HEPATITIS WEB STUDY HEPATITIS C ONLINE

State of the Art Therapy for HCV

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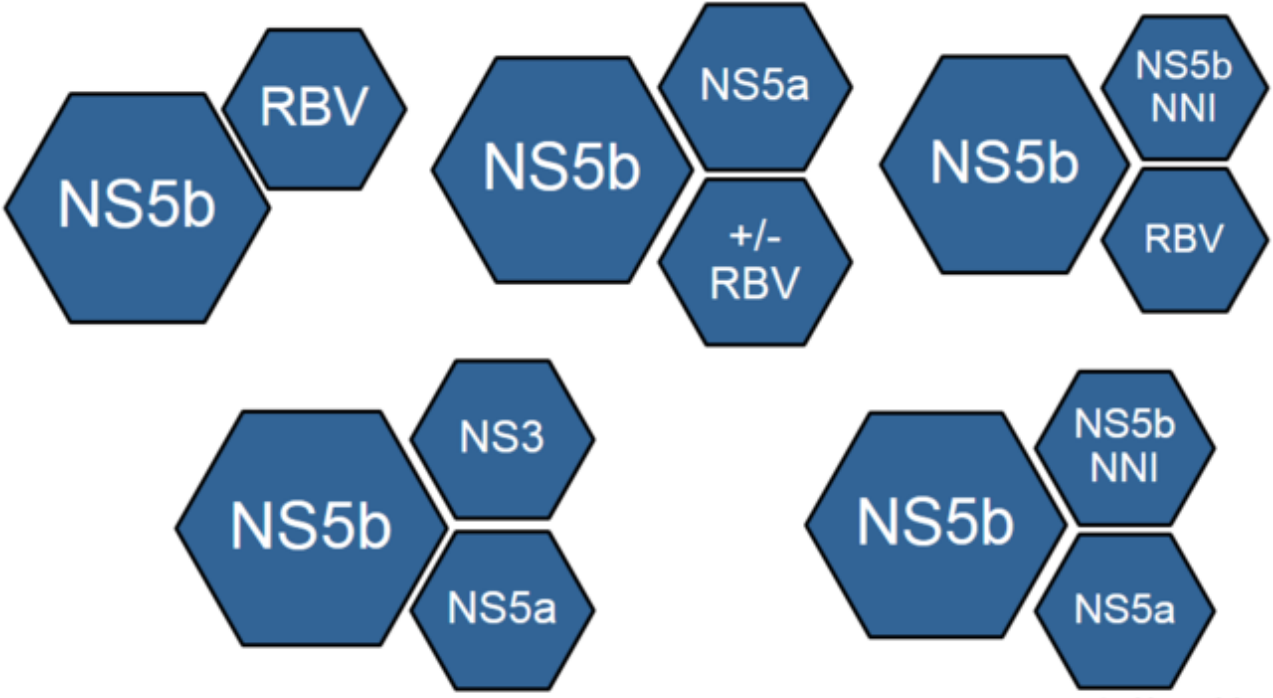
Hepatitis web study

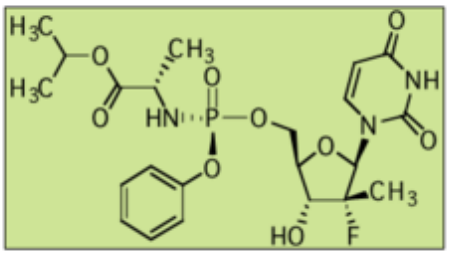
Components for Achieving SVR in HCV: 2015 and beyond



Foundations for Interferon-Free, All Oral Regimens

Sofosbuvir (SOF, *Sovaldi*)

- HCV-specific NS5b nucleotide polymerase inhibitor (chain terminator)
- Potent antiviral activity against HCV genotypes 1–6
- High barrier to resistance
- Once-daily, oral, 400-mg tablet



- Favorable clinical pharmacology profile
  - No food effect
  - No significant drug interactions
- Generally safe and well tolerated in clinical studies to date
  - More than 2000 patients studied
  - No safety signal in preclinical/clinical studies

Sofosbuvir with NS5a or NNI: ELECTRON Study

- **Ledipasvir**
  - HCV NSA5A inhibitor
  - NS5A essential for RNA replication, postreplication assembly, & secretion
  - Once daily dosing
  - Picomolar potency against HCV genotypes 1a and 1b
  - Effective against NS5A resistance associated variant S282T

