ILC 2016: RG-101 Phase II Results Webcast & Conference Call

RG-101, a Novel microRNA Therapeutic to Target miR-122, a HCV Host Factor

REGULUS THERAPEUTICS™

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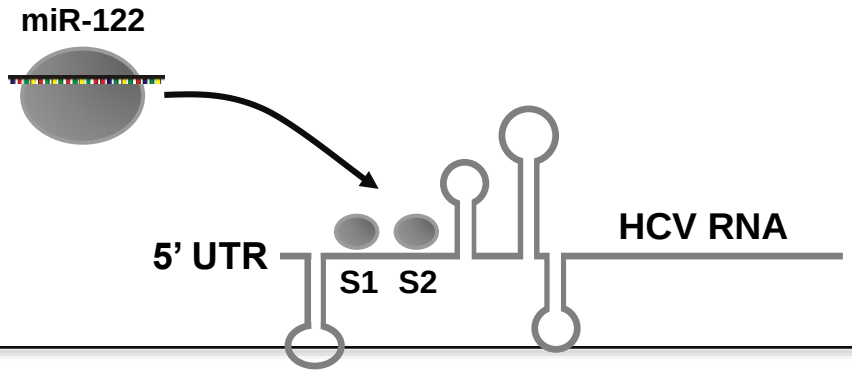
MicroRNA-122 (miR-122) is Essential for HCV Replication

miR-122

- Highly conserved liver-specific micro-RNA
- Most abundant micro-RNA in the liver
- Key regulator of cholesterol and fatty-acid synthesis [1,2]

miR-122 and HCV

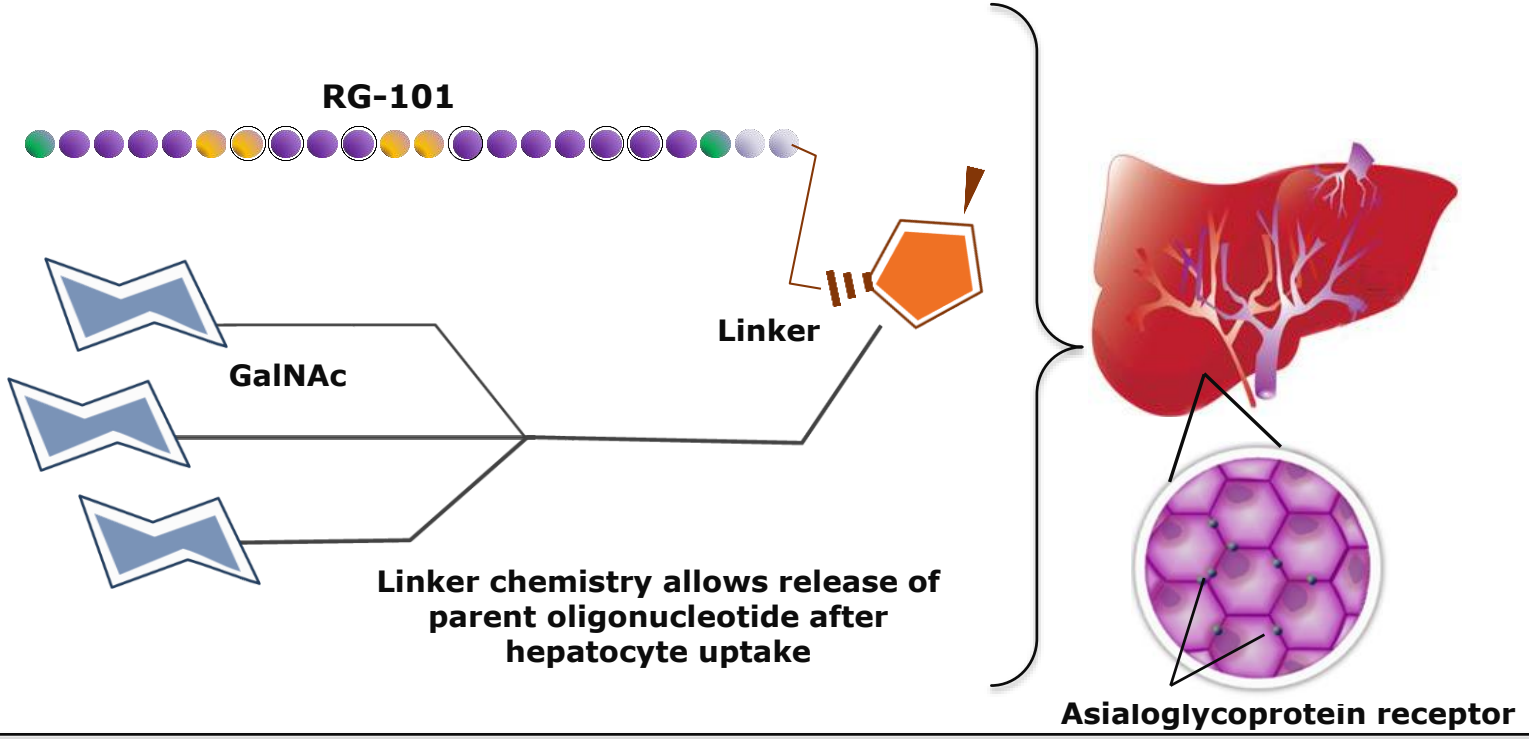
- miR-122 is essential host factor for hepatitis C virus replication
- 5' untranslated region (UTR) contains two highly-conserved miR-122 binding sites (S1 and S2) in all known genotypes [3,4]
- miR-122 binding promotes HCV RNA stability and accumulation [3,5], protects HCV genome from degradation [6,7,8]



