

Frequencies of Resistance-Associated Amino Acid Variants Following Combination Treatment with Boceprevir Plus PEGINTRON (PegInterferon Alfa-2b)/Ribavirin in Patients With Chronic Hepatitis C (CHC), Genotype 1 (G1)

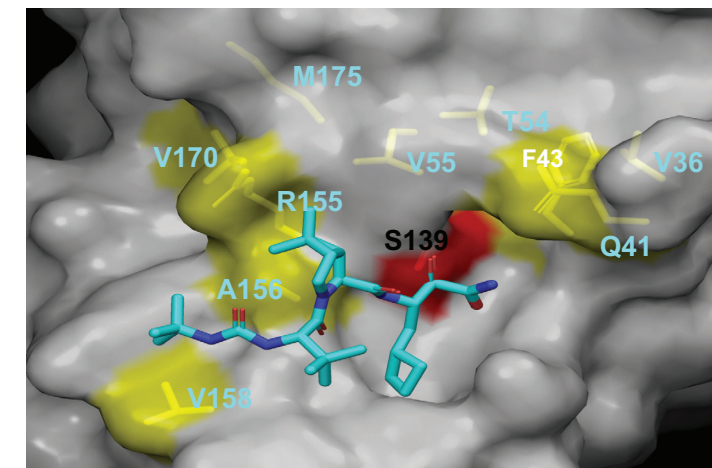
John M. Vierling¹, Paul Y. Kwo², Eric J. Lawitz³, Jonathan McCone⁴, Eugene R. Schiff⁵, David Pound⁶, Mitchell N. Davis⁷, Joseph S. Galati⁸, Stuart C. Gordon⁹, Natarajan Ravendhran¹⁰, Lorenzo Rossaro¹¹, Frank H. Anderson¹², Ira M. Jacobson¹³, Raymond Rubin¹⁴, Lisa D. Pedicone¹⁵, Eirum Chaudhri¹⁵, Xiao Tong¹⁵, Ping Qiu¹⁵, Richard J.O. Barnard¹⁵, Clifford A. Brass¹⁵, Janice K. Albrecht¹⁵, Patricia Mendez¹⁵, and Robert Ralston¹⁵

¹Baylor College of Medicine, Houston, TX; ²Indiana University School of Medicine, Indianapolis, IN; ³Alamo Medical Research, San Antonio, TX; ⁴Mt. Vernon Endoscopy Center, Alexandria, VA; ⁵University of Miami, Miami, FL; ⁶Indianapolis Gastroenterology Research Foundation, Indianapolis, IN; ⁷DigestiveCARE-South Florida Center of Gastroenterology, Wellington, FL; ⁸Liver Specialists of Texas, Houston, TX; ⁹Henry Ford Hospital, Detroit, MI; ¹⁰University of Maryland Medical System and Digestive Disease Associates, Baltimore, MD; ¹¹University of California-Davis Medical Center, Sacramento, CA; ¹²Liver and Intestinal Research Centre, Vancouver, British Columbia, Canada; ¹³Weill Cornell Medical College, New York, NY; ¹⁴Liver Center of Atlanta, Atlanta, GA; ¹⁵Merck, Whitehouse Station, NJ

Background

- Chronic Hepatitis C Virus (HCV) Infection and Therapy:
 - Nearly 180 million people are chronically infected with hepatitis C virus (HCV) worldwide.¹
 - Standard-of-Care treatment of HCV is combination therapy with pegylated interferon and ribavirin.^{2,4}
 - Of the six major HCV genotypes, genotype 1 is the least responsive to currently approved therapies, with sustained virologic response rates of less than 50%.^{2,5-7}
- Direct Acting Antiviral Therapy:
 - The investigational focus for treatment of HCV has shifted toward direct acting antiviral therapy (Figures 1 and 2).⁸⁻¹¹
 - Boceprevir (SCH503034) is a structurally novel, peptidomimetic ketoamide protease inhibitor that binds reversibly to the HCV NS3 active site (Figure 3).⁸
- HCV SPRINT-1 (Serine Protease Inhibitor Therapy-1) Clinical Trial
 - A Phase 2 study conducted in patients with chronic hepatitis C genotype 1 who were treatment-naïve. The primary objective was to determine the safety and efficacy of boceprevir when added to peginterferon and ribavirin.¹²
 - The SPRINT-1 study included an analysis of amino acid variants associated with differential response to boceprevir