- **GS 9669**
  - HCV NS5B non-nucleoside inhibitor
  - Binds at polymerase thumb site II
  - Once daily dosing
  - Nanomolar potency against HCV genotyes 1a and 1b

ELECTRON: Sofosbuvir + RBV with either Ledipasvir or GS-9669 12 week Treatment Regimens in HCV GT1

Patients (%) with HCV RNA <LOD* over time, n/N (%)

	SOF + RBV		SOF + LDV + RBV		SOF + GS-9669 + RBV	
	Naïve (n=25)	Null (n=10)	Naïve (n=25)	Null (n=9)	Naïve (n=25)	Null (n=10)
Week 1	8/25 (32)	1/10 (10)	11/25 (44)	0/9 (0)	3/25 (12)	0/10 (0)
Week 2	17/25 (68)	7/10 (70)	22/25 (88)	4/9 (44)	15/25 (60)	2/10 (20)
Week 4	25/25 (100)	10/10 (100)	25/25 (100)	8/9 (89)	23/25 (92)	10/10 (100)
EOT	25/25 (100)	10/10 (100)	25/25 (100)	9/9 (100)	25/25 (100)	10/10 (100)
SVR4	22/25 (88)	1/10 (10)	25/25 (100)	9/9 (100)	23/25 (92)	10/10 (100)
SVR12	21/25 (84)	1/10 (10)	25/25 (100)†	9/9 (100)	23/25 (92)	3/3

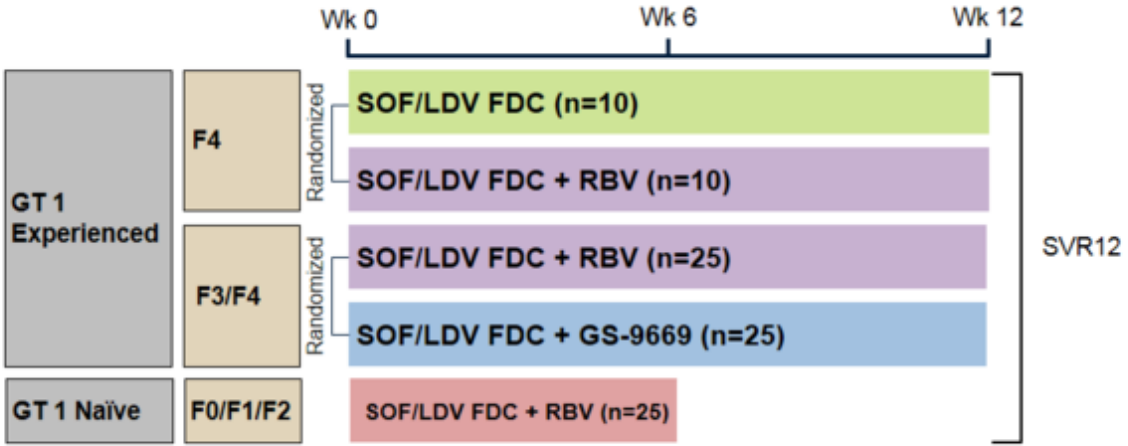
* Analyzed by TaqMan® HCV Test 2.0 with limit of detection (LOD) of 15 IU/mL.

† Includes 1 patient who stopped all treatment due to a serious adverse event (AE) at Week 8; this patient subsequently achieved SVR12.

EOT = end of treatment; SVR4 = sustained virologic response 4 weeks after EOT.

Source: Gane E, et al. 48th EASL; Amsterdam, Netherlands; 2013. Abstract 14.