1. Krützfeldt et al, *Nature* 2005
2. Esau et al, *Cell Metab* 2006
3. Jopling et al, *Science* 2005
4. Jopling et al, *Cell Host Microbe* 2008
5. Lanford et al, *Science* 2010
6. Machlin et al, *PNAS* 2011
7. Sedano et al, *Cell Host Microbe* 2014
8. Li et al, *J. Virol* 2015

RG-101 Targets miR-122

- Oligonucleotide inhibitor of miR-122 linked to N-acetylgalactosamine (GalNac) carbohydrate
- GalNac binds asialoglycoprotein receptor expressed on hepatocytes, actively concentrating drug into hepatocytes
- Increased potency (~20-fold) compared to non-conjugated oligonucleotide



Phase 2 Study Objectives

PRIMARY OBJECTIVE

- Efficacy of RG-101 in combination with direct acting antivirals (DAAs), based on proportion of subjects with virologic response* at 12 weeks post treatment

SECONDARY OBJECTIVES

- Efficacy of RG-101 in combination with DAAs at 24 and 48 weeks post treatment
- Safety and tolerability of RG-101 in combination with DAAs
- Time to viral clearance in each of the treatment arms

**Response defined as HCV RNA viral load below lower limit of quantitation (LLOQ) using RealTime HCV Assay (Abbott) with LLOQ = 12 IU/mL*

Phase 2 Study Key Eligibility Criteria

INCLUSION CRITERIA

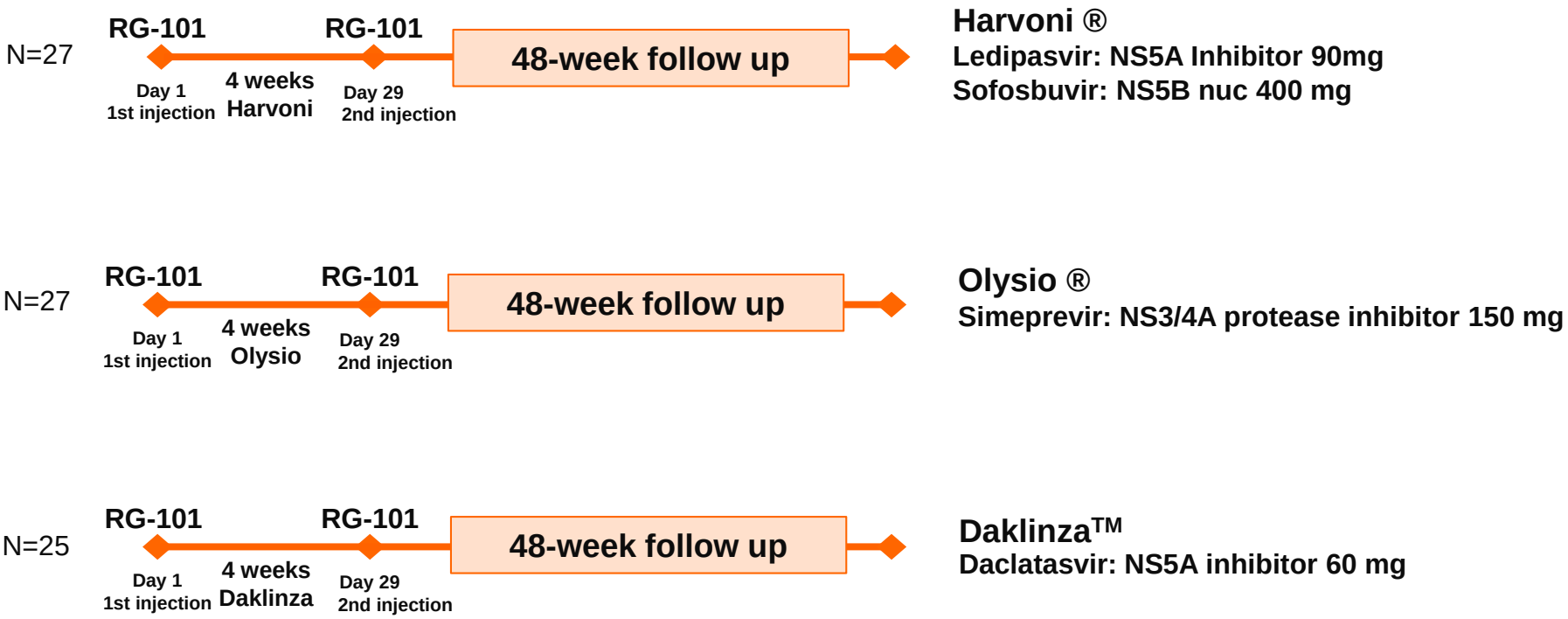
- Male or female, 18-65 years of age
- Chronic HCV infection, genotype 1 or 4 (viral load ≥75,000 IU/mL)
- Treatment-naïve, non-cirrhotic

