion of subjects with early virologic response (EVR), defined as ≥ 2 $\log_{10}$ decrease in HCV RNA from baseline at Week 12 (or HCV RNA < 10 IU/mL for subjects with baseline HCV RNA < 1000 IU/mL);
- Proportion of subjects with a sustained virologic response (SVR), defined as HCV RNA < 10 IU/mL at follow-up Week 12 (SVR_{12}) and Week 24 (SVR_{24}), respectively;
- Resistant variants associated with clinical failure.

Exploratory

- To explore the relationship between measures of safety or antiviral activity and exposure to BMS-790052 when co-administered with pegIFNα/RBV;
- To describe the pharmacokinetics of BMS-790052, RBV, and PegIFNα;

METHODOLOGY: This was a randomized, double-blind, placebo-controlled, multi-center study conducted in treatment-naive, genotype 1 hepatitis C virus (HCV)-infected subjects. Subjects were randomized in a 1:1:1:1 ratio to receive 3 mg, 10 mg, or 60 mg daily of BMS-790052 plus peginterferon alfa-2a (pegIFNα) and ribavirin (RBV) or to placebo daily plus pegIFNα/RBV for a total of 48 weeks followed by a 24-week post-treatment follow up period. Randomization was stratified by HCV subtype determined at screening (genotype 1a or 1b). The study is currently ongoing. This clinical study report (CSR) presents results obtained at the primary endpoint of the study, after each subject received 12 weeks of treatment with study medication. Therefore, methodology, analysis plans and results applicable to the Week 12 analysis are presented. Only Bristol-Myers Squibb (BMS) personnel were unblinded for the 12-week interim analysis; the site and subjects will remain blinded for the duration of the 72-week study.

HCV RNA level was determined at screening and on Day 1 prior to dosing. Antiviral effect was assessed by measurement of HCV RNA at 2-week intervals for the first 8 weeks of treatment, then every 4 weeks. Safety assessments (AEs, laboratory tests, targeted physical examinations, and vital signs) were made at 2-week intervals for the first 8 weeks of treatment, then every 4 weeks. In addition, electocardiograms (ECGs) were performed at Weeks 4 and 12. Blood samples for determination of pharmacokinetic (PK) parameters were obtained on Day 1 and at specified times at study visits on Weeks 4, 8, 12.

NUMBER OF SUBJECTS (Planned and Analyzed): The number of subjects planned to be randomized and treated was 48; 48 subjects were randomized and treated, 12 subjects in each of the BMS-790052 dose groups (3 mg, 10 mg and 60 mg) and 12 subjects in the placebo group. All 48 subjects were included in the 12-week analysis.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Adult men and women 18 to 70 years of age with chronic HCV genotype 1 infection who: 1) had less than 4 weeks of total therapy with IFN, pegIFNα, or RBV at any time, and none in the 24 weeks prior to randomization; 2) had no evidence of human immunodeficiency virus (HIV) or hepatitis B virus (HBV) co-infection; and 3) had no evidence of advanced liver disease.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Subjects received BMS-790052 doses of 3 mg, 10 mg or 60 mg given orally once daily. Treatment was to continue for 48 weeks. Investigational Product Information appears in Table 1.

Table 1: Investigational Product Identification

Drug Product	Formulation	Product Batch Number
BMS-790052, 3 mg	Film-coated tablet	9C55374
BMS-790052, 10 mg	Film-coated tablet	8J43343
BMS-790052, 30 mg	Film-coated tablet	9C55376
Placebo for 3 mg, 10 mg and 30 mg	Film-coated tablet	9B54032 9B54029

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Subject received treatment with placebo given once daily. Treatment was to continue for 48 weeks. All subjects also received pegIFNα/RBV treatment for HCV infection: pegIFNα given once weekly and RBV given twice daily, in the morning and evening with food. BMS sourced and supplied sufficient marketed pegIFNα and RBV product as follows: pegIFNα as 1 mL, pre-filled syringes containing 180 mg/0.5 mL, manufactured by Roche Laboratories, Inc, batch number B1097 (expiration: Jan 2011); RBV as 200-mg film-coated tablets (Copegus®) manufactured by Roche Laboratories, Inc, batch numbers 104764 (expiration: 31-Mar-2011) and 118765 (expiration: 09-Apr-2009).