Electron Study Design

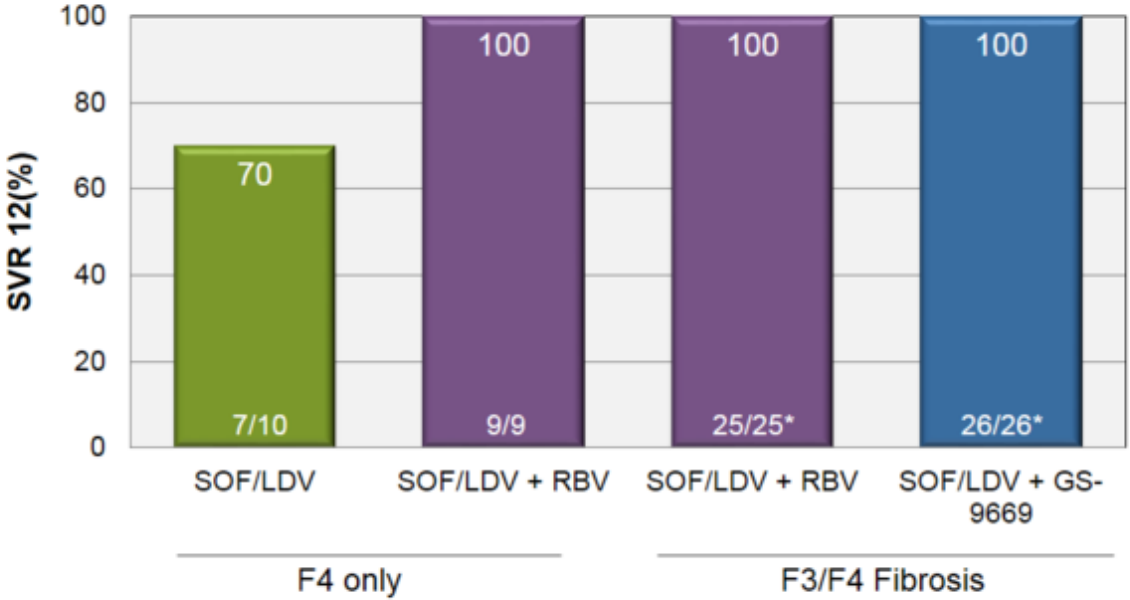


- Primary endpoint: SVR12 (HCV RNA <LLOQ)
- Patients enrolled in ELECTRON or ELECTRON 2 (GT1, F3/F4)
- All groups were open label

Source: Gane EJ, et al. AASLD. Washington, DC 2013, Abstract 73.

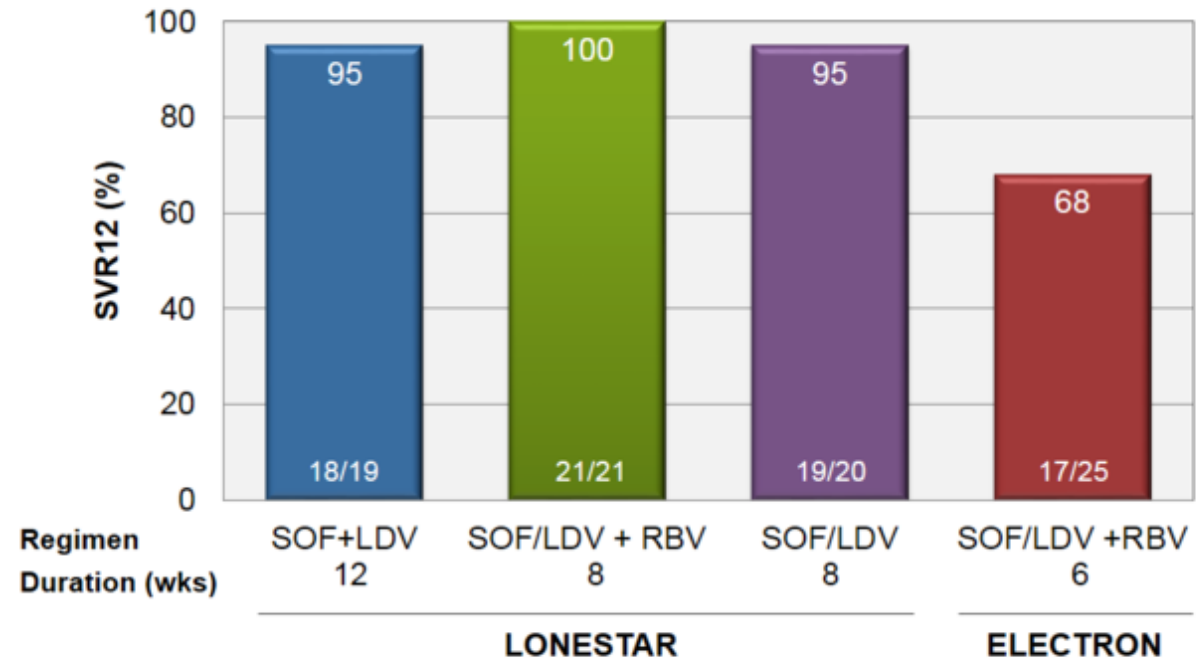
SVR12 Results: GT 1 Treatment-Experienced Patients with Advanced Fibrosis/Cirrhosis

