Dual, Triple, and Quadruple Combination Treatment with a Protease Inhibitor (GS-9256) and a Polymerase Inhibitor (GS-9190) alone and in Combination with Ribavirin (RBV) or PegIFN/RBV for up to 28 days in Treatment Naïve, Genotype 1 HCV Subjects

S Zeuzem,[1] P Buggisch,[2] K Agarwal,[3] M Manns,[4] P Marcellin,[5]
GR Foster,[6] D Sereni,[7] H Klinker,[8] C Moreno,[9] JP Zarksi,[10] Y Horsmans,[11] M Shelton,[12]
S West,[12] J Zong,[12] J Harris,[12] J McHutchison,[12] W Lee,[12] W Delaney,[12] D Oldach[12]

[1]Medizinische Klinik I, Frankfurt, Germany; [2]IFI Studien-und Projekte, Hamburg, Germany; [3]Institute of Liver Studies, King's College Hospital, London, United Kingdom; [4]Medizinische Hochschule Hannover, Zentrum für Innere Medizin Klinikum der J.W. Goethe- Hannover, Germany; [5]Service Hépatologie, Hôpital Beaujon APHP, University of Paris Denis Diderot and INSERM CRB3, Clichy, France; [6]Queen Mary University of London,United Kingdom; [7]Hôpital Saint-Louis, Service de Medecine Interne,Avenue Claude Vellefaux, Paris, France; [8]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany; [9]Department of Gastroenterology and Hepatopancreatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium; [10]CHU de Grenoble – Hopital MichallonLa Tronche, France; [11] Gastroenterology Unit, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Bruxelles, Belgium; [12]Gilead Sciences, Inc., Foster City, CA, USA.

61st Annual Meeting of the American Association
for the Study of Liver Diseases
October 29 - November 2, 2010
Boston, Massachusetts, USA
Oral # LB-1

Stefan Zeuzem, MD
Klinikum der J.W. Goethe-Universität

I have financial relationship(s) within the last 12 months relevant to my presentation with:

Consultancy for Abbott, Achillion, Anadys, BMS, Gilead, HGS, Intermune, Merck, Novartis, Pharmasset, Roche, Santaris, Tibotec, Vertex

AND

My presentation includes discussion of off-label or investigational use of GS-9256 and tegobuvir (GS-9190)

Introduction

- GS-9256 & GS-9190 (tegobuvir) are novel DAAs in Phase 2 development for chronic hepatitis C
- GS-9256 targets NS3 Protease
  - GT1 K_i = 0.09 nM, replicon EC_{50} 30 – 100 nM
  - 2.7 $\log_{10}$ mean maximal reduction in HCV RNA (75 mg BID)
- Tegobuvir targets NS5B polymerase (non-nuc)
  - GT1 replicon EC_{50} = 1 – 4 nM
  - 1.6 $\log_{10}$ mean maximal reduction in HCV RNA (40 mg BID)

