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A Phase 2b Trial Comparing 24 to 48 Weeks Treatment with Tegobuvir (GS-9190)/PEG/RBV to 48 Weeks Treatment with PEG/RBV for Chronic Genotype 1 HCV Infection

E Lawitz,[1] I Jacobson,[2] E Godofsky,[3] G Foster,[4] R Flisiak,[5] M Bennett,[6] M Ryan,[7] JM Pawlotsky,[8] Hinkle,[9] J Simpson,[9] J McHutchison,[9] D Oldach,[9] and M DeMicco[10]

[1]Alamo Medical Research, San Antonio, TX, USA; [2]Weill Medical College of Cornell University, NY, NY, USA; [3]Bach and Godofsky Infectious Diseases, Sarasota, FL, USA; [4]Barts and The London Hopsital, London, UK; [5]Klinika Chorob Zakaznych I Hepatologii, Bialystok, Poland; [6]Medical Associates Research Group, San Diego, CA, USA; [7]Digestive and Liver Disease Specialists, Norfolk, VA, USA; [8]Henri Mondor Hospital, Paris, France; [9]Gilead Sciences, Inc., Foster City, CA, USA; [10]Advanced Clinical Research Institute, Anaheim, CA, USA

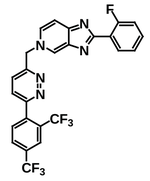
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: (650) 522-5001
Email: steven.knox@gilead.com

Introduction

- Tegobuvir (TGV) is a potent non-nucleoside HCV polymerase inhibitor, which interacts with NS5B close to the enzyme active site
- TGV was safe and well tolerated when administered for 8 days as monotherapy at a dose of 40 mg BID. At higher doses, QTcF prolongation was observed
- TGV + the HCV protease inhibitor GS-9256 + PEG/RBV achieved 100% RVR in Gilead Study GS-US-196-0112 (EASL 2011 Poster 340)
- We present the results of a Phase 2b evaluation of TGV versus placebo, in combination with PEG(IFN-2a)/RBV, for treatment of chronic Genotype 1 HCV infection, in treatment naïve study subjects

Tegobuvir (TGV)

- Replicon EC_{50}
  - GT 1a 3.6 nM
  - GT 1b 0.6 nM
- Resistance Mutations
  - C316Y, C445F, Y448H, C452H
- Monotherapy (8 day) Antiviral Activity:
  - Mean Maximal HCV RNA Decline
    - 40 mg BID: 1.6 Log_{10} IU/mL
    - 120 mg BID: 2.0 Log_{10} IU/mL



Non-nucleoside HCV NS5B (polymerase) inhibitor (GS-9190/TGV)

Objectives

- Primary Objective
  - Antiviral activity in the first 12 weeks of therapy
    - RVR: week 4 HCV RNA <LLOQ
    - cEVR: week 12 HCV RNA <LLOQ
- Secondary Objectives
  - SVR
  - Safety and tolerability of TGV + PEG/RBV
  - Pilot assessment of 24-week Response Guided Therapy (RGT) in Arm 3 of the study
  - Characterize TGV resistance mutations (EASL 2011 Poster 571)

Methods

- Inclusion Criteria included:
  - Male or Female, Age 18-70
  - Chronic HCV Genotype 1a or 1b infection, with detectable viremia
  - HCV treatment naïve status (no prior therapy)
  - Body Mass Index (BMI) between 19-36 kg/m^2
- Exclusion criteria included:
  - History of cirrhosis or other significant liver disease
  - HIV or HBV coinfection
  - QTcF > 450 msec
  - Conditions excluding eligibility for PEG/RBV (autoimmunity; advanced cardiac or pulmonary disease; severe psychiatric illness; pregnancy or desired pregnancy)
- Enrollment from North America (U.S. & Puerto Rico) and EU (Belgium, Germany, France, Ireland, Poland, UK)
  - Overall enrollment was predominantly North American (75%)
  - Randomization stratified by region (NA vs EU), HCV RNA (greater or less than 400,000 IU/mL) and race (black versus non-black)
- Study Assessments:
  - HCV RNA
    - Roche COBAS TaqMan RT-PCR Assay (Lower Limit of Quantification, 25 IU/mL)
  - Safety assessments
    - Laboratories: hematology, chemistry, coagulation tests, TSH
    - Adverse event monitoring
    - Physical examination
  - ECG collection
    - Screen, Baseline, Day-2, Weeks 2, 4, 12, 24, and 48
    - ECGs were read by a core cardiology laboratory
  - Specimens for resistance sequencing (EASL 2011 Poster 571)
  - IL28B Genotyping was retrospectively determined in a subset of patients
  - PEG/RBV
    - Pegylated IFNα-2a (Pegasys®) 180 µg QW
    - Ribavirin (Copegus®) 1000 – 1200 mg daily