SVR12 Rates in Patients who Receive 12 Weeks Duration of Therapy



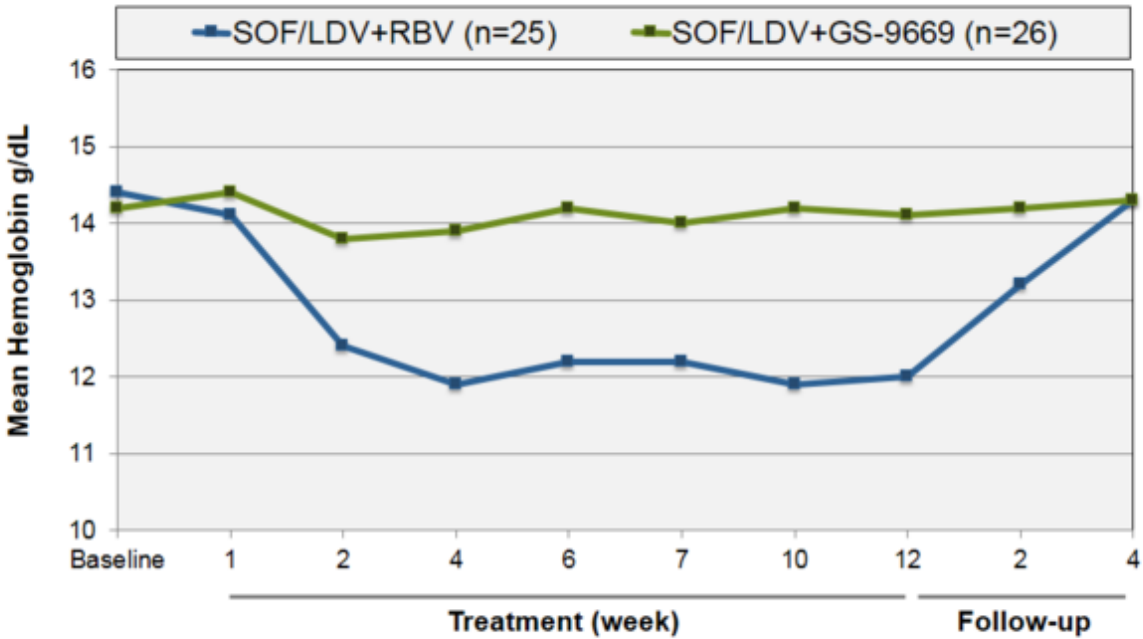
*Source: Gane EJ, et al. AASLD. Washington DC 2013, Abstract 73.

SVR12 Results: Treatment Duration
Genotype 1, Treatment-naïve, No cirrhosis



Source: Gane EJ, et al. AASLD. Washington DC 2013, Abstract 73.
Lawitz E, et al. Lancet. 2014:383:515-23.

Hemoglobin Levels During and After Therapy in Patients with Advanced Fibrosis/Cirrhosis



Source: Gane EJ, et al. AASLD. Washington, DC 2013, Abstract 73.

How will we treat PI Failure patients?

Disclosures

- Research Support: BMS, Gilead, BI, Merck
- Consulting board: BMS, Gilead, BI, Merck, Abbvie, Nanogen, Idenix
- Honoraria for promotional talks: BMS, Gilead, Merck

LONESTAR: Sofosbuvir-Ledipasvir FDC +/- Ribavirin Treatment-Naïve and Previously Treated GT 1

