Prevalence of Pre-Treatment NS5A Resistance Associated Variants in Genotype 1 Patients Across Different Regions Using Deep Sequencing and Effect on Treatment Outcome with LDV/SOF

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Objectives

In genotype 1 HCV-infected patients naïve to NS5A inhibitors:

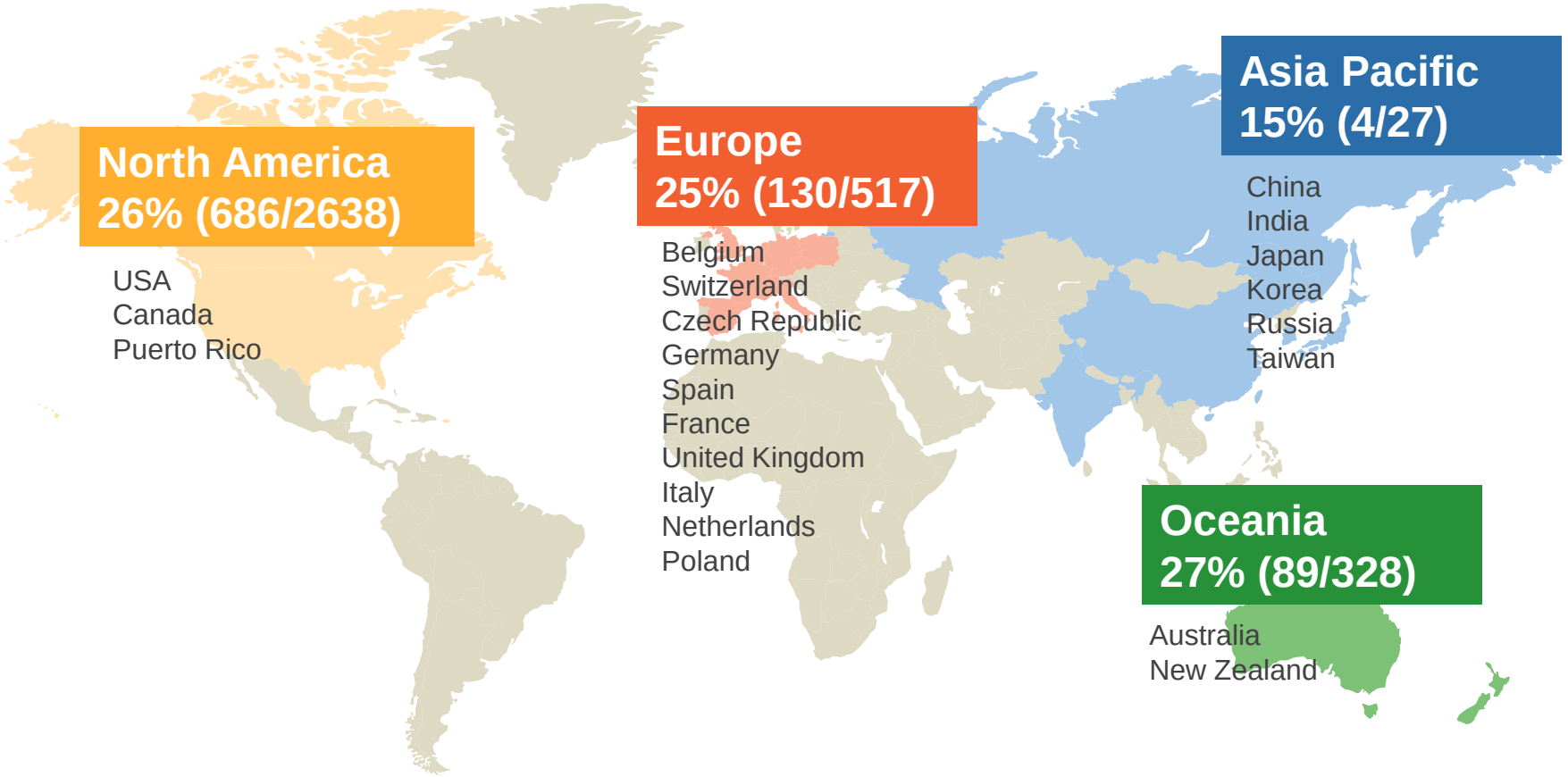
- To characterize baseline NS5A RAVs according to geographic regions
- To assess the effect of baseline NS5A RAVs on treatment outcome among patients treated with currently recommended LDV/SOF regimens