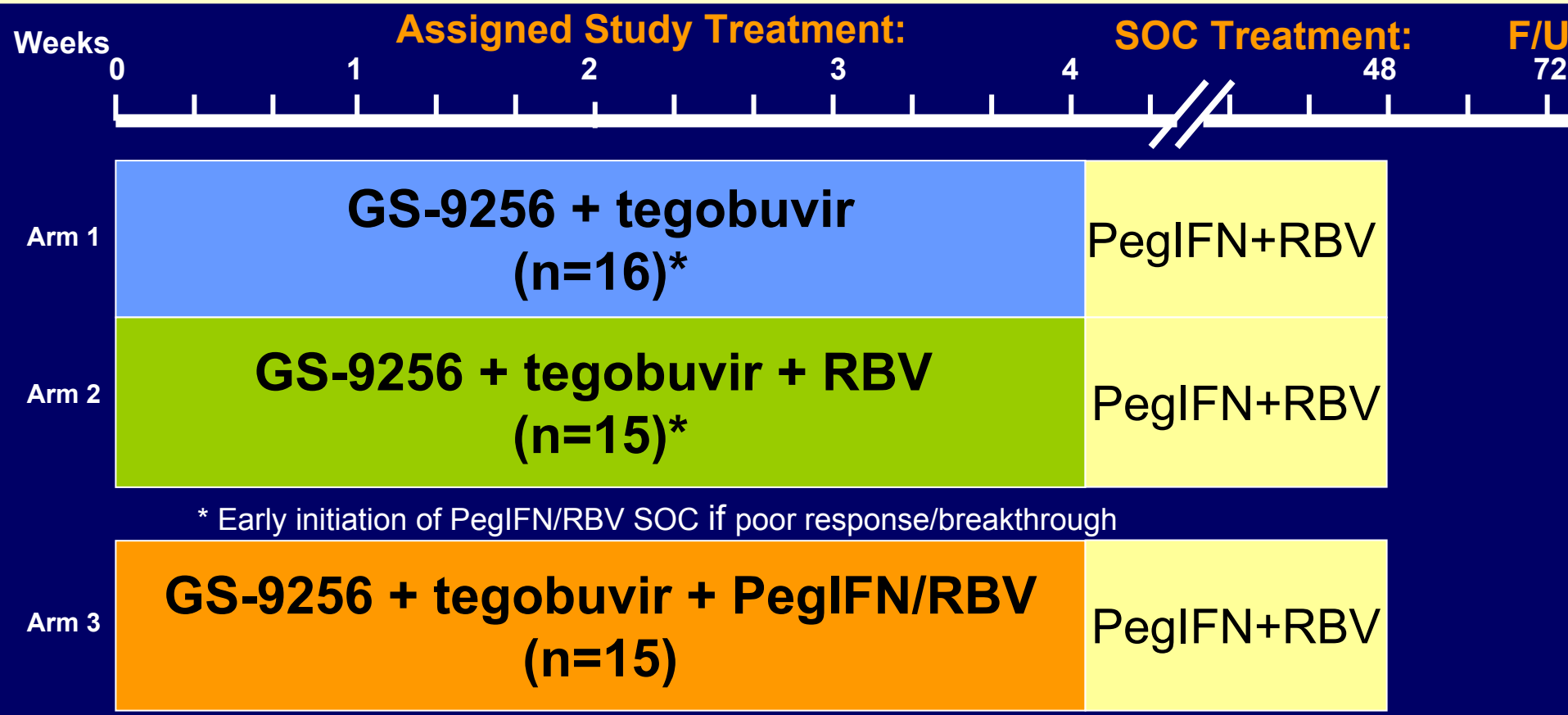
Zeuzem, et al., AASLD; Oral # LB-1.

Objectives

- To test the efficacy (RVR at HCV RNA < 25 IU/mL), safety, and tolerability of the following regimens in HCV patients:
  - GS-9256 + tegobuvir
  - GS-9256 + tegobuvir + RBV
  - GS-9256 + tegobuvir + RBV + PegIFN
- To evaluate the viral resistance during and following treatment with each regimen
- To characterize the PK of GS-9256 and tegobuvir (analysis ongoing)

Zeuzem, et al., AASLD; Oral # LB-1.

Study Design



- GS-9256 75 mg BID; tegobuvir 40 mg BID;
- RBV 1000-1200 mg/day; peginterferon alfa 2a 180µg SQ QW
- Safety & virologic monitoring 2 – 3X per week
- Serial PK evaluated at week 3 or 4

Zeuzem, et al., AASLD; Oral # LB-1.

Key Study Entry Criteria

- **Inclusion criteria:**
  - 18–70 years of age with chronic HCV infection (genotype 1)
  - HCV RNA: 3 - 7.2 $\log_{10}$ IU/mL
  - HCV treatment naïve, planning to start PegIFN/RBV
- **Exclusion criteria:**
  - contraindications to PegIFN/RBV SOC
  - ≥ Grade 3 ALT, AST, or GGT
  - co-infection with HIV, HBV, or another HCV genotype
  - active substance abuse
  - CYP 3A4/P-gp inhibitors, QT prolonging medications
  - history of cardiac disease or QTc > 450 msec

Zeuzem, et al., AASLD; Oral # LB-1.