Figure 3. HCV NS3/4A Protease Residues Associated with Boceprevir Resistance



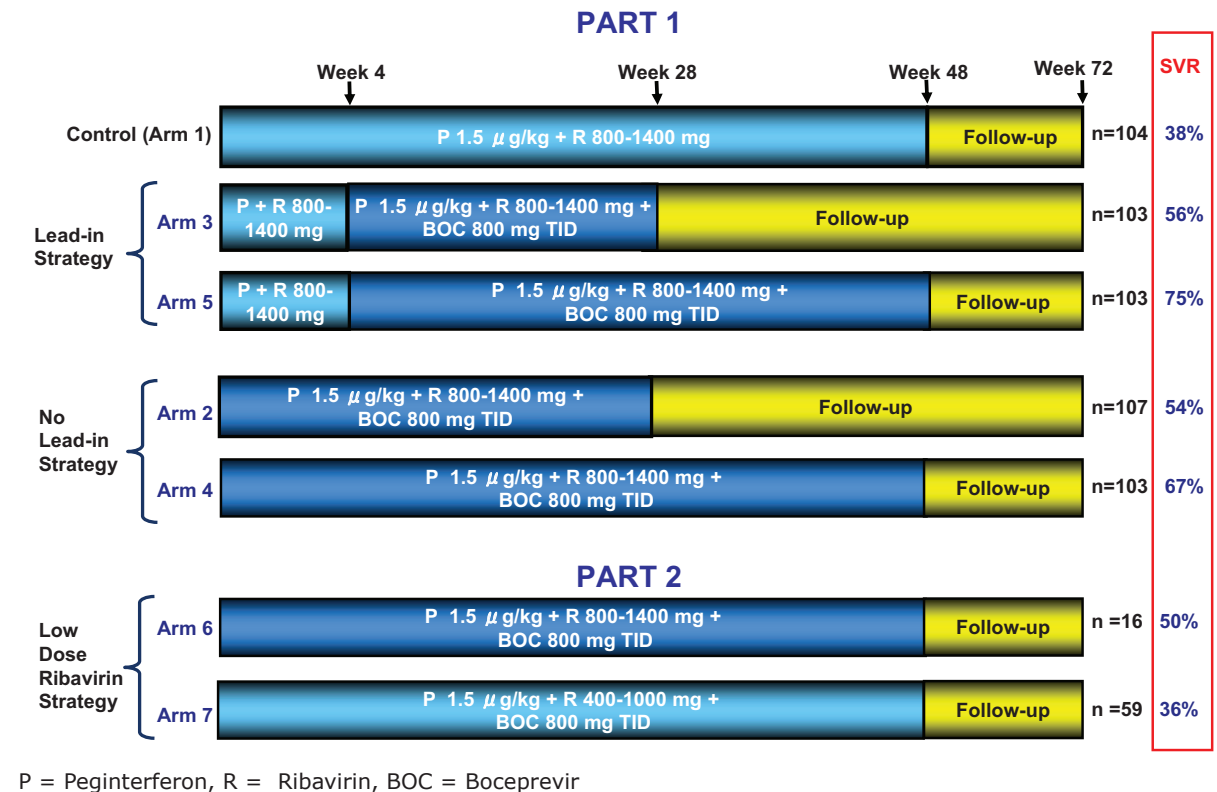
Adapted from Taremi et al. Protein Science (1998)

3D crystallographic model of boceprevir binding in the HCV NS3/4A protease binding pocket. Boceprevir resistance associated variants (RAVs) are highlighted by amino acid number. RAVs that appear at the surface of the binding pocket are highlighted in yellow. Boceprevir binds covalently to amino acid S139, highlighted in red.