EXCLUSION CRITERIA

- HBV or HIV co-infection
- Cirrhosis Child-Pugh B or C
- Other causes of liver disease
- History of hepatocellular carcinoma

Closed Faced “Sandwich” Designed to Test Safety and Efficacy with Marketed Oral DAAs

- Treated with: 2 mg/kg subcutaneous injection of RG-101 on Days 1 and 29 and a 4-week DAA treatment



Baseline Characteristics

	RG-101 + Harvoni (N=27)	RG-101 + Olysio (N=27)	RG-101 + Daklinza (N=25)	Overall (N=79)
Mean Age (years)	41.6	45.6	48.1	45.0
Female Gender (%)	40.7%	59.3%	64.0%	54.4%
White Race (%)	100%	100%	96.0%	98.7%
Mean Baseline Viral Load (Log_{10})	5.85	5.77	5.80	5.81
Genotype				
Genotype 1 (%)	77.8%	77.8%	76.0%	77.2%
Genotype 4 (%)	22.2%	22.2%	24.0%	22.8%
Fibroscan Grade				
Grade 0-1 (%)	88.9%	77.8%	92.0%	86.1%
Grade 2 (%)	3.7%	3.7%	0	2.5%
Grade 3 (%)	7.4%	18.5%	8.0%	11.4%
Grade 4 (%)	0	0	0	0