Methods

- Deep sequencing* of baseline samples was performed in 5,397 patients from 21 countries across HCV Gilead clinical trials from 2010 to 2015
- NS5A RAVs at positions 24, 28, 30, 31, 32, 58, 93 that confer >2.5-fold reduced susceptibility to NS5A inhibitors in vitro as tested in genotype 1a and 1b replicons
- IL28B genotype was determined by PCR amplification of the SNP, rs12979860
- SVR12 rates of 1,566 patients who were treated with guideline recommended regimens** in LDV/SOF clinical trials were analyzed according to NS5A RAVs and IL28B status

* 1% cut-off
**according to AASLD/IDSA, EASL guidelines

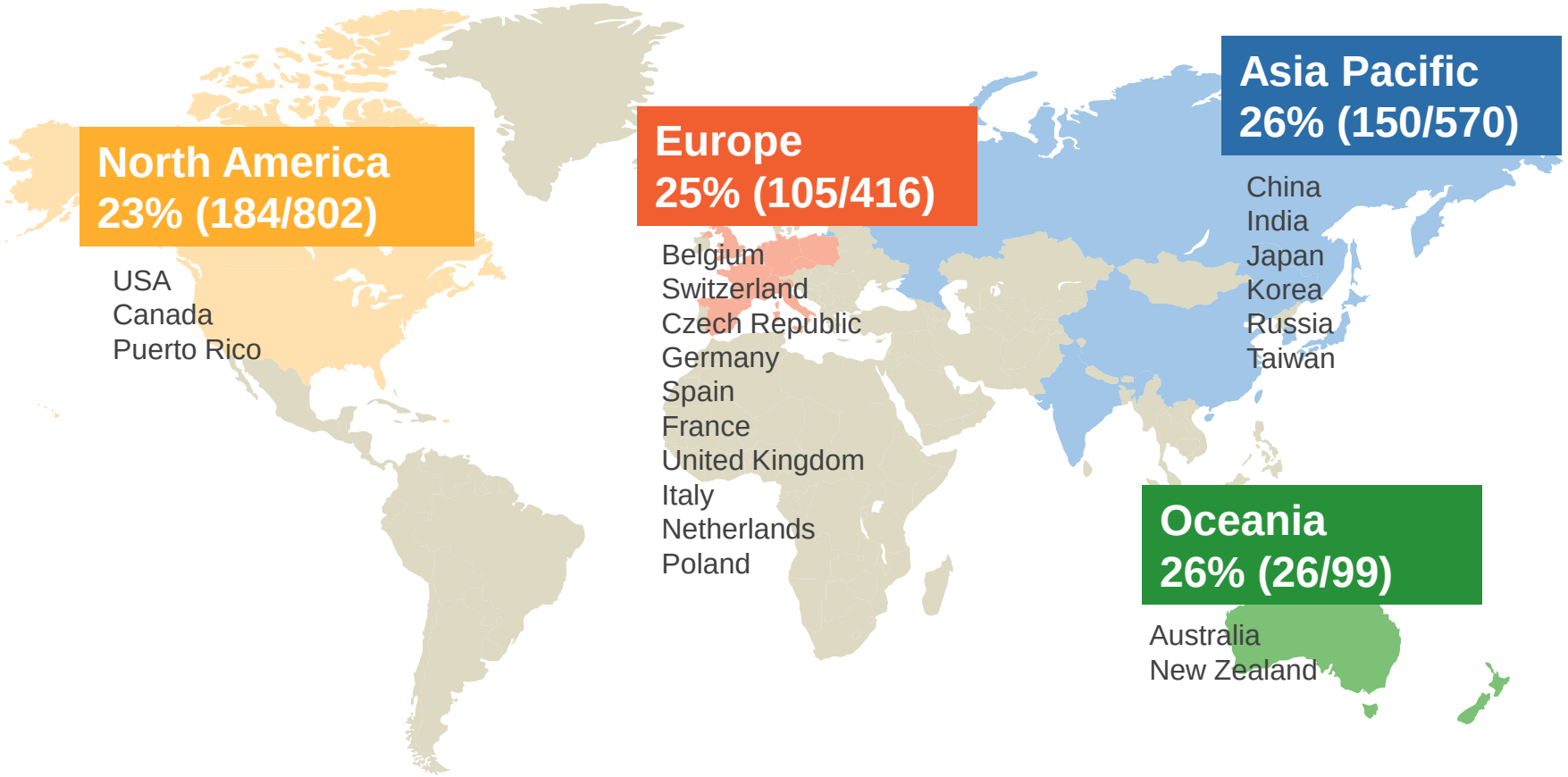
Results: GT 1a NS5A RAV Prevalence by Region (1% Cut-Off)