CRITERIA FOR EVALUATION:

Efficacy: The primary antiviral activity endpoint was the proportion of subjects with eRVR, defined as undetectable HCV RNA (HCV RNA less than the lower limit of detection [10 IU/mL]) at both Weeks 4 and 12. Other antiviral activity endpoints assessed in this analysis were the proportions of subjects with RVR defined as undetectable HCV RNA at Week 4; proportions of subjects with EVR defined as ≥ 2 $\log_{10}$ HCV RNA decrease from baseline in HCV RNA level or undetectable HCV RNA if baseline HCV RNA was <1,000 $\log_{10}$ IU/mL at Week 12; proportions of subjects with complete early virologic response (cEVR) defined as undetectable HCV RNA at Week 12; and $\log_{10}$ HCV RNA levels and changes from baseline through Week 12.

Post-hoc assessment of virologic failure was performed using the following criteria, with subjects classified according to the event that occurred first:

- < 1 $\log_{10}$ decrease in HCV RNA from baseline at Week 4 of treatment;
- Failure to achieve EVR, defined as < 2 $\log_{10}$ decrease in HCV RNA from baseline at Week 12 of treatment;
- Virologic breakthrough, defined as > 1 $\log_{10}$ increase over nadir or HCV RNA ≥ limit of quantification (LOQ) after confirmed undetectable HCV RNA while on treatment. Virologic breakthrough must be confirmed by HCV RNA measurements 4 weeks apart;
- detectable HCV RNA at Week 12 and HCV RNA > 50 IU/mL at Week 24 of treatment;
- detectable HCV RNA at end of treatment (EOT) (including early discontinuation); and
- Relapse: detectable HCV RNA during follow-up after undetectable HCV RNA at EOT.

Safety: Key safety endpoints included deaths, SAE, AEs leading to discontinuation, Grade 3 or 4 AEs, Grade 2 to 4 related AEs, and Grade 3 or 4 laboratory abnormalities.

Pharmacokinetics: Determination of PK parameters of BMS-790052 and RBV was part of the study design. Results will be presented in an addendum to this clinical study report (CSR). **Pharmacodynamics:** Pharmacodynamic (PD) analyses of the relationship between measures of safety/antiviral activity and exposure to BMS-790052 when co-administered with pegIFNα/RBV were exploratory endpoints. Results will be presented in an addendum to the CSR.

Other: Resistance testing of variants associated with clinical failure was a secondary endpoint. Results will be presented in an addendum to this CSR. **STATISTICAL CONSIDERATIONS:** An analysis of early safety and antiviral activity by coded treatment regimen was performed after all subjects reached Week 4. This unblinded analysis of safety and antiviral activity to support Phase 2b dose selection was conducted after all subjects reached Week 12. Future planned analyses include another unblinded analysis of safety and antiviral activity after all subjects complete 12 weeks of follow-up; and a final analysis after all subjects complete 24 weeks of follow-up.

The evaluation of the benefit/risk profile of BMS-790052 required a broad statistical assessment employing exploratory analyses of safety and antiviral activity that incorporated dose level and covariates such as HCV subtype (1a, 1b), race, and baseline HCV RNA. Formal criteria for assessing antiviral activity based solely on eRVR, or any other antiviral activity endpoint, were not pre-specified.

Safety and antiviral activity were assessed for treated subjects using descriptive and exploratory analyses. Binary antiviral activity endpoints were assessed using modified intent-to-treat (ITT) and observed values. In both analyses, the numerator was based on subjects meeting the response criteria. For modified ITT, the denominator was based on all treated subjects. For observed values, the denominator was based on subjects with available measurements at the analysis week(s). Response rates were presented with 2-sided 80% exact binomial confidence intervals (CIs). Cohort safety stopping rules were assessed as described in the protocol.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: A total of 48 subjects were randomized and treated: 12 subjects in each of the BMS-790052 dose groups and 12 in the placebo group (Table 2). Nine (9) subjects discontinued study therapy prior to the cut-off date; 4 subjects discontinued due to AEs, 1 in the 3-mg, 2 in the 60-mg BMS-790052 groups and 1 in the placebo group. Lack of efficacy resulted in discontinuation in 2 (16.7%) placebo subjects.