High Virologic Response Rates in all Treatment Groups at Interim Analysis

Number and Percentage of Patients with Response at Various Timepoints

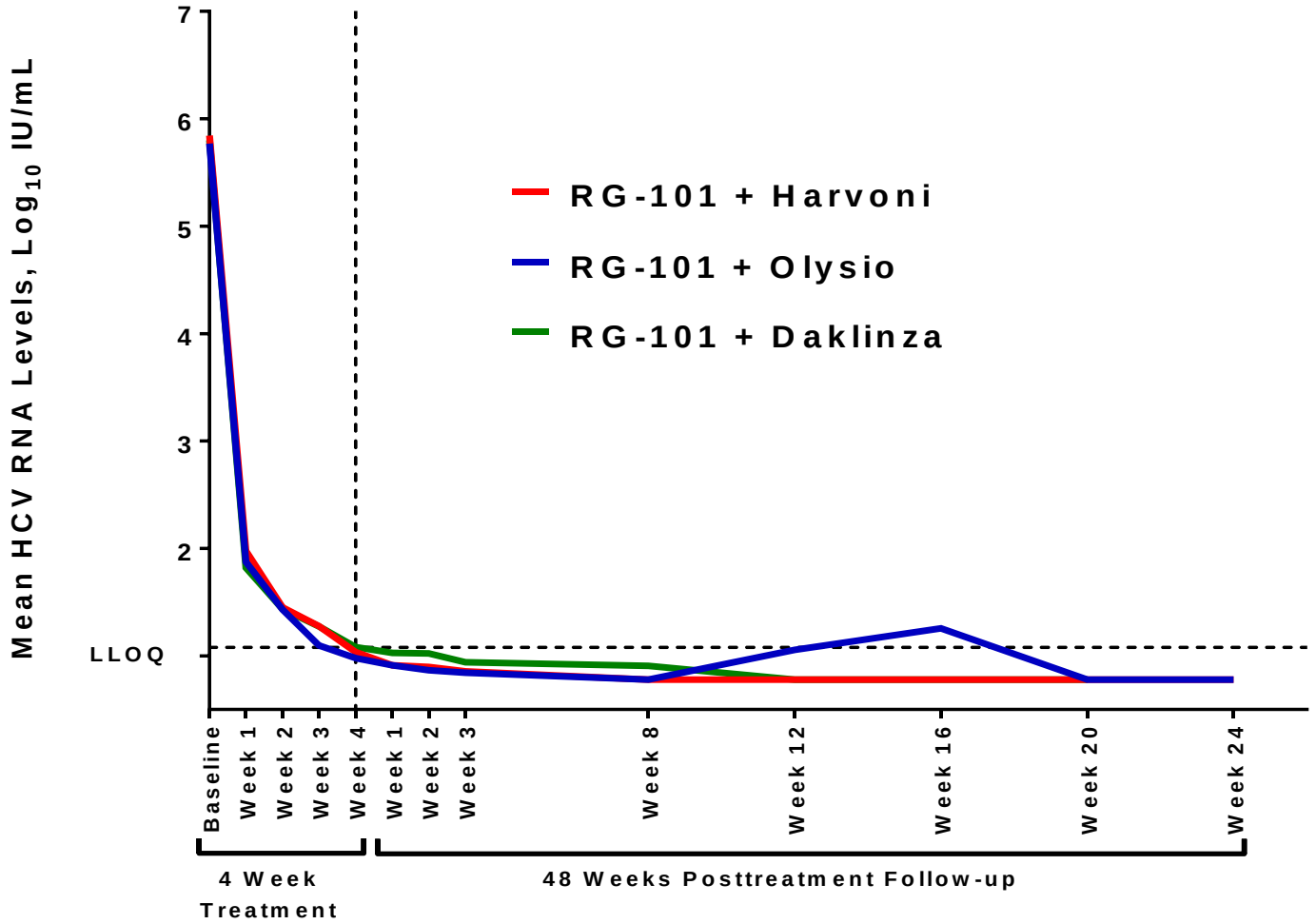
Follow-up Time*	RG-101 + Harvoni	RG-101 + Olysio	RG-101 + Daklinza
Week 8	21/21 (100%)	21/21 (100%)	20/22†,# (90.9%)
Week 12	14/14 (100%)	14/15# (93.3%)	12/12 (100%)
Week 16	9/9 (100%)	8/9# (88.9%)	9/9 (100%)
Week 20	2/2 (100%)	2/2 (100%)	2/2 (100%)
Week 24	1/1 (100%)	2/2 (100%)	-- (--)

Response defined as HCV RNA viral load below LLOQ using RealTime HCV Assay (Abbott) with LLOQ = 12 IU/mL

**Time since end of treatment (since second injection of RG-101)*
†*One slow-responder who subsequently achieved virologic response (<LLOQ) at Week 12*
#*One relapse in Daklinza arm at Week 8 and one relapse in Olysio arm at Week 12*