	Cohort A: treatment naïve patients			Cohort B: patients previously treated with protease inhibitors	
	Sofosbuvir plus ledipasvir for 8 weeks (n=20)	Sofosbuvir plus ledipasvir with ribavirin for 8 weeks (n=21)	Sofosbuvir plus ledipasvir for 12weeks (n=19)	Sofosbuvir plus ledipasvir for 12 weeks (n=19)	Sofosbuvir plus ledipasvir with ribavirin for 12 weeks (n=21)
Treatment week 4	20 (100%; 83-100)	20 (100%; 84-100)	19 (100%; 82-100)	18 (95%; 74-100)	21 (100%; 84-100)
End of Treatment	20 (100%; 83-100)	20 (100%; 84-100)	19 (100%; 82-100)	19 (95%; 74-100)	21 (100%; 84-100)
SV4	20 (100%; 83-100)	20 (100%; 84-100)	19 (100%; 82-100)	18 (95%; 74-100)	21 (100%; 84-100)
SVR12	19 (95%; 75-100)	21 (100%; 84-100)	18* (95%; 74-100)	18 (95%; 74-100)	21 (100%; 84-100)
Virological failure					
During treatment	0	0	0	0	0
Relapse	1 (5%)	0	0	1 (5%)	0

Source: Lawitz E, et al. Lancet. 2014:383:515-23.

NIAID SYNERGY: Sofosbuvir/Ledipasvir FDC Alone or In Combination with GS-9451 or GS-9669

- GS-9451: QD protease inhibitor (80 mg)
- Treatment naïve, genotype 1
  African American, 88%

Virologic response

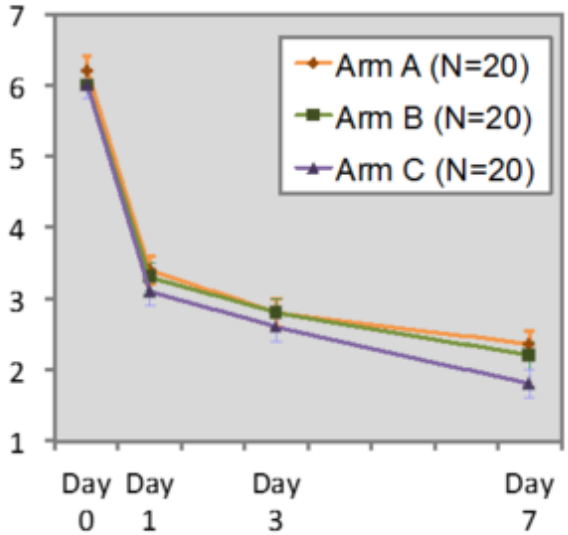
A: SOF/LDV x 12 wks (n=20)
  - SVR12 100%