Baseline Demographics

	GS-9256+tegobuvir (n=16)	GS-9256+tegobuvir +RBV (n=15)	GS-9256+tegobuvir +PegIFN/RBV (n=15)
Median Age (range)	47 (30, 66)	50 (27, 63)	56 (43, 71)
Sex (M:F)	14:2	11:4	12:3
Race	13 White 2 Black 1 Asian	12 White 2 Black 1 N. African	14 White 1 Black
Median HCV RNA (range)	6.2 (5.3, 7.3)	6.3 (5.4, 7.2)	6.7 (4.6, 7.4)
Genotype (1a:1b:other)	8:7:1[1]	3:10:2[1]	4:10:1[2]
IL28B Genotype	2: CC 4: TT 10: CT	6: CC 1: TT 8: CT	4: CC 2: TT 8: CT 1: pending

[1] several subjects identified as rare subtypes (1e, 1l, 1m/1e) on further testing

[2] historic genotype of 1a – further testing identified genotype 4r

Zeuzem, et al., AASLD; Oral # LB-1.

Virologic Response

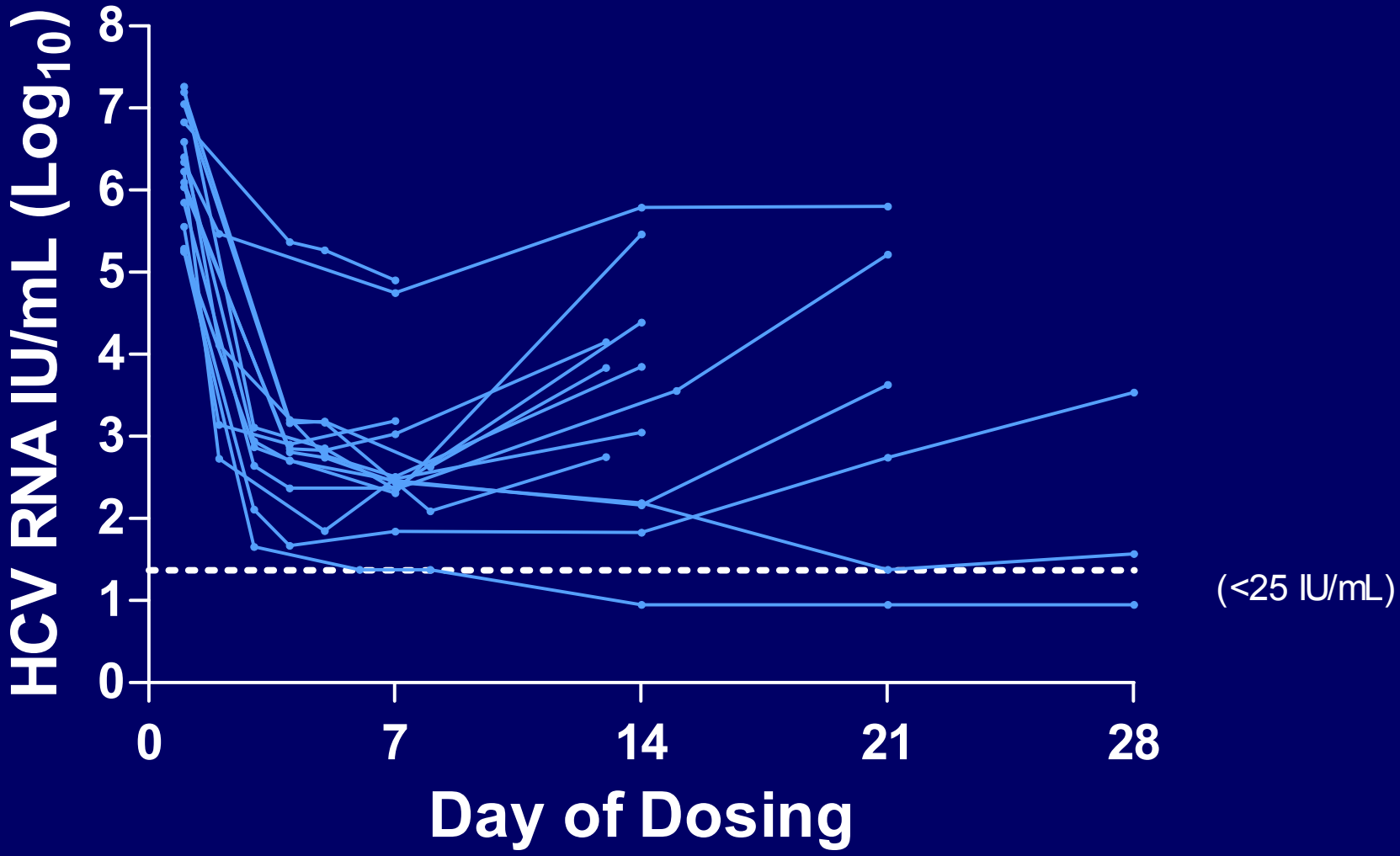
	GS-9256+tegobuvir (n=15)[1]	GS-9256+tegobuvir +RBV (n=13)[1]	GS-9256+tegobuvir +PegIFN/RBV (n=14)[2]
Median maximal change from baseline (range, log_{10} IU/mL)	-4.1 (-5.1, -1.6)	-5.1 (-5.6, -4.1)	-5.7 (-6.5, -3.6)
Achieved nadir ≤ 25 IU/mL	2/15 (13%)	8/13 (62%)	14/14 (100%)
Day 14 HCV RNA ≤ 25 IU/mL	1/15 (7%)	6/13 (46%)	10/14 (71%)
Day 28 HCV RNA ≤ 25 IU/mL (RVR)	1/15 (7%)	5/13 (38%)	14/14 (100%)