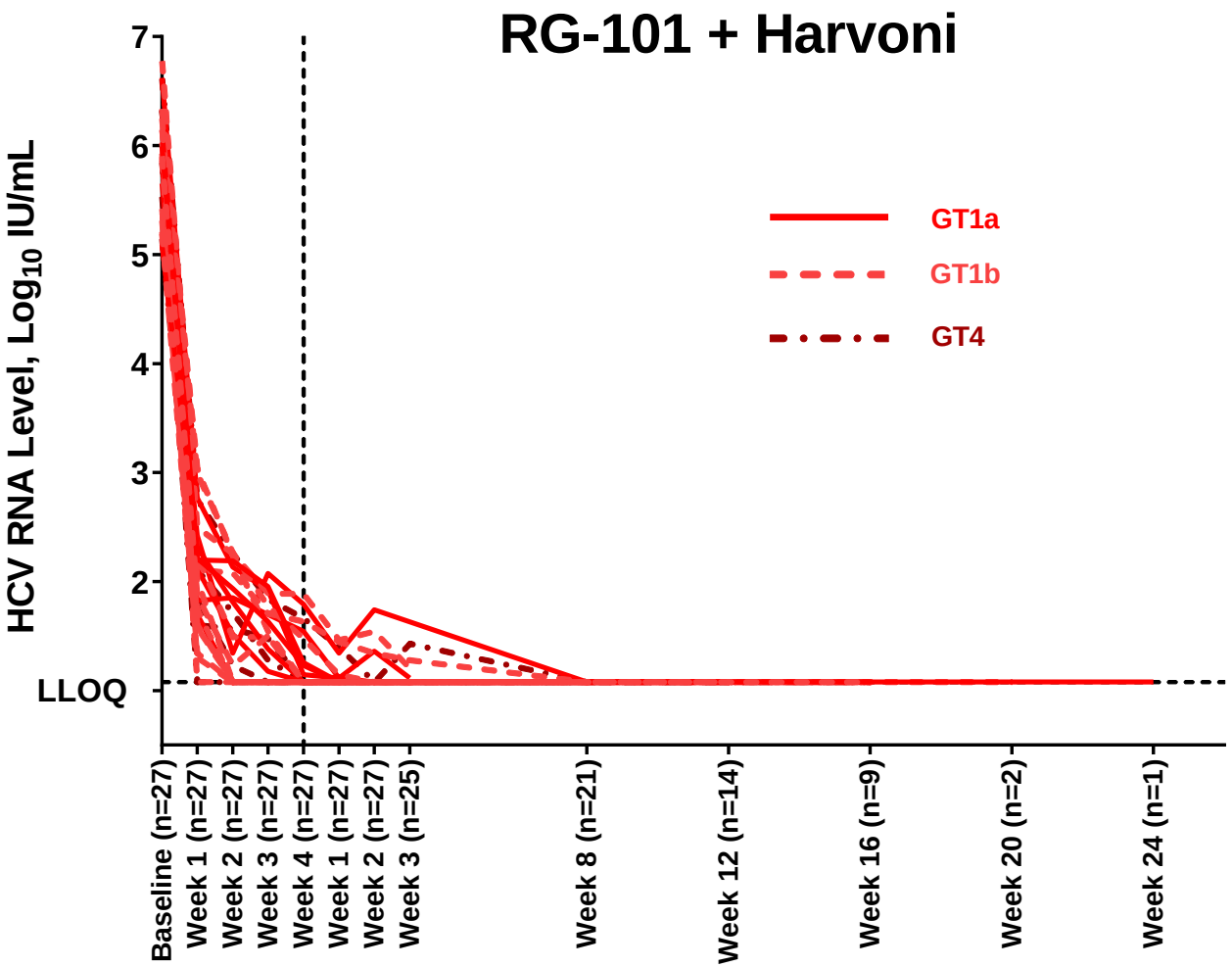
Viral Kinetics

Mean Reduction in HCV RNA by Treatment Arm