Table 2: Subject Disposition: Treated Subjects

	BMS-790052 3 mg	BMS-790052 10 mg	BMS-790052 60 mg	Placebo	Overall
No. of Subjects Treated	12	12	12	12	48
No. (%) of Subjects Discontinued	3 (25.0)	0	2 (16.7)	4 (33.3)	9 (18.8)
Lack of efficacy	0	0	0	2 (16.7)	2 (4.2)
Adverse Event	1 (8.3)	0	2 (16.7)	1 (8.3)	4 (8.3)
Lost to Follow-up	1 (8.3)	0	0	1 (8.3)	2 (4.2)
Other	1 (8.3)	0	0	0	1 (2.1)

The demographic characteristics for treated subjects are summarized in Table 3. The majority of subjects were male (66.7%) and 89.6% of subjects were < 65 years. Most subjects were white (72.9%). Subjects in the placebo group were slightly younger than those in the BMS-790052 dose groups with a mean age of 48.0 years as compared with 52.0 years, 53.2 years, and 52.0 years in the 3-mg, 10-mg and 60-mg dose groups, respectively. The remaining demographic characteristics were consistent among the BMS-790052 and placebo groups.

Table 3: Summary of Demographic Characteristics: Treated Subjects

	BMS-790052 3 mg (N = 12)	BMS-790052 10 mg (N = 12)	BMS-790052 60 mg (N = 12)	Placebo (N = 12)	Overall (N = 48)
Age (years)					
Mean	52.0	53.2	52.0	48.0	51.3
Standard Deviation	8.56	9.11	7.34	10.20	8.80
Min, Max	38, 66	37, 68	43, 67	28, 67	28. 68
Age Categorization (n, %)					
21 - <65 years	11 (91.7)	10 (83.3)	11 (91.7)	11 (91.7)	43 (89.6)
≥65 years	1 (8.3)	2 (16.7)	1 (8.3)	1 (8.3)	5 (10.4)
Gender (n, %)					
Male	9 (75.0)	8 (66.7)	7 (58.3)	8 (66.7)	32 (66.7)
Female	3 (25.0)	4 (33.3)	5 (41.7)	4 (33.3)	16 (33.3)
Race (n, %)					
White	7 (58.3)	9 (75.0)	9 (75.0)	10 (83.3)	35 (72.9)
Black	3 (25.0)	2 (16.7)	2 (16.7)	2 (16.7)	9 (18.8)
American Indian/ Alaska native	1 (8.3)	0	1 (8.3)	0	2 (4.2)
Asian	0	1 (8.3)	0	0	1 (2.1)
Other	1 (8.3)	0	0	0	1 (2.1)

Efficacy Results:

The primary antiviral activity endpoint was the proportion of subjects with eRVR defined as undetectable HCV RNA (HCV RNA < 10 IU/mL) at both Weeks 4 and 12. All BMS-790052 dose groups exhibited greater efficacy than placebo in inducing eRVR. Based on the modified intent-to-treat (ITT) analyses, eRVR rates of 41.7% (5/12), 83.3% (10/12), and 75% (9/12) were achieved for the 3-, 10- and 60-mg BMS-790052 dose groups as compared with 8.3% (1/12) for placebo (Table 4). Response rates for the 10-mg and 60-mg BMS-790052 dose groups were higher than those achieved with the 3-mg BMS-790052 dose, and were greater than the placebo group. For the 10- and 60-mg BMS-790052 dose groups, the lower bound of the 80% CIs for eRVR rates were above 50%.

At Week 2, the mean decreases from baseline in HCV RNA in the 3-, 10-, and 60-mg BMS-790052 dose groups were 4.3, 4.7, and 4.9 $\log_{10}$ IU/mL, respectively, as compared with 1.7 $\log_{10}$ IU/mL for placebo. This improvement in HCV RNA was maintained through Week 12 for all BMS-790052 dose groups.

As observed for eRVR, response rates for the secondary antiviral endpoints of RVR, EVR, and cEVR for the 10-mg and 60-mg BMS-790052 dose groups were higher than those achieved with the 3-mg BMS-790052 dose and the placebo group. The lower bound of the 80% CIs for the 10- and 60-mg BMS-790052 dose groups were above 50% for these endpoints.