[1] Three "GT-1b" subjects were not included due to misidentification of GT.
[2] One subject was not included due to misidentification of GT

Zeuzem, et al., AASLD; Oral # LB-1.

Antiviral Response

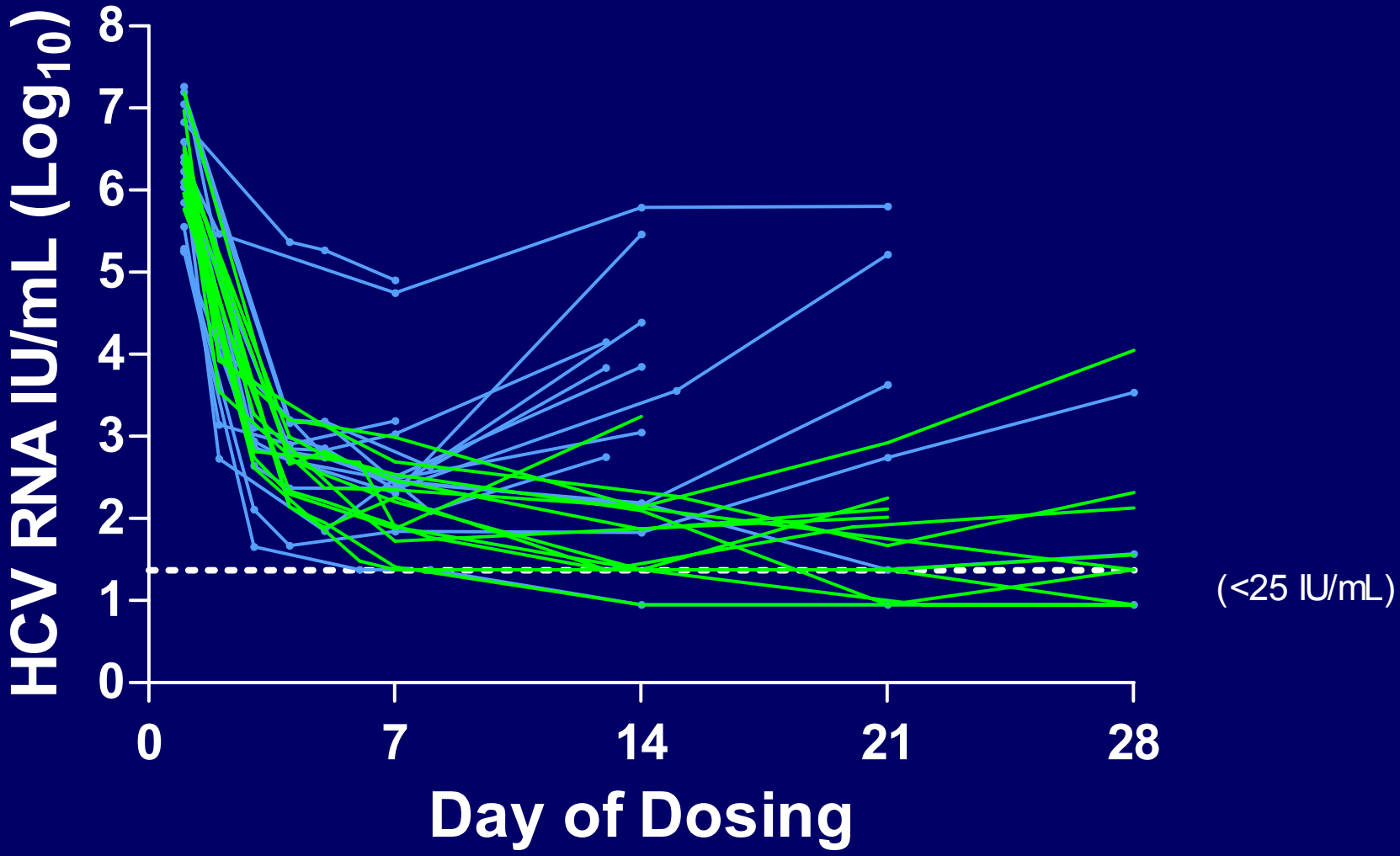
Arm 1: GS-9256 + tegobuvir



Antiviral Response

Arm 1: GS-9256 + tegobuvir

Arm 2: GS-9256 + tegobuvir + RBV

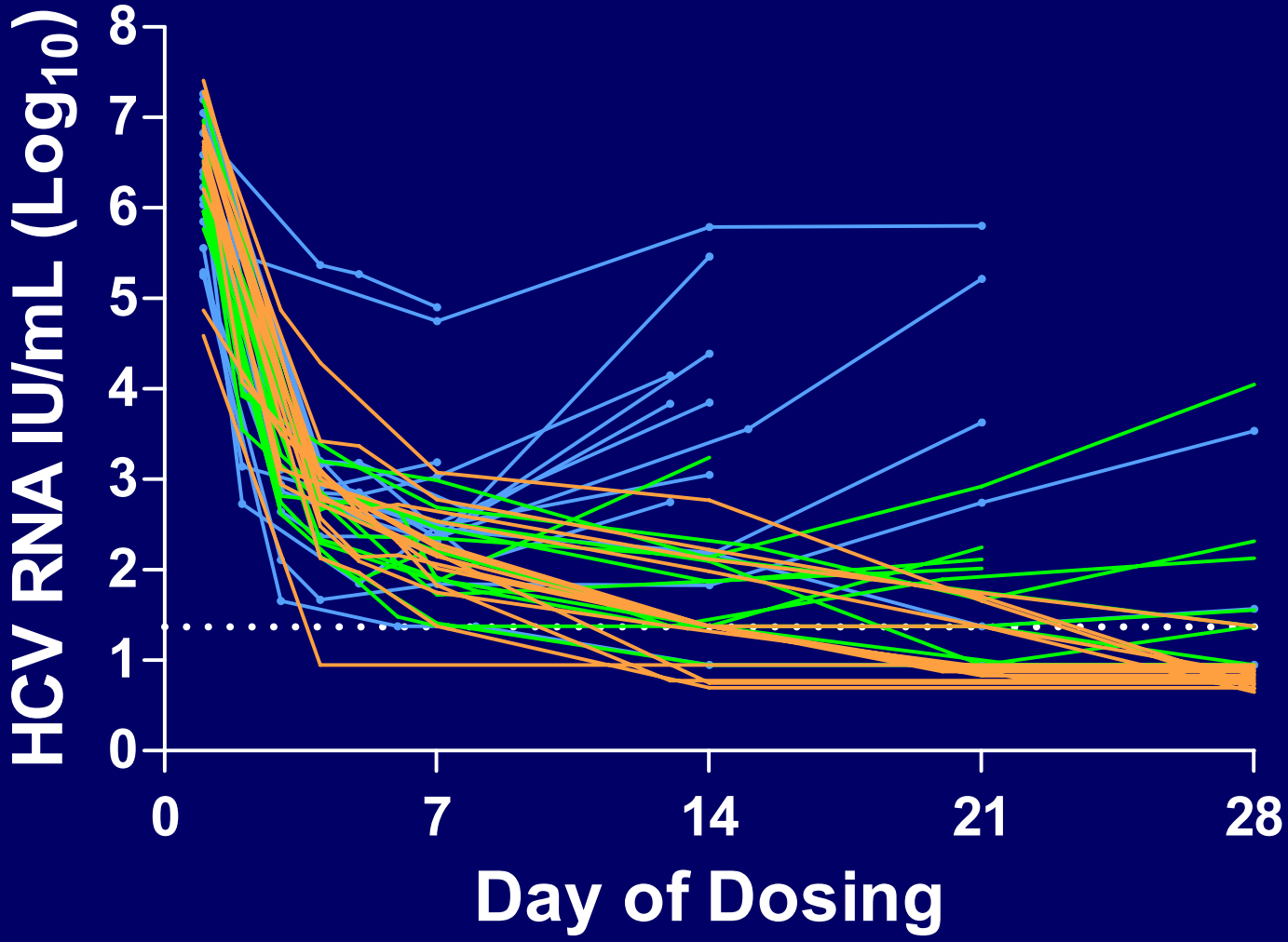