Methods

- SPRINT-1 Study
 - Previously untreated adults with genotype 1 HCV were enrolled across the United States, Canada, and European Union
 - Two-part, open-label trial (Figure 4)
 - Part 1** - 520 patients randomized to receive peginterferon plus ribavirin for 48 weeks (control) or one of four boceprevir regimens
 - Part 2** - 75 patients randomized to receive peginterferon and low-dose ribavirin to evaluate the possibility of using a lower dose of ribavirin to reduce complications associated with anemia
 - Arms 2 and 3 of Part 1 received a 4 week lead-in with peginterferon/ribavirin prior to the addition of boceprevir to:
 - Achieve steady state of peginterferon/ribavirin prior to adding 3rd drug
 - Upregulate immune response elements
 - Decrease viral load and quasispecies, thereby decreasing resistance
- Virological Testing:
 - HCV-RNA was detected using Roche Taqman (LLD <15 IU/mL)
 - Amino acid variants at boceprevir resistance loci in the NS3/4A protease were detected using population sequencing
 - Baseline samples - any sample obtained prior to receiving any study medication - were obtained from all subjects
- Definitions
 - Sustained Virologic Response (SVR): Plasma HCV-RNA level below the lower limit of detection at follow-up week 12
 - Incomplete Virologic Response (IVR): A $\geq 2 \log_{10}$ increase in HCV-RNA viral load compared with the previous two visits and HCV viral load $\geq 50,000$ IU/mL
 - Viral Breakthrough (BT): Undetectable HCV-RNA and subsequent HCV-RNA $\geq 2 \log_{10}$ elevation during therapy
 - Relapser (RL): Undetectable HCV-RNA at end of treatment and detectable HCV-RNA at follow-up week 24
 - Nonresponder (NR) (treatment failure):
 - Subjects in Arm 1 with detectable HCV-RNA at treatment week 24 who crossed over to boceprevir
 - Subjects in any of the seven treatment arms with detectable HCV-RNA at end of therapy and at follow-up week 24
 - Subjects in any of the seven treatment arms with missing HCV-RNA values at follow-up week 24 and do not have an undetectable HCV-RNA at follow-up week 12

Figure 4. SPRINT-1 Study Design and Sustained Virologic Response¹²



P = Peginterferon, R = Ribavirin, BOC = Boceprevir

Purpose

- To determine factors associated with a differential frequency of resistance associated variants (RAVs) in the SPRINT-1 study

Hypotheses

- Specific baseline amino acid variants in NS3/4A are associated with differential antiviral activity of boceprevir
- Specific post-baseline amino acid variants in NS3/4A are associated with differential antiviral activity of boceprevir