Table 4: Summary of Undetectable HCV RNA Endpoints: Treated Subjects - Modified Intent to Treat Analysis

	BMS-790052 3 mg (N = 12)	BMS-790052 10 mg (N = 12)	BMS-790052 60 mg (N = 12)	Placebo (N = 12)
Primary Antiviral Endpoint				
Extended Rapid Virologic Response[a]				
Responder/Evaluable (%)	5/12 (41.7)	10/12 (83.3)	9/12 (75.0)	1/12 (8.3)
80% Confidence Interval	(21.9, 63.8)	(61.4, 95.5)	(52.5, 90.4)	(0.9, 28.7)
Secondary Antiviral Endpoints				
Rapid Virologic Response[b]				
Responder/Evaluable (%)	5/12 (41.7)	11/12 (91.7)	10/12 (83.3)	1/12 (8.3)
80% Confidence Interval	(21.9, 63.8)	(71.3, 99.1)	(61.4, 95.5)	(0.9, 28.7)
Early Virologic Response[c]				
Responder/Evaluable (%)	9/12 (75.0)	12/12 (100)	10/12 (83.3)	8/12 (66.7)
80% Confidence Interval	(52.5, 90.4)	(82.5, 100.0)	(61.4, 95.5)	(44.1, 84.6)
Complete Early Virologic Response[d]				
Responder/Evaluable (%)	7/12 (58.3)	10/12 (83.3)	10/12 (83.3)	5/12 (41.7)
80% Confidence Interval	(36.2, 78.1)	(61.4, 95.5)	(61.4, 95.5)	(21.9, 63.8)

[a] Undetectable HCV RNA (< 10 IU/mL) at both Weeks 4 and 12.

[b] Undetectable HCV RNA at Week 4.

[c] ≥ 2 $\log_{10}$ HCV RNA decrease from baseline in HCV RNA level or undetectable HCV RNA at Week 12.

[d] Undetectable HCV RNA at Week 12.

Four (4) subjects in the placebo group met the virologic failure criteria: 1 subject with < 1 $\log_{10}$ decrease from baseline at Week 4; 1 subject who failed to achieve EVR; and 2 subjects with detectable HCV RNA at end of treatment. Four (4) subjects in the 3-mg BMS-790052 group met the virologic failure criteria: 2 subjects with virologic breakthrough and 2 subjects with detectable HCV RNA at end of treatment. One subject in the 60-mg BMS-790052 group relapsed at the Week 4 post-treatment follow-up visit after discontinuing treatment due to an AE at Week 8 with undetectable HCV RNA. No subject in the 10-mg BMS-790052 group satisfied the virologic failure criteria.

Safety Results: A summary of safety is presented in Table 5. No BMS-790052 treatment group satisfied the cohort safety stopping rules as specified in the protocol during the 12-week period.

Table 5: Summary of Safety: All Treated Subjects

	Number (%) of Subjects			
	BMS-790052 3 mg (N = 12)	**BMS-790052 10 mg (N = 12)**	**BMS-790052 60 mg (N = 12)**	**Placebo (N = 12)**
Deaths	0	0	0	0
Serious Adverse Events	1 (8.3)	1 (8.3)	1 (8.3)	0
Discontinuation due to Adverse Events	1 (8.3)	0	2 (16.7)	1 (8.3)
Adverse Events	12 (100)	12 (100)	11 (91.7)	12 (100)
Grade 3 or 4 Adverse Events	1 (8.3)	1 (8.3)	2 (16.7)	3 (25%)
Grade 2 to 4 Related AEs	4/12 (33.3)	4/12 (33.3)	7/12 (58.3)	6/12 (50%)

As of database lock on 18-Dec-2009, the data cut-off for this analysis, no deaths were reported. SAEs were reported for 3 subjects, 1 in each of the 3-, 10-, and 60-mg BMS-790052 dose groups. One subject in the 3-mg BMS-790052 group was hospitalized during Week 4 because of severe epistaxis requiring transfusion, severe anemia, severe chest pain, and mild syncope. The anemia and epistaxis were considered related to study drugs, and the chest pain and syncope were considered unrelated. Study medication was interrupted for 5 days, and restarted with a lower dose of RBV with no further recurrence of the events. One subject in the 10-mg BMS-790052 group was hospitalized during Week 20 in Mexico with symptoms of gastroenteritis and an episode of severe syncope that were considered unrelated to study drugs. The subject was discharged the following day. No interruption of study medication occurred. One subject in the 60-mg BMS-790052 group was hospitalized during Week 6 with acute bronchitis considered unrelated to study drugs. Treatment with BMS-790052 and RBV were interrupted for 4 days. The subject later discontinued due to worsening of baseline anxiety during Week 8.