Antiviral Response

Arm 1: GS-9256 + tegobuvir

Arm 2: GS-9256 + tegobuvir + RBV

Arm 3: GS-9256 + tegobuvir + PegIFN/RBV



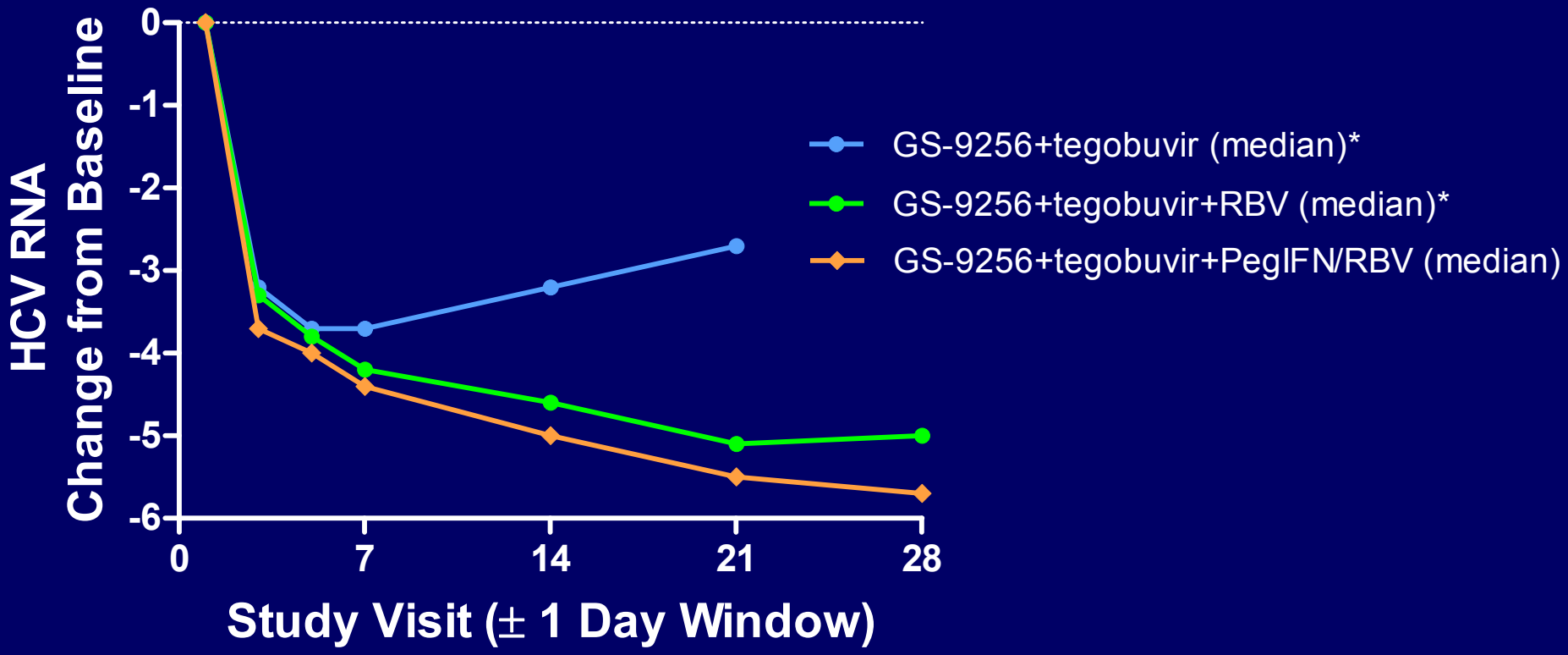
(<25 IU/mL)