Figure 1. Life Cycle of HCV and Potential Direct Acting Antiviral (DAA) Targets

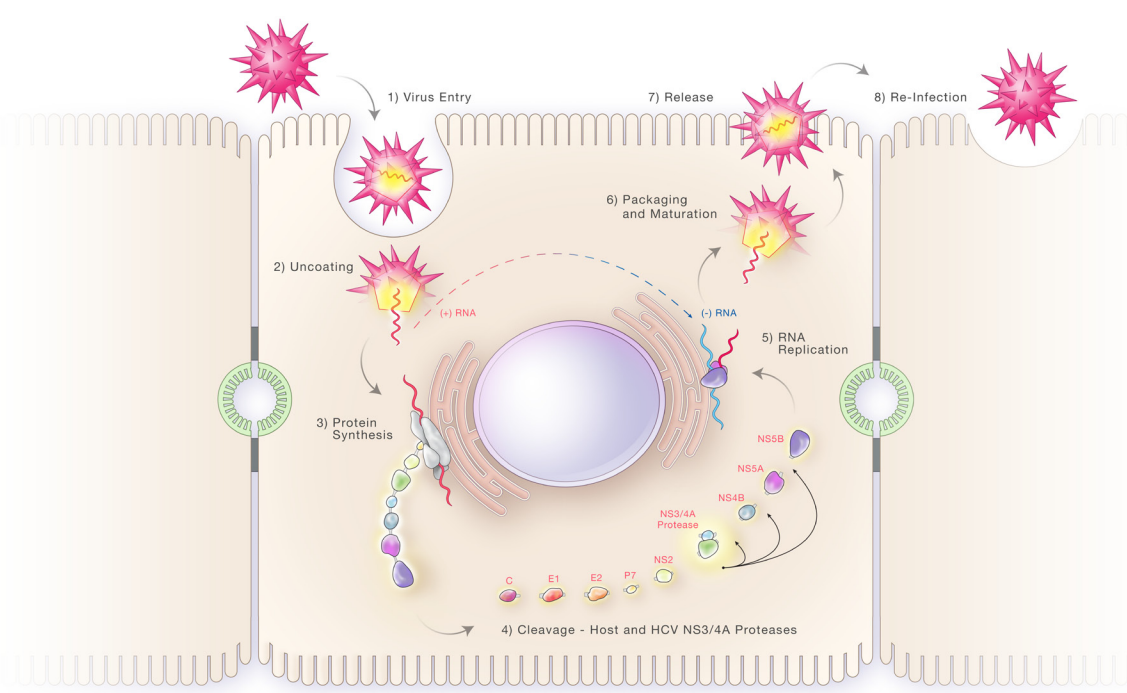
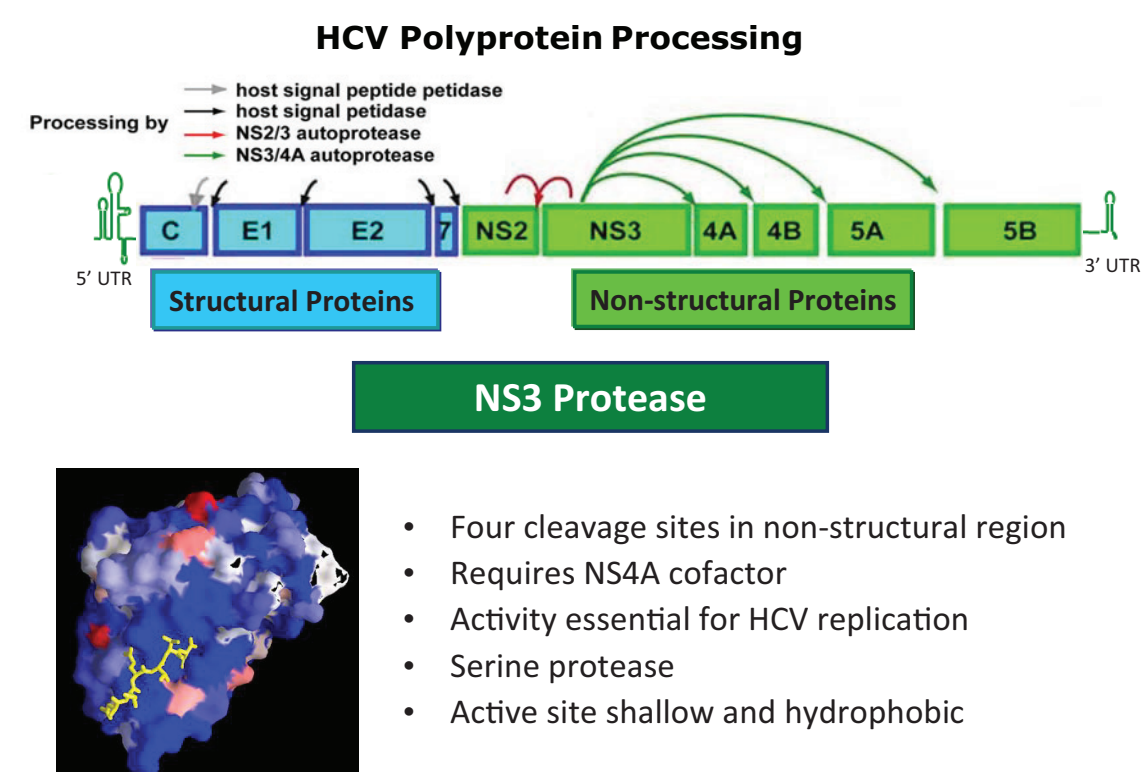


Figure 2. Direct Acting Anti-viral Therapy Targeting the Viral NS3 Protease



- Four cleavage sites in non-structural region
- Requires NS4A cofactor
- Activity essential for HCV replication
- Serine protease
- Active site shallow and hydrophobic

Results

Figure 6. Number of Subjects Having RAVs Detected Post-baseline, Including All Patients Treated with Boceprevir