B: SOF/LDV + 9669 x 6 wks (n=20)
  - SVR4 90%; Relapse, n=1

C: SOF/LDV + 9451 x 6 wks (n=20)
  - SVR4 100%

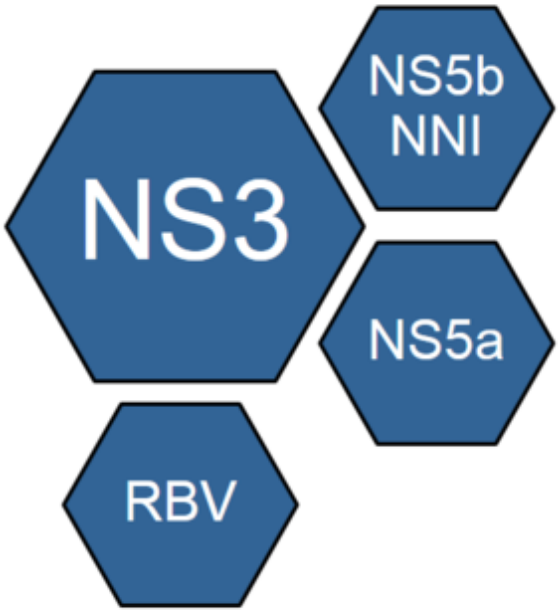
- No discontinuation or SAE

HCV RNA Log10 IU/mL
Decline Baseline to Day 7

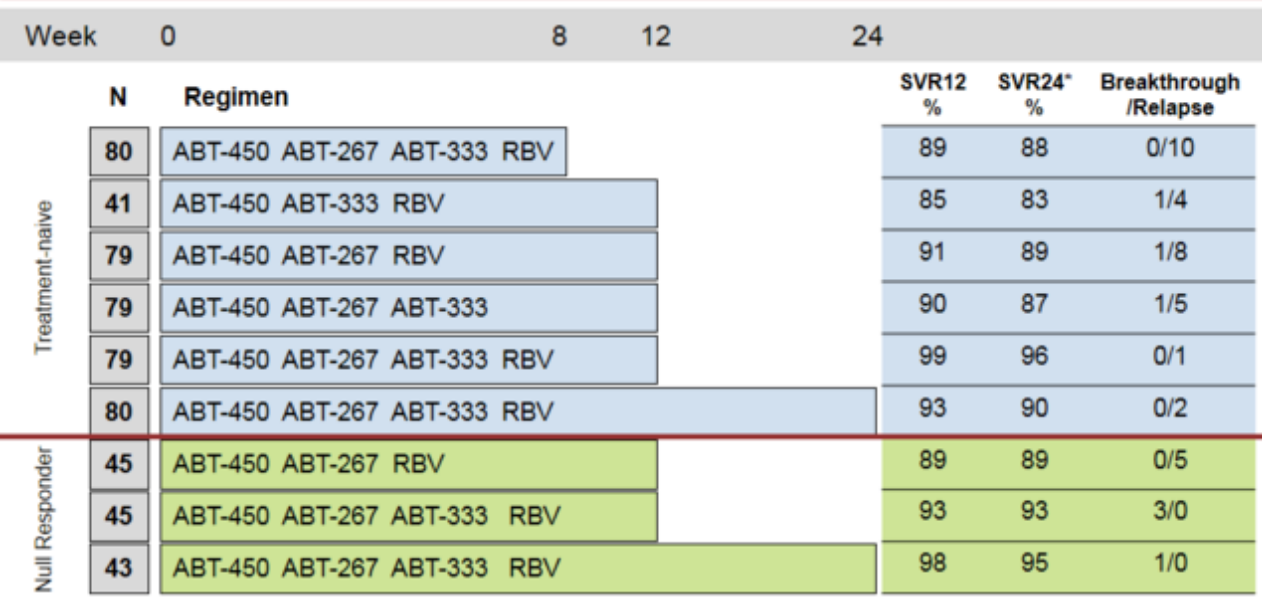


Source: Kohli A, et al. 64th AASLD; Washington, DC; 2013. Abstract LB-8.

The components of SVR in HCV
High SVR rates without a nucleotide polymerase inhibitor



AVIATOR Study: ABT-450/r, ABT-267, ABT-333 ± RBV in Non-Cirrhotic, Naïve and Null Responders



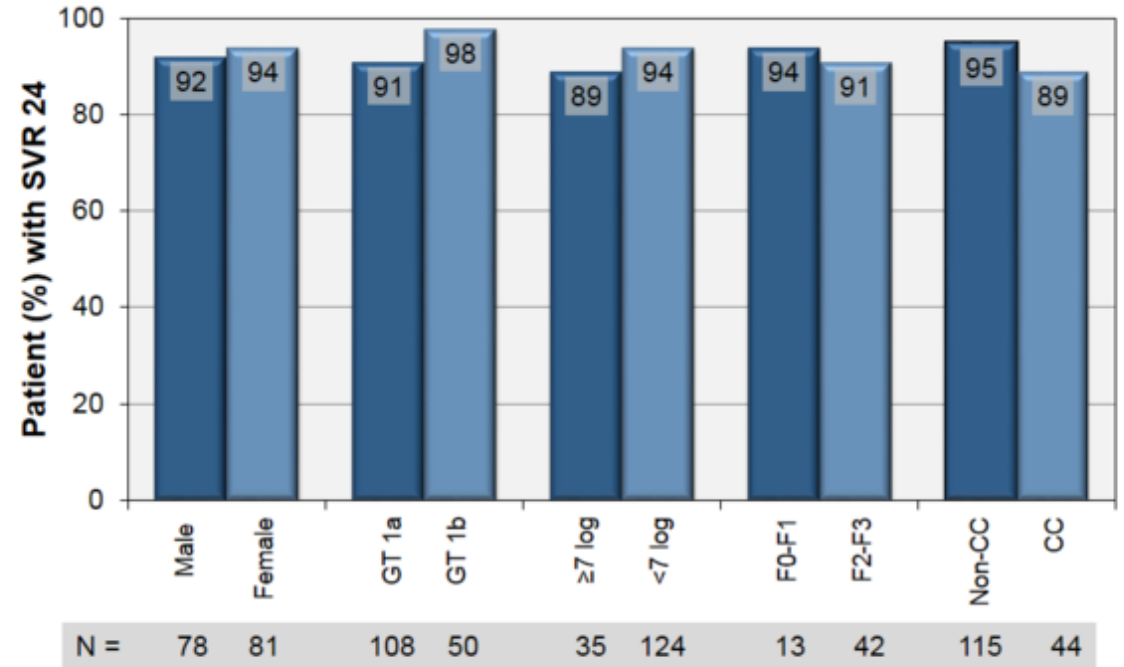
	N	Regimen	SVR12 %	SVR24* %	Breakthrough /Relapse
Treatment-naive	80	ABT-450 ABT-267 ABT-333 RBV	89	88	0/10
	41	ABT-450 ABT-333 RBV	85	83	1/4
	79	ABT-450 ABT-267 RBV	91	89	1/8
	79	ABT-450 ABT-267 ABT-333	90	87	1/5
	79	ABT-450 ABT-267 ABT-333 RBV	99	96	0/1
	80	ABT-450 ABT-267 ABT-333 RBV	93	90	0/2
Null Responder	45	ABT-450 ABT-267 RBV	89	89	0/5
	45	ABT-450 ABT-267 ABT-333 RBV	93	93	3/0
	43	ABT-450 ABT-267 ABT-333 RBV	98	95	1/0