- Using a 15% cut-off (akin to population sequencing), the prevalence of NS5A RAVs was 13% in North America, 14% in Europe; 7% in Asia Pacific, 16% in Oceania

GT1a NS5A RAVs: K24G/N/R, K26E, M28A/G/T/V, Q30C/E/G/H/I/L/K/R/S/T/Y, L31I/F/M/V, P32L, S38F, H58D/L, A92K/T, Y93C/F/H/L/N/R/S/T/W

Results: GT 1b NS5A RAV Prevalence by Region (1% Cut-Off)



- Using a 15% cut-off, prevalence of NS5A RAVs was 16% in North America, 17% in Europe; 20% in Asia Pacific, 19% in Oceania

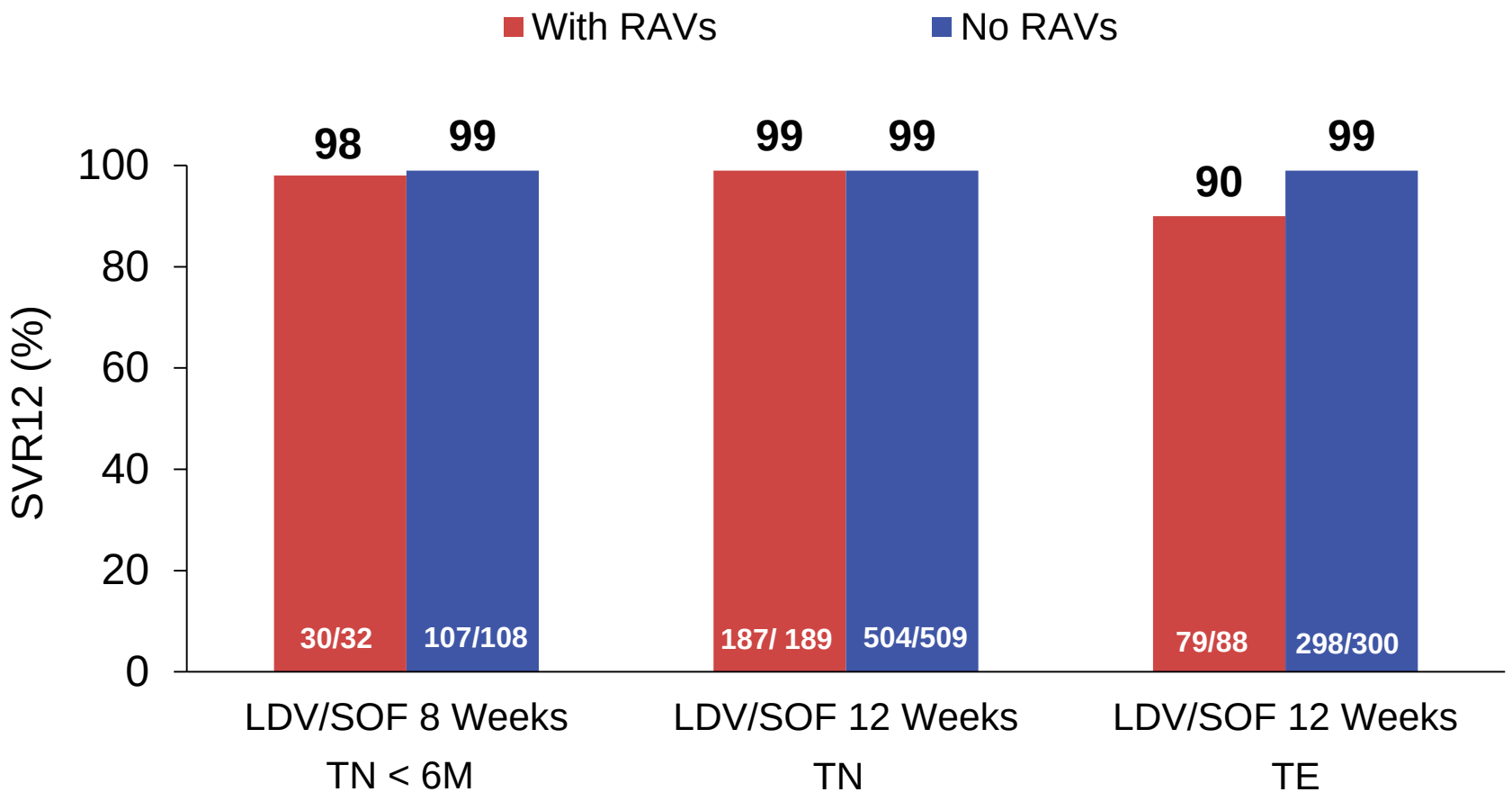
GT1b RAVs: L28M, L31I/F/M/V, P32L, P58D, A92K, Y93C/H/N/S