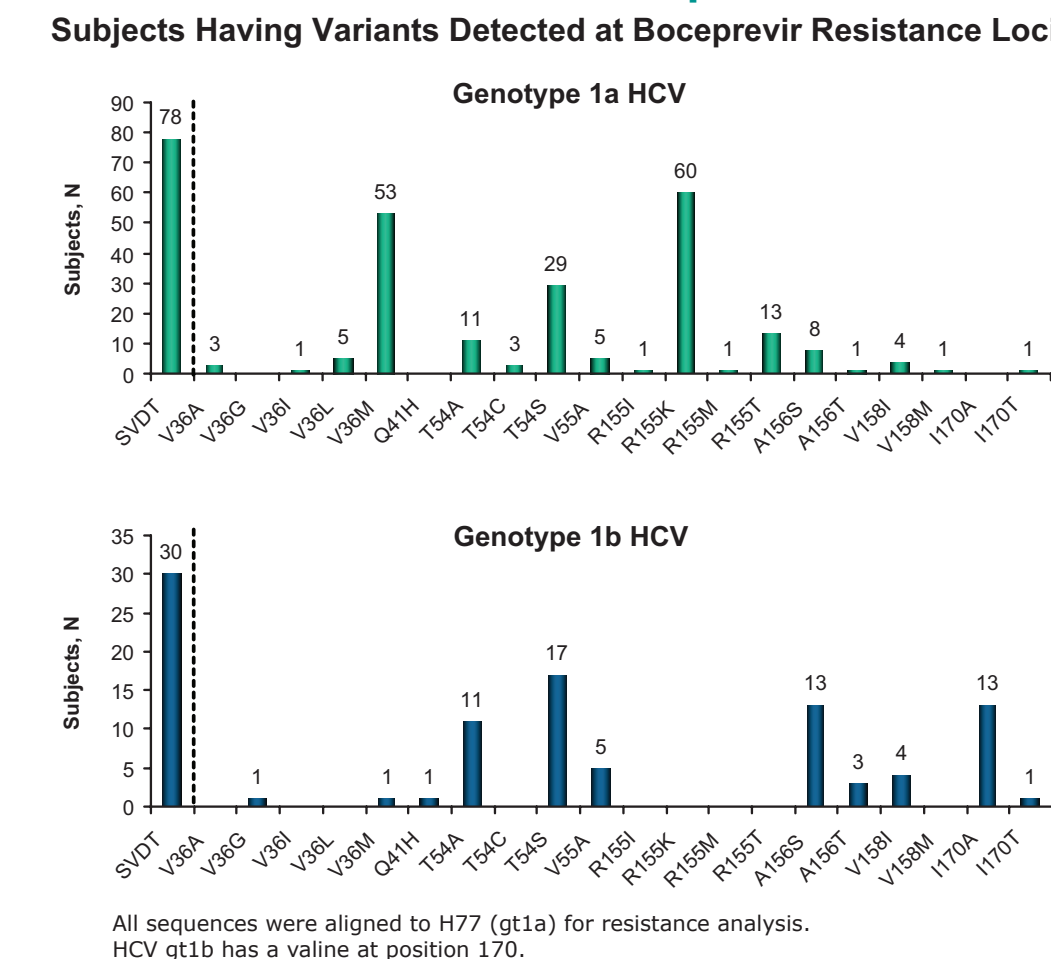
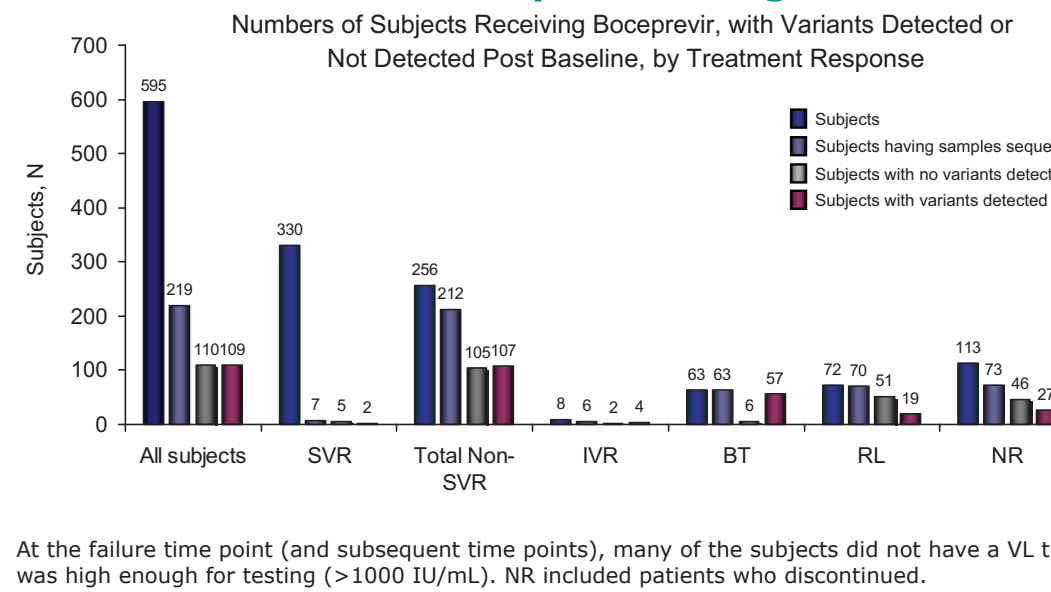