Arm 3 RVR

14/14 < 25 IU/ml

13/14 < 10 IU/ml

Antiviral Response
HCV RNA Decline From Baseline By Regimen

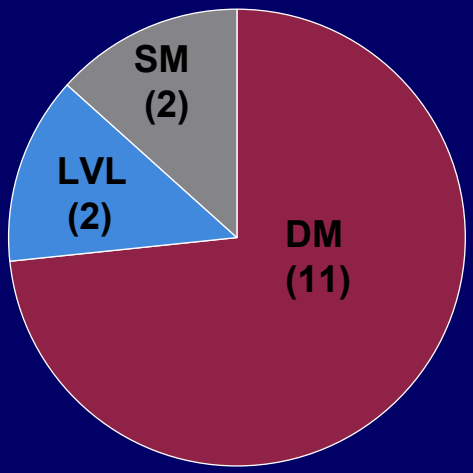


*** Censored after discontinuation or addition of PegIFN/RBV**
Subjects with rare subtypes (non 1a or 1b) were excluded

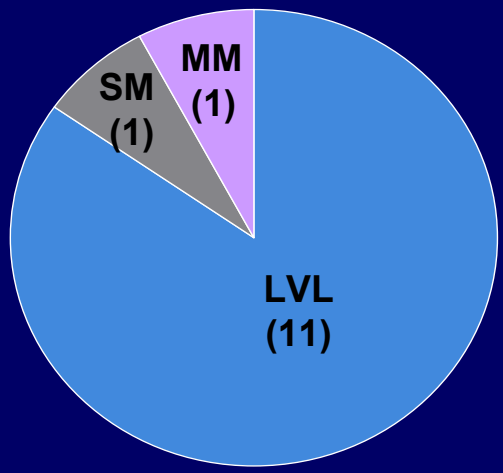
Zeuzem, et al., AASLD; Oral # LB-1.

Resistance Mutations Identified by Population Sequencing (On Treatment)

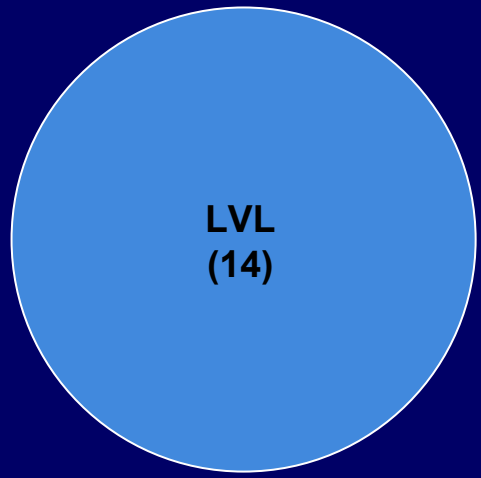
GS-9256 + tegobuvir (n=15)



GS-9256 + tegobuvir + RBV (n=13)



GS-9256 + tegobuvir + PegIFN/RBV (n=14)



LVL=low viral load during treatment (<1000 IU/ml)
SM=single mutant in NS3, DM=double mutants in NS3 and NS5B, MM= triple mutants in NS3 and NS5B
Observed mutations : 168/155 (NS3) + 445/448 (NS5B)

Zeuzem, et al., AASLD; Oral # LB-1.