Results

Figure 1. Study Design

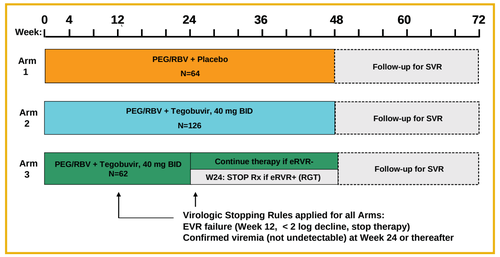


Table 1. Subject Demographics & Baseline Characteristics

	Arm 1 (PBO) n=64	Arm 2 (TGV) n=126	Arm 3 (TGV-RGT) N=62
Mean Age (years)	47	47	47
Male Sex	51.6%	65.1%	59.7%
Race: White Black Other	85.9% 7.8% 6.3%	85.7% 7.9% 6.4%	83.9% 8.1% 8.0%
Hispanic	15.6%	15.1%	21.0%
Mean BMI (kg/m^2)	27.5	27.0	27.3
Mean ALT (U/L)	89	82	68
Mean HCV RNA Log_{10}IU/mL	6.3	6.3	6.3
HCV: GT1a	57.8%	54.8%	59.7%
IL28B Genotype (tested) CC CT TT	 18/40 (45.0%) 21/40 (52.5%) 1/40 (2.5%)	 19/55 (34.5%) 26/55 (47.3%) 10/55 (18.2%)	 9/31 (29.0%) 17/31 (54.8%) 5/31 (16.1%)

In Arm 3, 25 subjects with eRVR stopped therapy at Week 24

Figure 2. Antiviral Efficacy

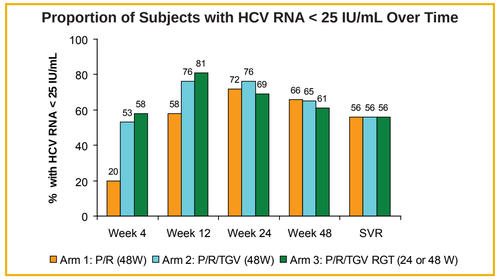
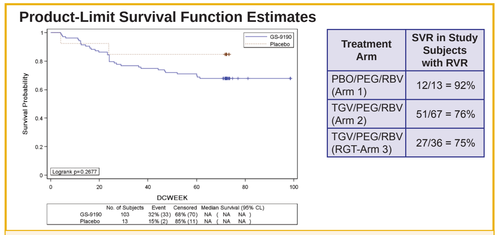


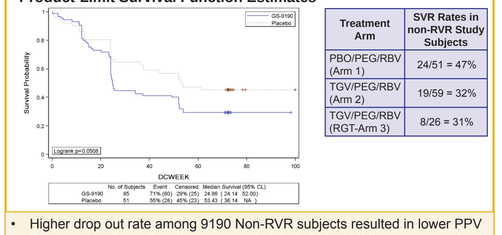
Figure 3. Kaplan-Meier On-Therapy Estimator for Study Subjects Who Achieved RVR



Treatment Arm	SVR in Study Subjects with RVR
PBO/PEG/RBV (Arm 1)	12/13 = 92%
TGV/PEG/RBV (Arm 2)	51/67 = 76%
TGV/PEG/RBV (RGT-Arm 3)	27/36 = 75%

- Higher drop out rate among 9190 RVR subjects resulted in lower PPV
- Reasons for discontinuation were varied, and were generally not related to virologic failure

Figure 4. Kaplan-Meier On-Therapy Estimator for Study Subjects Who Did Not Achieve RVR