Recommended LDV/SOF Regimens According to Prior Treatment History and Cirrhosis Status

		LDV/SOF Treatment
Treatment Naïve	No cirrhosis HCV RNA <6M	8 weeks
	Cirrhosis	± RBV 12 weeks or LDV/SOF 24 weeks
Treatment Naive or Experienced	No cirrhosis	12 weeks
Treatment Experienced	Cirrhosis	+ RBV 12 weeks or LDV/SOF 24 weeks

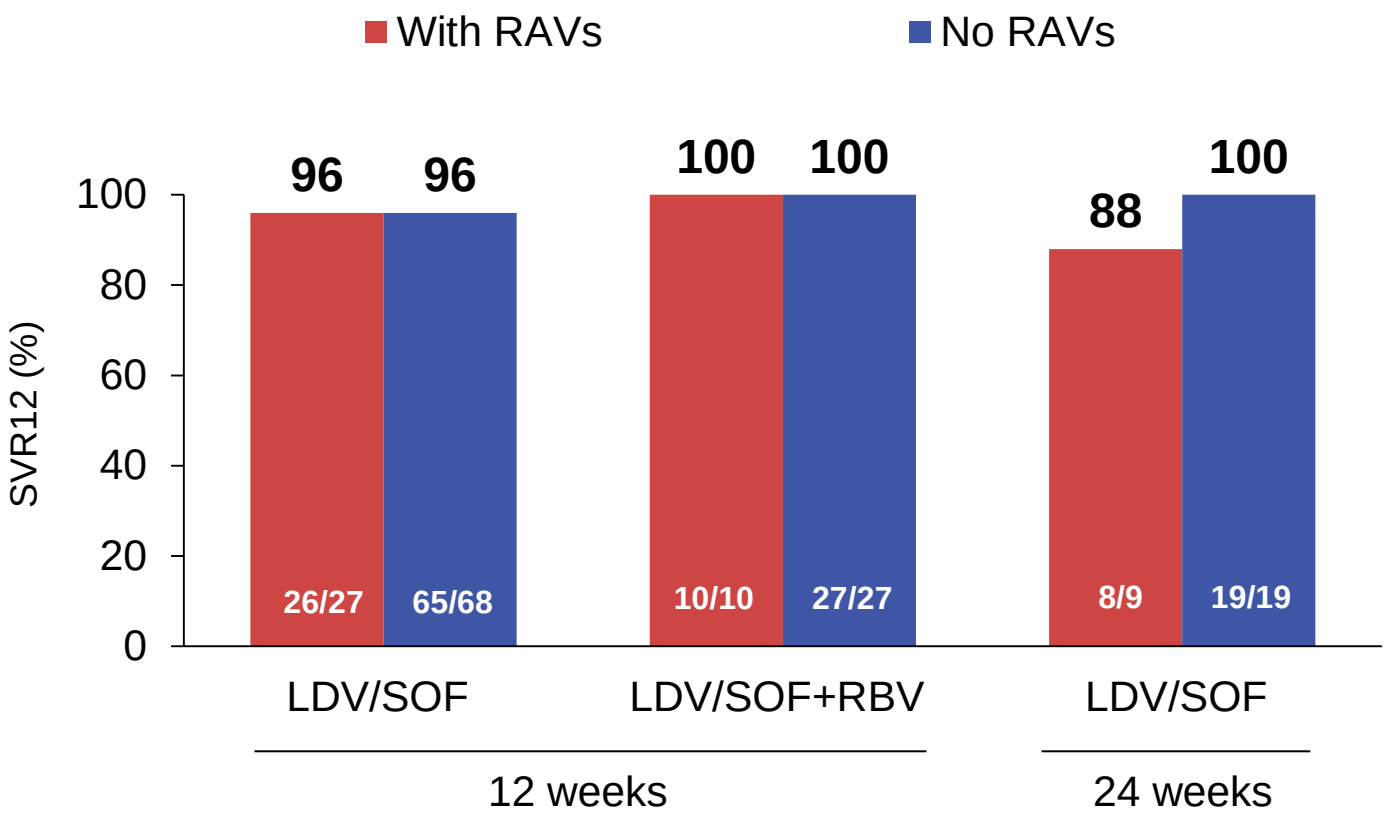
- Effect of baseline NS5A RAVs on SVR12 was assessed in these patient groups