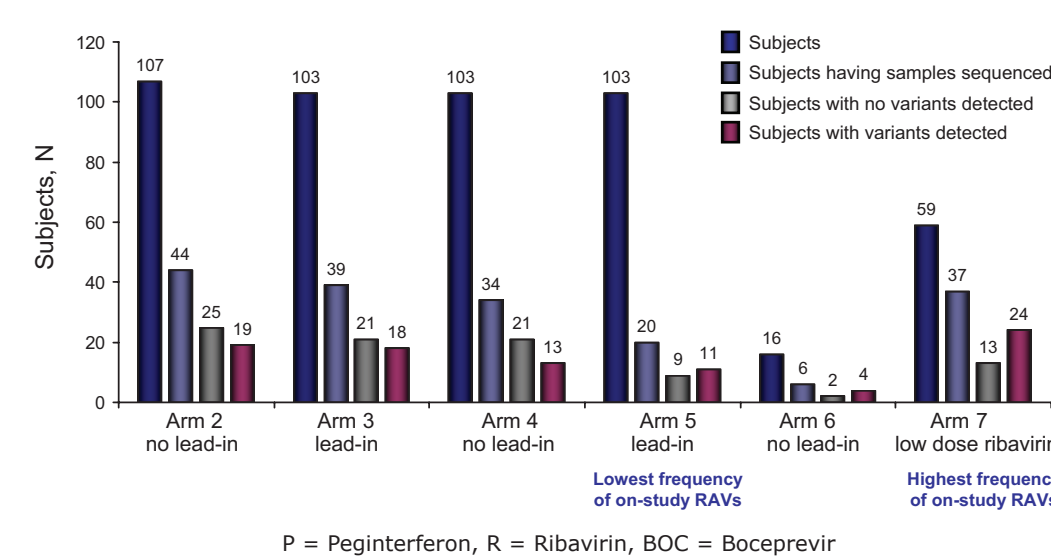