Treatment Arm	SVR Rates in non-RVR Study Subjects
PBO/PEG/RBV (Arm 1)	24/51 = 47%
TGV/PEG/RBV (Arm 2)	19/59 = 32%
TGV/PEG/RBV (RGT-Arm 3)	8/26 = 31%

- Higher drop out rate among 9190 Non-RVR subjects resulted in lower PPV
- Reasons for discontinuation were varied, but virologic failure was prominent
- Unexpectedly high PPV for non-RVR subjects in the placebo arm

Table 2. GS-9190: No Unique Safety Concerns through 48 Weeks

G3/G4 TE Lab Abnls	9190 n=188	PBO n=64
ALT	3.2%	3.1%
AST	4.3%	1.6%
Bilirubin	1.1%	0%
Hemoglobin	7.4%	12.5%
Neutrophils	30.9%	37.5%
Lymphocytes	19.1%	12.5%
Platelets	2.1%	3.1%
QTcF Outcomes		
Max Observed QTcF >450 but < 480 msec >480 but < 500 msec >500 msec	 3.7% 0.5% 0%	 3.2% 0 % 0 %
Max QTcF Change from BL < 30 msec > 30 msec but < 60 msec > 60 msec	 89.4% 10.6% 0%	 98.4% 1.6% 0%

AEs and Discontinuations	9190 n=188	PBO n=64
Any TE Adverse Event	95.7%	95.3%
Any G3/G4 AE	25.0%	28.1%
SAE	4.8%	4.7%
Reasons for Early Treatment Discontinuation		
Rx Early D/C for Safety or Tolerability Reason	17.6%	12.5%
Rx D/C for Week 12 RNA	4.3%	6.3%
Rx D/C for Week 24 Viremia	11.2%	10.9%
Rx D/C for Viral Breakthrough	0.5%	1.6%
Rx D/C, other causes*	8.0%	6.3%
Total (Early D/C of Rx)	**41.5%**	**37.5%**

*Included investigator discretion, withdrew consent, and lost-to-f/u
Relapse rates, Rx completers: 8.0% (GS-9190) and 9.4% (PBO)

Table 3. Treatment-Emergent Adverse Events Reported by > 10% in Any Treatment Arm

System Organ Class Preferred Term AE	Arm 1: Placebo n=63 (% of subjects)	Arm 2:9190 n=126 (% of subjects)	Arm 3:9190 n=62 (% of subjects)
Headache	31.3	44.4	38.7
Fatigue	42.2	41.3	43.5
Insomnia	31.3	30.2	29.0
Alopecia	15.6	27.0	32.2
Pyrexia	6.3	28.6	24.2
Nausea	21.9	21.4	38.7
Pruritus	17.2	23.0	25.8
Flu-Like Illness	20.3	27.0	14.5
Cough	12.5	19.0	29.0
Myalgia	9.4	21.4	22.6
Depression	20.3	22.2	17.7
Diarrhea	15.6	19.8	19.4
Irritability	20.3	19.0	21.0
Rash	17.2	19.0	21.0
Chills	10.9	11.9	24.2
Arthralgia	7.8	15.9	11.3
Anxiety	18.8	15.9	8.1
Asthenia	3.1	14.3	9.7
Back Pain	7.8	15.1	6.5
Dyspnoea	17.2	12.7	11.3
Anorexia	12.5	11.1	11.3
Dizziness	9.4	9.5	14.5
Weight Decreased	10.9	9.5	11.3
Inj Site Erytherma	3.1	6.3	17.7
Dry Skin	9.4	10.3	8.1
Vomiting	3.1	6.3	12.9
Dyspepsia	12.5	5.6	6.5

Conclusions

- **Similar SVR rates of 56% were observed with TGV/PEG/RBV and PEG/RBV, despite a ~30% improvement in RVR and a ~20% improvement in cEVR**
- **SVR in the PEG/RBV/9190 RGT arm was 96% (24 of 25) in subjects with RVR who completed 24w treatment**
- **The PPV for SVR in both RVR and non-RVR groups was lower in the PEG/RBV/9190 arms compared with PEG/RBV**
  - **More discontinuations due to tolerability in RVR pts**
  - **More discontinuations due to virologic failure in non-RVR pts**
  - **12% imbalance in IL28B CC favoring PEG/RBV**
- **No new adverse events with 9190/PEG/RBV (overall AE profiles were similar)**

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