SVR12 Rates by Treatment Regimen and Duration: Patients without Cirrhosis



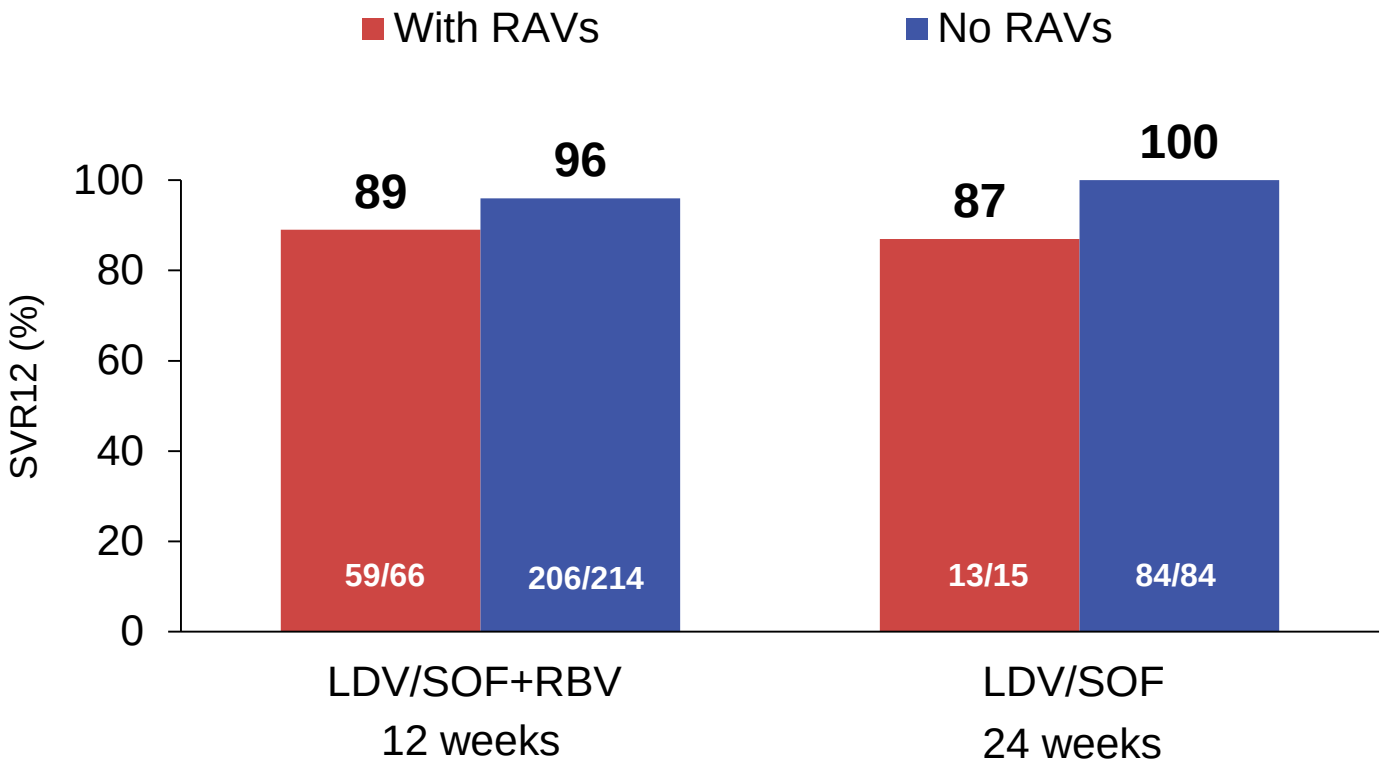
Studies included for analysis:
LDV/SOF 8 weeks: GS-US-337-0118 (LONESTAR 1), GS-US-337-0108 (ION-3); **LDV/SOF 12 Wks TN**: GS-US-GS-US-334-1274 (Bleeding Disorder), GS-US-337-0102 (ION-1), GS-US-337-0108 (ION-3), GS-US-337-0113 (Japan 1), GS-US-337-0115 (ION-4), GS-US-337-0122 (Electron 2), GS-US-337-0131(China), GS-US-337-0118 (LONESTAR 1), GS-US-337-1406, GS-US-337-1468 (LEPTON); **LDV/SOF 12 Wks TE**: GS-US-337-0109 (ION-2), GS-US-337-0113 (Japan 1), GS-US-337-0115 (ION-4), GS-US-337-0124 (SOLAR-2), GS-US-334-1274 (Bleeding Disorder), GS-US-337-0118 (LONESTAR 1) , GS-US-337-0131(China), GS-US-337-1406, GS-US-337-1468 (LEPTON)

