Boceprevir Plus Peginterferon/Ribavirin for the Treatment of HCV/HIV Co-Infected Patients: End of Treatment (Week 48) Interim Results

J Mallolas[1], S Pol[2], A Rivero[3], H Fainboim[4], C Cooper[5], J Slim[6], S Thompson[7], J Wahl[7], W Greaves[7], M Sulkowski[8]

[1]Hospital Clinic-University of Barcelona, Barcelona, Spain; [2]Universite Paris Descartes, APHP, Hopital Cochin, Paris, France; [3]University Hospital Reina Sofia, Córdoba, Spain, [4]Muñiz Hospital, Buenos Aires, Argentina; [5]University of Ottawa, Ottawa, ON, Canada; [6]Saint Michael's Medical Center, Newark, NJ; [7]Merck Sharp & Dohme, Whitehouse Station, NJ; [8]John Hopkins University School of Medicine, Baltimore, MD.

Abstract #366
International Liver Congress 2012
47th Annual Meeting of the European Association for the Study of the Liver
Barcelona, Spain
April 20, 2012

Background

- Approximately one-third of all HIV-infected individuals are coinfected with HCV
  - HIV/HCV coinfected patients have increasing morbididty and mortality due to liver disease

- Boceprevir is an HCV-NS3/4A protease inhibitor that binds to the active site of the protease
  - Boceprevir plus PegIFN/RBV showed improved efficacy compared to PegIFN/RBV alone in HIV uninfected patients with chronic HCV genotype 1 infection who were previously untreated or who had failed prior treatment

PEG/RBV, peginterferon alfa/ribavirin.

Study Objectives

- **Primary Objective:**
  - To compare the efficacy of boceprevir plus PEG2b/RBV (B/PR) to PEG2b/RBV (PR) alone in previously untreated Genotype 1, chronic HCV patients coinfected with HIV

- **Secondary Objectives:**
  - To evaluate the safety of B/PR
  - To define predictors of SVR such as epidemiologic factors, disease characteristics and on-treatment response
  - To assess the steady state PK of boceprevir using population-based pharmacokinetic modeling

PK, pharmacokinetics; SVR, sustained virologic response.

Study Methods

- Key inclusion criteria
  - Male/female patients, 18 to 65 years of age
  - Chronic HCV Genotype 1
  - Previously untreated for HCV
  - Liver biopsy within 2 years unless prior cirrhosis
  - CD4 ≥200 cells/mm^3, HIV RNA <50 copies/mL (on ART)
- Key exclusion criteria
  - Decompensated cirrhosis or coinfection with HBV
  - Use of zidovudine (AZT), didanosine (ddI), stavudine (d4T), efavirenz, etravirine, or nevirapine
  - Labs
    - Hemoglobin <11 g/dL for females, <12 g/dL for males
    - Neutrophils <1500/mm^3 (<1200/mm^3 for blacks)
    - Platelets <100,000/mm^3