Figure 7. Frequency of RAVs for Different Treatment Response Categories



At the failure time point (and subsequent time points), many of the subjects did not have a VL that was high enough for testing (>1000 IU/mL). NR included patients who discontinued.

Figure 8. Frequency of RAVs by Study Arm



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Disclosure

JMV has received research grants from Abbott, Conatus, Excalenz, Gilead, GlobetImmune, Hyperion, Idenix-Novartis, Intercept, Merck, Schering-Plough (now part of Merck), Novartis, Ocera, Pharmasset, Pfizer, Sunovion, Vertex, and Zymogenetics; and is on the speakers' bureau for Bristol Myers Squibb, Chromosom, Schering-Plough, Gilead, Roche, and Merck.

Figure 9A. RAVs Detected with No Lead-in (Arm 2) vs. Lead-in (Arm 3) Study Arms (i.e. Arms where Patients Received a Shorter Duration of Treatment with Boceprevir)

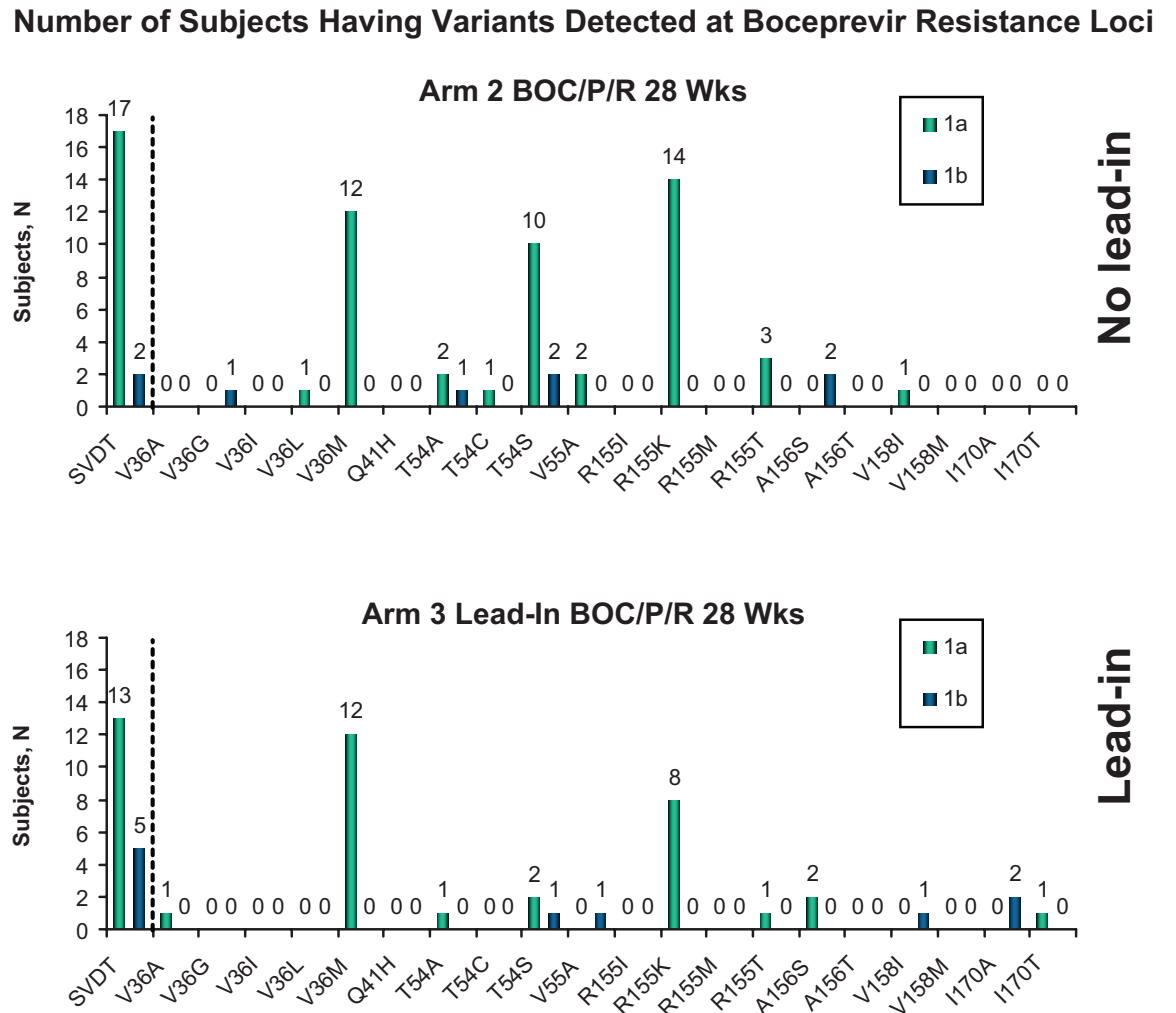
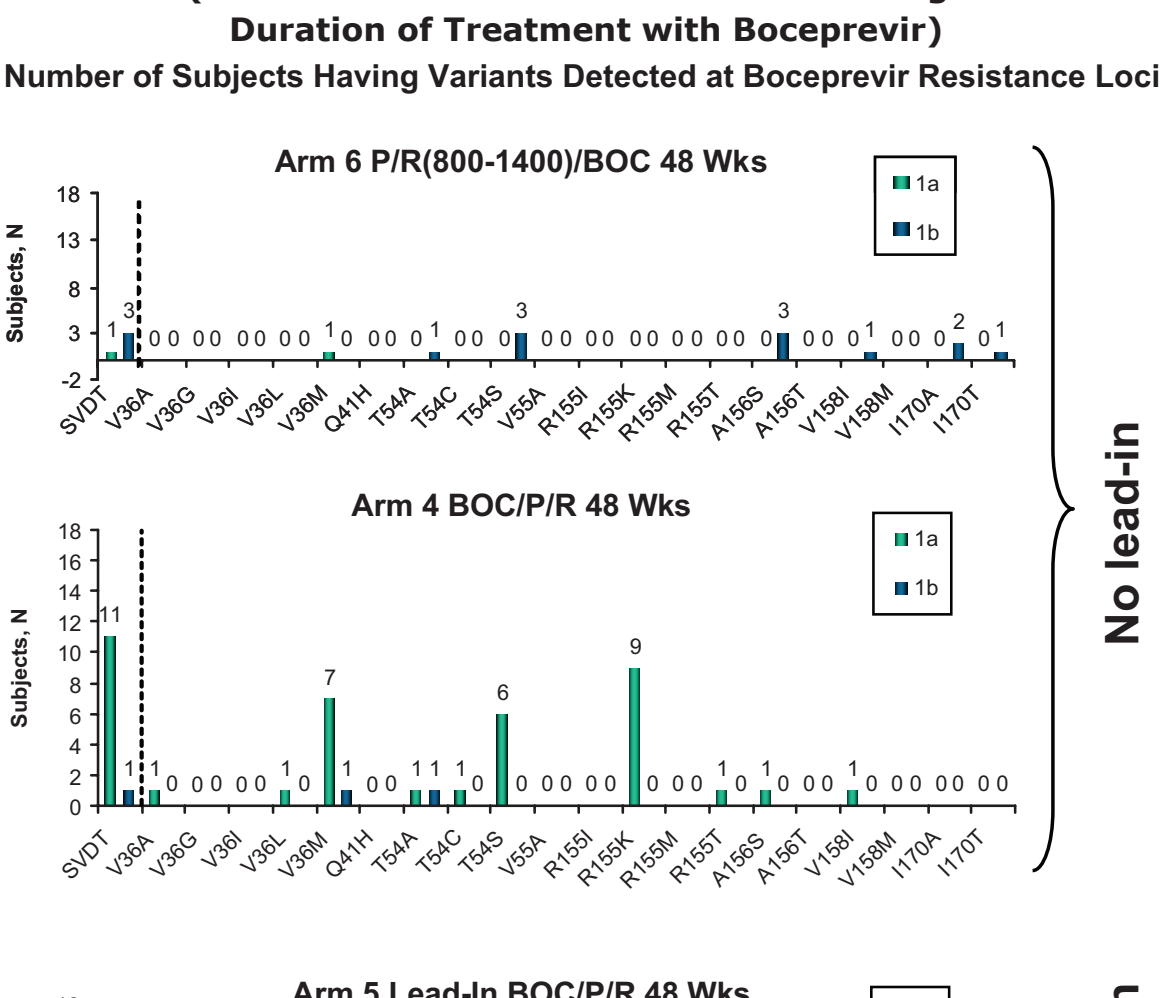


Figure 9B. RAVs Detected with No Lead-in (Arms 4 and 6) vs. Lead-in (Arm 5) Study Arms (i.e. Arms where Patients Received a Longer Duration of Treatment with Boceprevir)



Conclusions

- In SPRINT-1, combination therapy with boceprevir and peginterferon plus ribavirin increased SVR rates with shorter treatment durations.
- The most common RAVs in genotype 1a patients not achieving SVR were V36M, T54S, and R155K.
- The most common RAVs in genotype 1b patients not achieving SVR were T54A, T54S, A156S, and V170A.
- In subjects with detectable RAVs at baseline, the majority achieved SVR.
- Lead-in therapy may reduce the frequency of on-study RAVs, especially T54S.