SVR12 Rates by Treatment Regimen and Duration: TN Patients with Cirrhosis



Studies included for analysis:
LDV/SOF 12 Wks: GS-US-334-1274 (Bleeding Disorder), GS-US-337-0102 (ION-1), GS-US-337-0113 (Japan 1), GS-US-337-0115 (ION-4), GS-US-337-0122 (ELECTRON-2), GS-US-337-0131(China), GS-US-337-1406; **LDV/SOF+RBV 12 Wks**: GS-US-337-0102 (ION-1), GS-US-337-0113 (Japan 1), GS-US-337-0122 (ELECTRON-2); **LDV/SOF 24 Wks**: GS-US-337-0102 (ION-1), GS-US-334-1274 (Bleeding Disorder)

SVR12 Rates by Treatment Regimen and Duration: TE Patients with Cirrhosis



Studies included for analysis:
LDV/SOF+RBV 12 Wks: GS-US-337-0109 (ION-2), GS-US-337-0113 (Japan 1), GS-US-337-0118 (LONESTAR-1), GS-US-337-0122 (ELECTRON-2), GS-US-337-0123 (SOLAR-1), GS-US-337-0124 (SOLAR-2), GS-US-337-1118 (Retreatment), P7977-0523 (ELECTRON); **LDV/SOF 24 Wks**: GS-US-337-0109 (ION-2), GS-US-337-0121 (SIRIUS), GS-US-334-1274 (Bleeding Disorder)

Conclusions

- The prevalence and type of pretreatment NS5A RAVs do not differ substantially across regions in GT1 HCV-infected patients
- Pretreatment NS5A RAVs have no clinically meaningful impact on treatment outcome with LDV/SOF when used according to recommended guidelines in the vast majority of patient populations
- The clinical relevance of NS5A RAVs on treatment outcome in treatment-experienced patients with cirrhosis needs to be further defined

1. Itakura et al., Hepatology Research 2015 (PMID: 25564756)
2. Pfeiffer et al., Hepatology 2015 (PMID: 26406534)

Concordance of Population and Consensus Sequences for 50 Patient Sequences Using 15%, 20%, or 25% Variant Prevalence Cutoffs

Prevalence of Variant Necessary for Inclusion in Consensus	Number of Nucleotide Differences Between Population and Consensus Sequences	Total Number of Nucleotides Analyzed	Percent Concordance	Number of Amino Acid Differences Between Population and Consensus Sequences	Total Number of Amino Acids Analyzed	Percent Concordance
25%	244	88605	99.72	35	29585	99.88
20%	227	88605	99.74	41	29585	99.86
15%	379	88605	99.57	63	29585	99.79