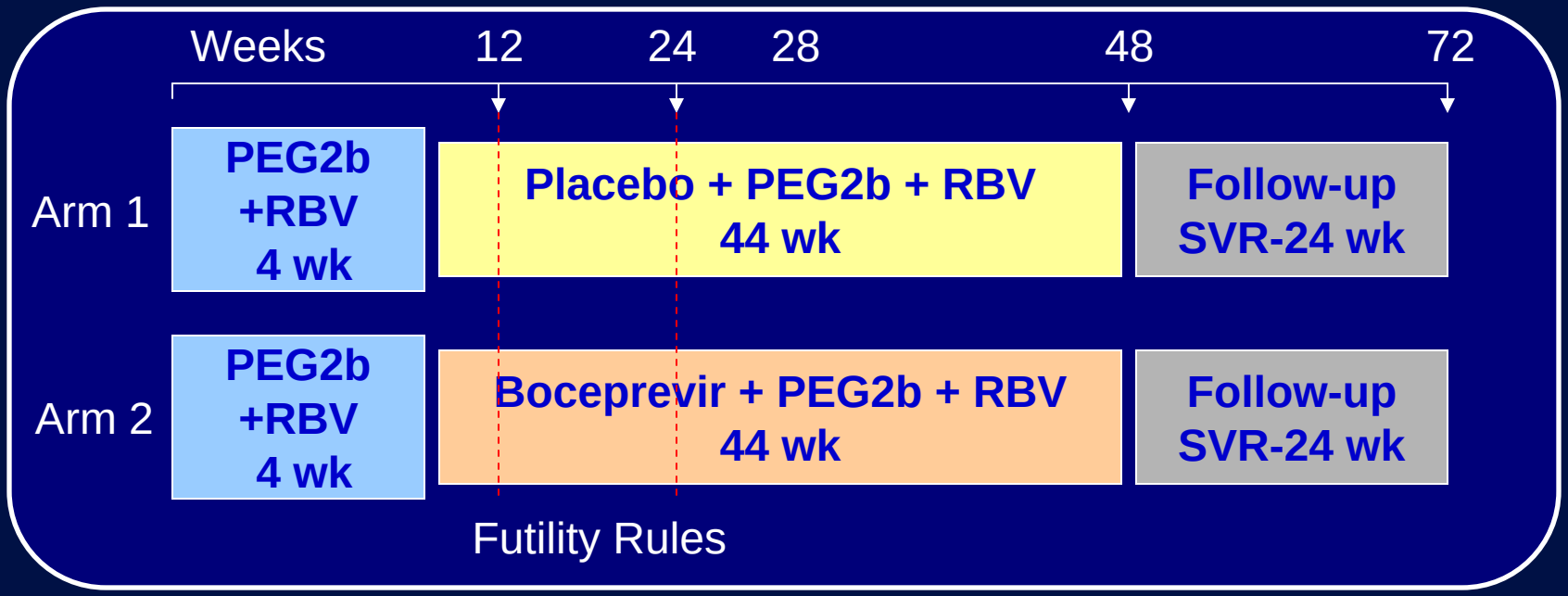
HBV, hepatitis B virus

Study Methods (cont)

- Interim analysis based on patients who received ≥1 dose of study drug (PR, n=34; B/PR, n=64)
  - Assessment of SVR-12 excludes 3 patients who are at FW4 and have not yet reached FW12
  - Primary efficacy endpoint (SVR-24) is not assessed
- Assessments
  - HIV RNA and CD4: TW 4, 12, 24, EOT, FW4, FW12
  - HCV RNA: TW 4, 8, 12, 16, 24 and EOT, FW4, FW12
  - % HCV undetectable at TW 4, 8, 12, 16, 24, EOT, FW12
- Futility Rules
  - TW 12: Detectable HCV RNA and <2 $\log_{10}$ decline
    - Roche COBAS® TaqMan® v 2.0, LOD = 9.3 IU/mL
  - TW 24: HCV RNA $\geq$LLOQ
    - Roche COBAS® TaqMan® v 2.0, LLOQ = 25 IU/mL

LOD, limit of detection; LLOQ, lower limit of quantitation; TW, treatment week.

Study Design



- Two-arm study, double-blinded for BOC, open-label for PEG2b/RBV
  - 2:1 randomization (experimental: control)
  - Boceprevir dose 800 mg TID
- 4-week lead-in with PEG2b/RBV for all patients
  - PEG-2b 1.5 µg/kg QW; RBV 600-1400 mg/day divided BID
- Control arm patients with HCV-RNA ≥ LLOQ at TW 24 were offered open-label PEG2b/RBV+BOC via a crossover arm

Demographics and Baseline Characteristics

	PR (N=34)	B/PR (N=64)
Age (years), mean (SD)	45 (9.8)	43 (8.3)
Male, n (%)	22 (65)	46 (72)
Race, n (%)		
White	28 (82)	52 (81)
Non-white	6 (18)	12 (19)
Body mass index, mean (SD)	26 (4)	25 (4)
Cirrhosis, n (%)	1 (3)	4 (6)
HCV genotype subtype, n (%)*		
1a	22 (65)	42 (66)
1b	10 (29)	15 (23)
HCV RNA level >800,000 IU/mL, n (%)	30 (88)	56 (88)
HIV RNA <50 copies/mL, n (%)	33 (97)	62 (97)
CD4 count (cells/mm^3), median (range)	586 (187-1258)	577 (230-1539)