Results: AEs on Assigned Study Treatment

Adverse Events	GS-9256 + tegobuvir (n=16)	GS-9256 + tegobuvir + RBV (n=15)	GS-9256 + tegobuvir + PegIFN/RBV (n=15)
Grade 1 or 2*			
Headache	5 (31%)	7 (47%)	6 (40%)
Diarrhea	3 (19%)	3 (20%)	6 (40%)
Nausea	3 (19%)	3 (20%)	6 (40%)
Fatigue	1 (6%)	4 (27%)	5 (33%)
Asthenia	0	2 (13%)	1 (7%)
Insomnia	0	3 (20%)	1 (7%)
Dry skin	0	2 (13%)	0
Pruritus	1 (6%)	2 (13%)	1 (7%)
Anemia	0	0	2 (13%)
Eye Pain	0	0	2 (13%)
Abdominal pain	0	1 (7%)	2 (13%)
Vomiting	0	0	2 (13%)
Influenza-like illness	0	0	12 (80%)
Anorexia	0	0	2 (13%)
Myalgia	0	1 (7%)	3 (20%)
Sleep disorder	0	0	2 (13%)
Cough	0	0	3 (20%)
Dyspnea	0	0	2 (13%)
Grade 3			
Neutropenia	0	0	1 (7%)
Vasovagal collapse	0	0	1 (7%)

* Events occurring in >1 subject

Results – Selected Treatment-Emergent Laboratory Abnormalities on Assigned Study Treatment

Laboratory Parameter	GS-9256 + tegobuvir (n=16)	GS-9256 + tegobuvir + RBV (n=15)	GS-9256 + tegobuvir + PegIFN/RBV (n=15)
Total bilirubin			
Grade 1	3 (19%)	2 (13%)	4 (27%)
Grade 2	1 (6%)	1 (7%)	2 (13%)
Grade 3	0	2 (13%)	0
Direct bilirubin > ULN [Max value in mg/dL, fold>ULN]	2 (13%) [0.5, 1.3X ULN]	1 (7%) [0.6, 1.5X ULN]	2 (13%) [1.2, 3X ULN]
Hemoglobin			
Grade 1	0	2 (13%)	2 (13%)
Grade 2	0	0	0
Grade 3	0	0	1 (7%)
Neutrophil Count			
Grade 1	0	0	4 (27%)
Grade 2	0	0	2 (13%)
Grade 3	0	0	4 (27%)

Zeuzem, et al., AASLD; Oral # LB-1.

Safety Summary

- No Grade 4 AEs or lab values on assigned treatment
- 1/46 patients discontinued study drugs due to AEs
  - fatigue with onset after addition of PegIFN/RBV
- 2 SAEs reported:
  - 1 patient experienced vasovagal collapse attributed to gastroenteritis while receiving 9256 + tegobuvir + PegIFN/RBV
  - 1 patient had bursitis of the knee after discontinuing study drugs (while receiving PegIFN/RBV)
- Maximum observed QTc was 452 msec
  - only 1 patient had QTc > 450 msec

Zeuzem, et al., AASLD; Oral # LB-1.

Conclusions

- **GS-9256 + tegobuvir has robust antiviral activity.**
- **The addition of RBV to GS-9256 + tegobuvir demonstrated greater virologic suppression, decreased resistance emergence, and was well tolerated.**
- **GS-9256 + tegobuvir + PegIFN/RBV achieved 100% RVR, without breakthroughs.**
- **GS-9256 + tegobuvir + PegIFN/RBV was well-tolerated, with a typical PegIFN/RBV safety profile.**
- **Phase 2b evaluation of a 4 month regimen of GS-9256 + tegobuvir + PegIFN/RBV is ongoing.**

Zeuzem, et al., AASLD; Oral # LB-1.

Acknowledgements

- Patients, Investigators, and Clinical Research Staff at:
  - Institute of Liver Studies, King's College Hospital, London (Agarwal)
  - Queen Mary University of London (Foster)
  - Klinikum der J.W. Goethe-Universität Frankfurt (Zeuzem)
  - Medizinische Hochschule Hannover (Manns)
  - Universitätsklinikum Würzburg (Klinker)
  - IFI Studien-und Projekte, Hamburg, Germany (Buggisch)
  - Hôpital Saint-Louis (Sereni)
  - CHU de Grenoble – Hopital Michallon (Zarski)
  - Service Hépatologie, Hôpital Beaujon APHP, University of Paris Denis Diderot and INSERM CRB3, Clichy, France (Marcellin)
  - Department of Gastroenterology and Hepatopancreatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium (Moreno)
  - Université catholique de Louvain (Horsmans)