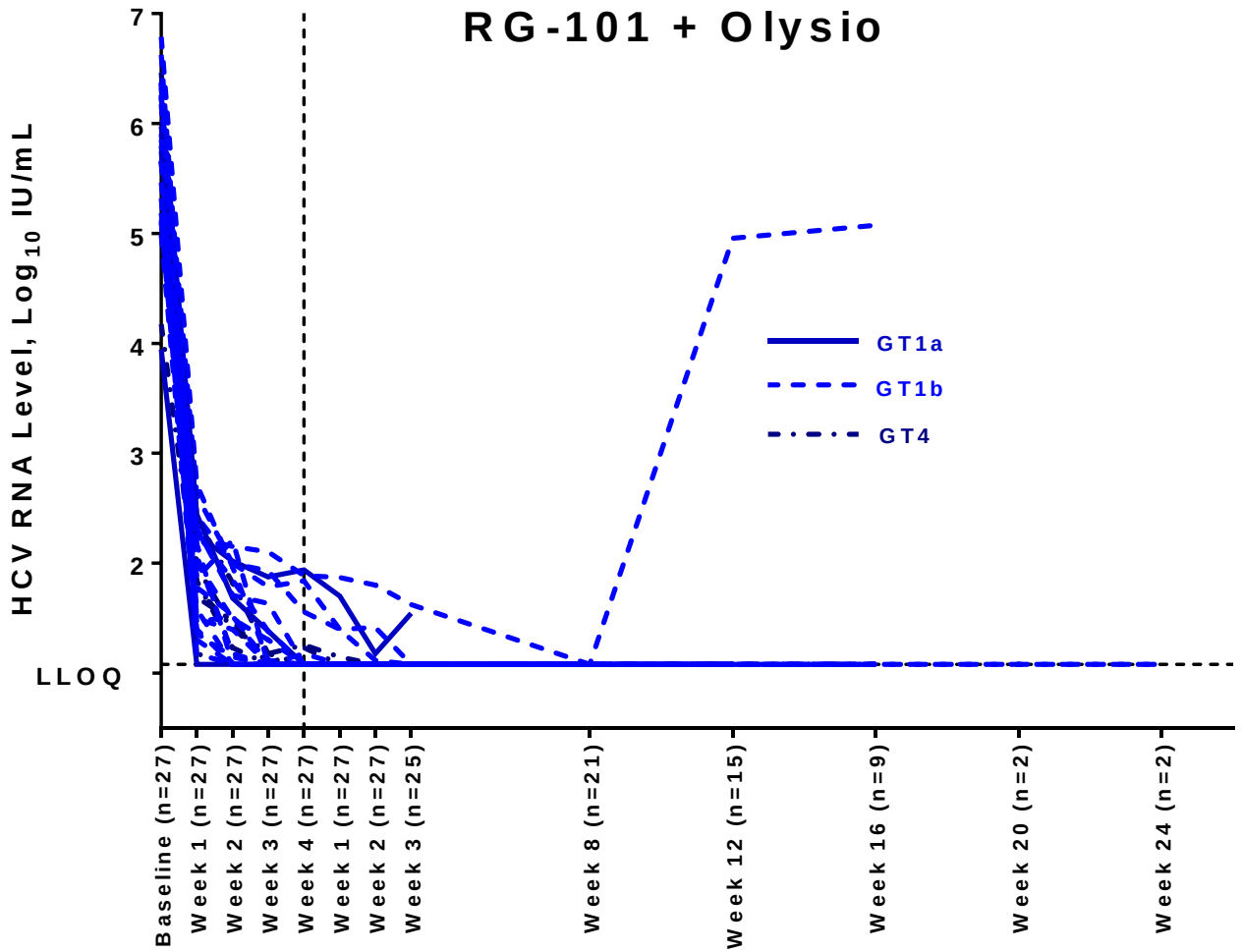


HCV RNA viral load assessed using RealTime HCV Assay (Abbott) with LLOQ = 12 IU/mL