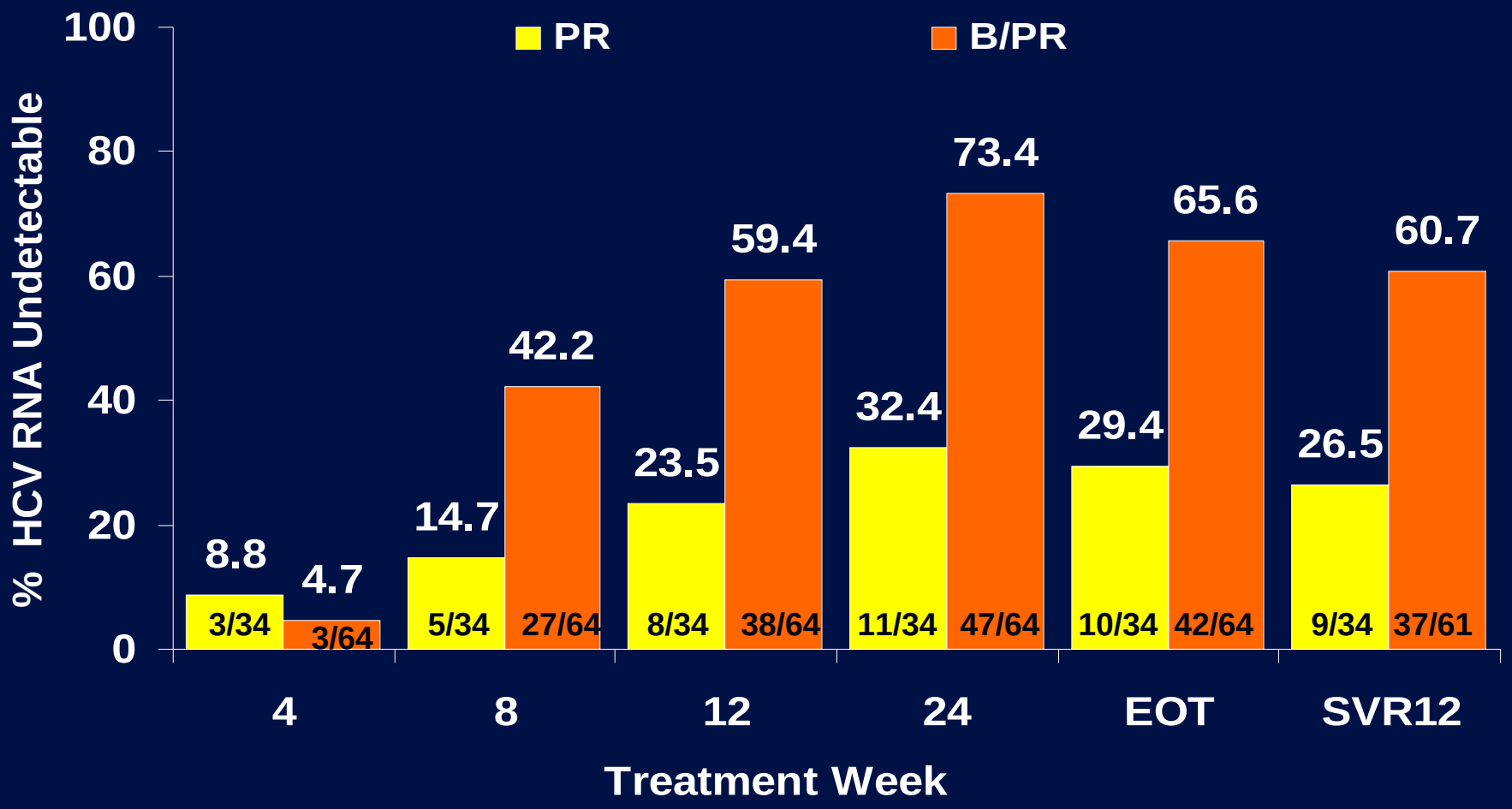
*Subtyping not reported for 9 patients with Genotype 1.

Patient Disposition

	PR (N=34)	B/PR (N=64)
Treated	34 (100)	64 (100)
Discontinued during treatment phase	18 (53)	24 (38)
Adverse event	3 (9)	13 (20)
Treatment failure	14 (41)	6 (9)
Lost to follow up	0	1 (2)
Did not wish to continue	1 (3)	3 (5)
Non-compliance with protocol	0	1 (2)
Completed treatment phase	12 (35)	40 (63)
Ongoing	0	0
Entered crossover	4 (12)	-

All data shown as number (%) of patients.

Virologic Response Over Time†



† Three patients undetectable at FW4 have not yet reached FW12 and were not included in SVR12 analysis.