AEs that led to discontinuation included mild fatigue, irritability, ageusia, disturbance in attention, headache and auditory hallucinations in 1 subject (3-mg); moderate anxiety (60-mg); moderate generalized rash (60-mg) and mood swings (placebo).

The most commonly reported AEs in all treatment groups were fatigue and nausea. Most AEs were Grade 1 or 2 in intensity; no Grade 4 AEs were reported. There were no clinically relevant trends in AEs through Week 12. The most common Grade 2 to 4 related AEs were asthenia, neutropenia, and fatigue. Most of the Grade 2 to 4 related AEs were Grade 2 in intensity; no Grade 4 related AEs were reported.

No clinically relevant trends in laboratory abnormalities were observed. The most common laboratory abnormalities were hematologic abnormalities consistent with those seen with pegIFNα/RBV. Most laboratory abnormalities were Grade 1 or 2; 2 subjects in the placebo group had Grade 4 neutropenia. Erythropoietin use was allowed in this study; however, only 7 subjects reported the use of this drug for treatment-associated anemia: 1 in the 3-mg BMS-790052 group and 2 subjects in each of the 10-mg BMS-790052, 60-mg BMS-790052 and placebo groups. Only 4 subjects reported the use of filgrastim for treatment-associated neutropenia (1 in each of the 3-mg and 10-mg BMS-790052 groups and 2 in the placebo group). Improvement in ALT from baseline was observed in all treatment groups. The median decrease in ALT from baseline ranged from 22 to 39 U/L at Week 12 for the BMS-790052 groups compared to 8.5 U/L for the placebo group.

Several subjects in each of the BMS-790052 and placebo groups had QTc intervals > 450 msec reported pre-treatment and/or during treatment; QT prolongation (QTc(B): 472 msec; QTc(F): 443 msec) was

reported as an AE in 1 subject in the 60 mg BMS-790052 dose group (baseline values: QTc(B): 450 msec, QTc(F): 443 msec). No subjects discontinued due to an abnormal ECG.

CONCLUSIONS: This study represents the first demonstration that BMS-790052, a novel, first-in-class NS5A inhibitor combined with pegIFNα/RBV, can achieve significant antiviral suppression of HCV genotype 1, based on the following observations:

- Safety results demonstrated that BMS-790052 plus pegIFNα/RBV is well tolerated through 12 weeks at doses up to 60 mg as no significant findings in the key safety endpoints of death, SAEs, or discontinuation due to AEs were reported. Additional safety and antiviral activity data will be needed to confirm the findings of this Week 12 analysis.
- Antiviral activity of BMS-790052 plus pegIFNα/RBV was demonstrated by eRVR and RVR rates that were higher in the 10-mg and 60-mg BMS-790052 groups compared to placebo at Week 12, and by EVR rates which were greater in the 3-mg, 10-mg and 60-mg BMS-790052 groups compared to placebo at Week 12.
- HCV RNA suppression is durable through Week 12 for subjects who adhered to treatment; no cases of virologic breakthrough occurred in any subject who achieved undetectable HCV RNA and adhered to treatment.
- BMS-790052 doses of 10 mg and 60 mg appear to have activity in subjects with baseline demographic and virologic characteristics that are typically associated with sub-optimal treatment responses to pegIFNα/RBV therapy. The sample sizes of these study populations are too small to draw definitive conclusions, and larger studies are needed to evaluate the impact of baseline subject characteristics on response to therapy.
- Based on the efficacy and safety results from this Week 12 primary analysis, the continued evaluation of doses between 10 mg to 60 mg BMS-790052 combined with pegIFNα/RBV is warranted in subsequent Phase 2b studies.

DATE OF REPORT: 05-Nov-2010