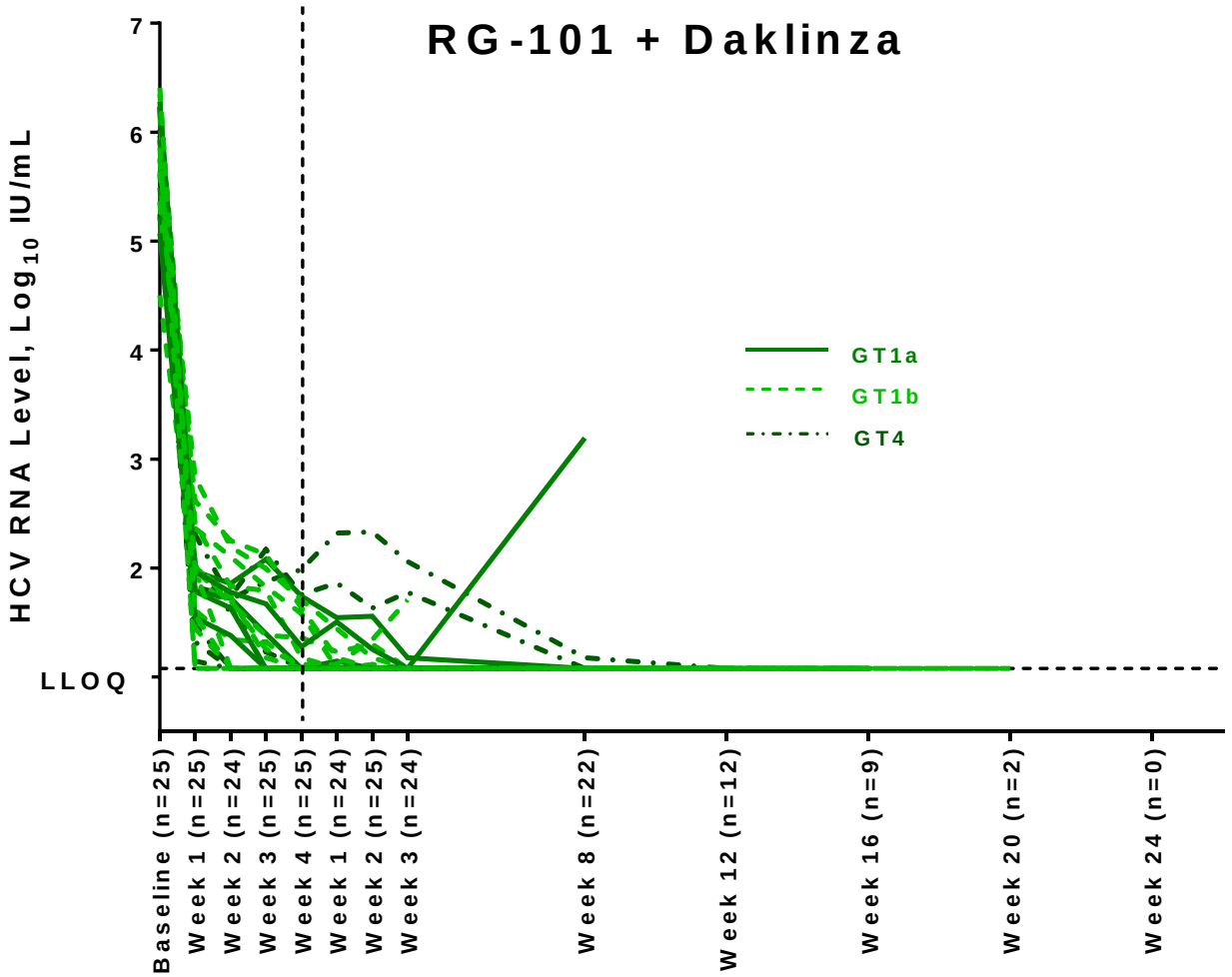
Viral Kinetics
RG-101 + Harvoni



Viral Kinetics
RG-101 + Olysio



Viral Kinetics
RG-101 + Daklinza



Summary of Adverse Events (AEs)
RG-101 in Combination with Oral DAAs Generally Well Tolerated

Type of Adverse Event	RG-101 + Harvoni (N=27) n (%)	RG-101 + Olysio (N=27) n (%)	RG-101 + Daklinza (N=25) n (%)	Overall (N=79) n (%)
Any AE	20 (74.1%)	20 (74.1%)	18 (72.0%)	58 (73.4%)
AE Leading to Premature Withdrawal	0	0	0	0
AE Causing Death	0	0	0	0
Serious AE (SAE)	0	1* (3.7%)	1* (4.0%)	2 (2.5%)
AEs by Severity				
Grade 1: Mild	11 (40.7%)	7 (25.9%)	9 (36.0%)	27 (34.2%)
Grade 2: Moderate	8 (29.6%)	13 (48.1%)	8 (32.0%)	29 (36.7%)
Grade 3: Severe	1 (3.7%)†	0	1 (4.0%)†	2 (2.5%)
Most Common AEs				
Fatigue	2 (7.4%)	7 (25.9%)	4 (16.0%)	13 (16.5%)
Headache	5 (18.5%)	4 (14.8%)	1 (4.0%)	10 (12.7%)
Injection site reactions	2 (7.4%)	5 (18.5%)	2 (8.0%)	9 (11.4%)

**One SAE of dyspnea in Olysio arm and one SAE of jaundice in Daklinza arm (details on next slide)*
†One severe AE of headache in Harvoni arm and one severe AE of jaundice in Daklinza arm (same event as SAE)

Low Rates of Serious Adverse Events

2 patients reported SAEs

Dyspnea (Olysio arm) – *Unrelated to Study Drug*

- 54 year old male reported event >2 months after completion of therapy. Admitted to hospital 1 night and recovered. Patient remains active in study with favorable virologic response.

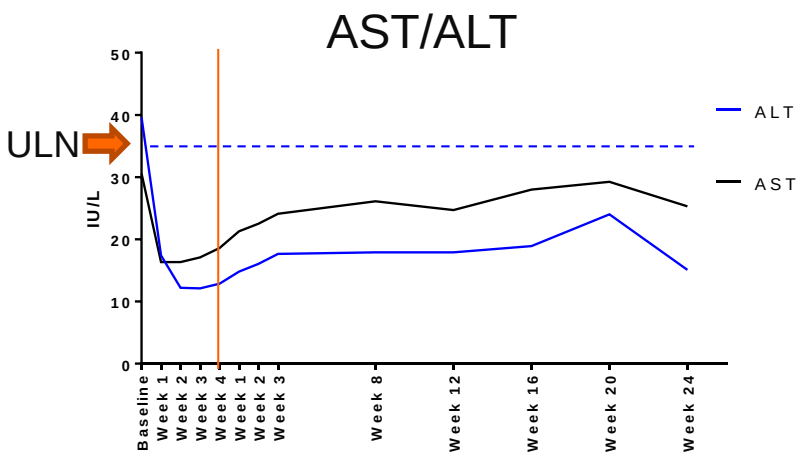
Jaundice (Daklinza arm) – *Possibly related to Study Drug*