SVR-12 by ARV Regimen on Day 1

	PR (N=34)	B/PR (N=61)
Atazanavir/r	8/13 (62%)	12/18† (67%)
Lopinavir/r	0/10 (0%)	10/15†† (67%)
Darunavir/r	0/5 (0%)	8/12 (67%)
Other PI/r*	0/3 (0%)	4/7 (57%)
Raltegravir**	1/3 (33%)	3/7 (43%)
Other¶	0	0/2 (0%)

†Excludes 2 patients not yet at FW12 but undetectable at FW4 and †† 1 not yet at FW12 but undetectable at FW4.

*Includes saquinavir, fosamprenavir and tipranavir

**Raltegravir without concurrent HIV PI/r

¶Other ARVs were maraviroc or efavirenz plus emtricitabine+tenofovir

HIV Breakthroughs in B/PR Group

- Overall, 7 patients had HIV breakthrough (>50 copies HIV RNA at 2 consecutive visits): 3/64 randomized to B/PR, and 4/34 to PR

Regimen	HIV RNA (copies/mL)						
	BL	TW4	TW12	TW24	TW36	EOT	FW4
ATV/r	<50	<50	---	659	---	53	2990
†LPV/r	<50	<50	<50	55	59	67	68
ATV/r	<50	<50	<50	<50	243	---	7870

ATV/r, atazanavir/ritonavir; LPV/r, lopinavir/ritonavir

†The only subject to change ART. LPV/r changed to ATV/r at TW42; ATV/r to DRV/r at FW24.

Summary of Safety

	PR (N=34)	B/PR (N=64)
Any AE	34 (100)	63 (98)
Serious AEs	7 (21)	11 (17)
Death	0	0
Treatment-related treatment-emergent AEs	34 (100)	61 (95)
Study discontinuation due to an AE	3 (9)	13 (20)
Any drug modification due to an AE	8 (24)	18 (28)

All data shown as number (%) of patients.

Most Common Adverse Events With a Difference of ≥10% Between Groups

	PR (N=34)	B/PR (N=64)
Anemia	26%	41%
Pyrexia	21%	36%
Asthenia	24%	34%
Decreased appetite	18%	34%
Diarrhea	18%	28%
Dysgeusia	15%	28%
Vomiting	15%	28%
Flu-like illness	38%	25%
Neutropenia	6%	19%

Hematologic Adverse Events

	PR (N=34)	B/PR (n=64)
Anemia		
SAEs	6%	3%
AEs leading to discontinuation	3%	2%
WHO, Grade 1-4 (<11.0 g/dL)	53%	63%
Grade 3-4 (<8.0 g/dL)	3%	5%
Erythropoietin use	21%	38%
Transfusions	6%	6%
Neutropenia		
WHO, Grade 1-4 (≤1.5x10^9/L)	74%	86%
Grade 3-4 (<0.75x10^9/L)	12%	27%

Interim Analysis Summary

- HCV-HIV co-infected patients who were previously untreated had higher rates of HCV response on BOC
  - SVR-12: 61% of patients on B/PR had undetectable HCV RNA vs. 27% of patients on PR
- Preliminary safety data of B/PR in co-infected patients is consistent with that observed in mono-infected patients
- HIV Breakthroughs were observed in 3/64 patients in the BOC group and 4/34 patients in the control group
- Further studies with ARVs and boceprevir are planned in collaboration with the AIDS Clinical Trials Group (ACTG)

Acknowledgements

We thank the patients who participated in this international study

France
Stanislas Pol
Christine Katlama
Laurent Cotte
Germany
Stefan Mauss
Lutwin Wietner
Christian Hoffman
Spain
Josep Mallolas
Antonio Rivero Roman
Juan Antonio Pineda Vergara
Argentina
Hugo Fainboim
Brazil
Carlos Eduardo Brandão

USA
Jihad Slim
Kenneth Sherman
Robert Schooley
David Wyles
Mark Sulkowski
Raymond Chung
Jay Kostman
Ben Maliakkal
Richard Sterling
Andrew Talal
Eliot Godofsky
Canada
Curtis Cooper
Stephen Shafran

Belgium
Jean-Christophe Moreno
Eric Florence
Italy
Giampiero Carosi
Adriano Lazzarin
Portugal
Manuela Doroana
Rui Sarmento e Castro
Poland
Waldemar Halota
Andrzel Horban
Netherlands
Andy Hoepelman