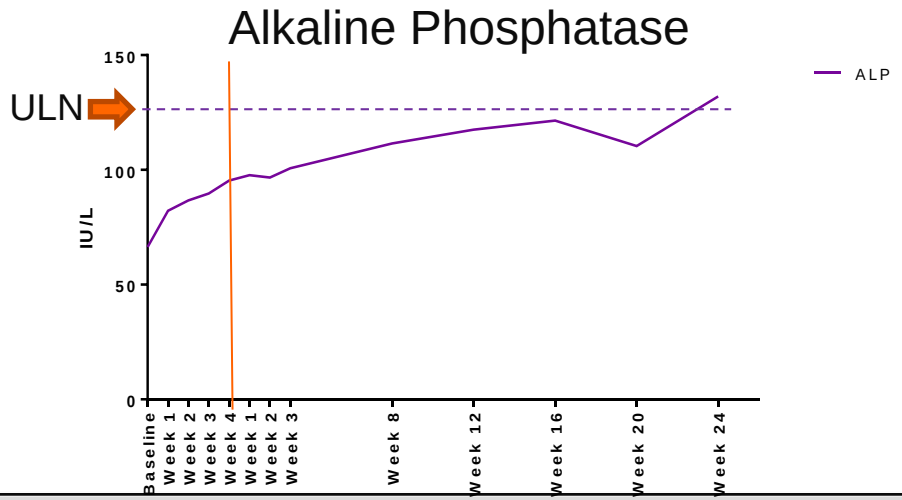
- 56-year old male presented with jaundice, fatigue, abdominal pain, and nausea 21 days after completion of therapy. Clinical chemistry showed significantly elevated total and direct bilirubin with minimal changes in transaminases. Ultrasound indicated potential sludge/debris in biliary tract and gallbladder wall thickening. Additional medical history included diabetes (not well-controlled) and alcohol use. Work-up ongoing to determine etiology. Patient currently recovering and remains active in study with favorable virologic response.

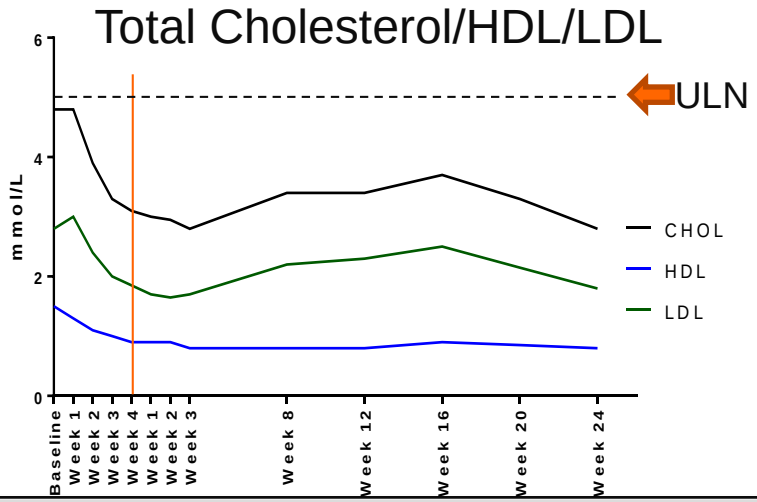
Pharmacodynamic (PD) Markers Consistent with Prior Experience

PD effects consistent with pre-clinical and Phase 1 results

- AST and ALT - Decreased with RG-101 therapy
- ALP – Increased (~1.5X) as direct effect of miR-122 inhibition
- Cholesterol - Decreased as indirect effect of miR-122 inhibition







Conclusions

- RG-101, a potent antagonist vs. miR-122, in combination with 4 weeks of oral DAA therapy resulted in high virologic response rates
  - Similar efficacy regardless of DAA used (NS5A inhibitor + NS5B polymerase inhibitor, protease inhibitor, or NS5A inhibitor)
- RG-101 well-tolerated in combination with oral DAAs
  - AEs generally mild or moderate in severity; low incidence of SAEs
  - No AEs led to discontinuation
- Changes in pharmacodynamic markers indicative of effective target engagement; consistent with previous experience with miR-122 inhibition
- Follow-up ongoing; full primary endpoint results (response at Follow-up Week 12) for all patients expected late Q2 2016

Significant Catalysts for RG-101 Anticipated in 2016

- ✓Phase 2 combination data presented at ILC 2016
  - ✓Oral presentation during general session
  - ✓Three posters
- Primary endpoint analysis (12 week follow-up) for all patients in late Q2 2016
- Safety and PK in US Phase 1 CKD+HCV population in 2H2016
- Interim data from open-faced sandwich with GSK-175 by YE2016

RG-101 Positioned as Potential Backbone HCV Therapy

Efficacy & safety data consistent with prior interim analysis

- Potent, durable, pan-genotypic
- Compelling efficacy in combination with Harvoni®, Olysio®, Daklinza™
- Safe and well tolerated to date
- Acts on important host factor of HCV, miR-122

Promising Product Profile

- Subcutaneous dosing may provide compliance benefits in real world
- Addition of RG-101 to any oral regimen – NS3/4A protease inhibitor, NS5A inhibitor, NS5B polymerase inhibitor – may shorten treatment regimen to 4 weeks
  - Current SOC is 8 to 12 weeks of oral DAA agents
  - May provide potential benefit to patients, physicians, payors

Thank You

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