N =571

*8 patients with SVR12 have not returned for >24 weeks and are counted as virologic failures for SVR24; 3 patients relapsed between SVR12 and SVR24.

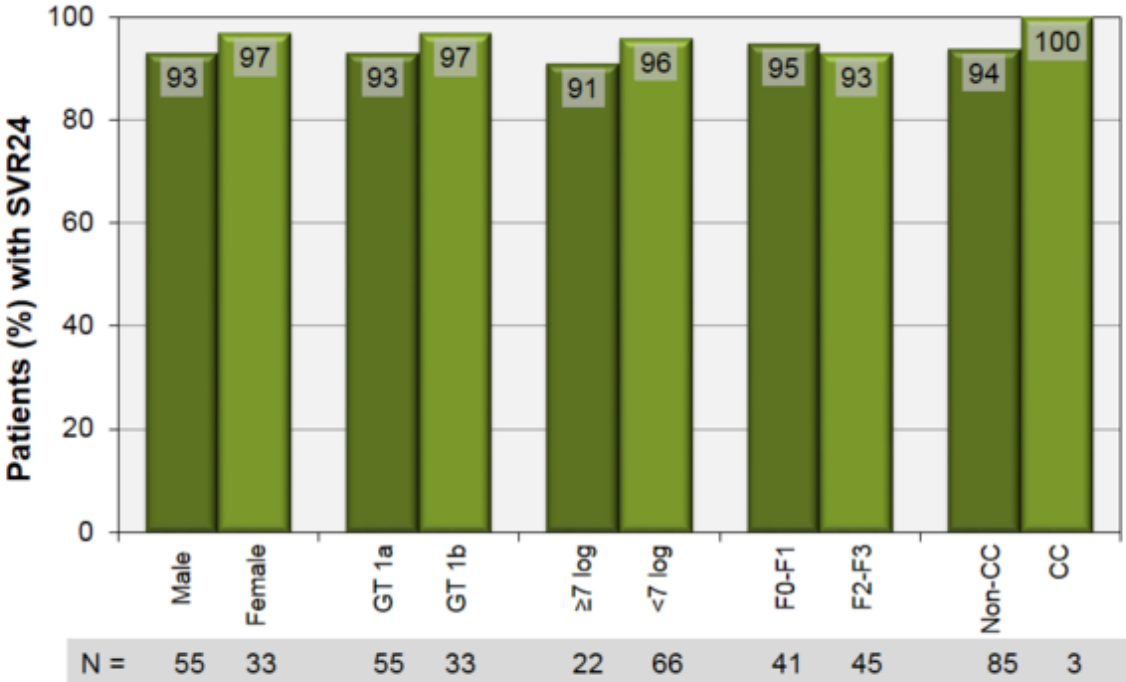
Source: Kowdley K, et al. 48th EASL; Amsterdam, Netherlands. 2013. Abstract 3.

AVIATOR Study
SVR24 by Baseline Subgroups – Treatment-Naïve Patients



Source: Kowdley K, et al. 48th EASL; Amsterdam, Netherlands. 2013. Abstract 3.

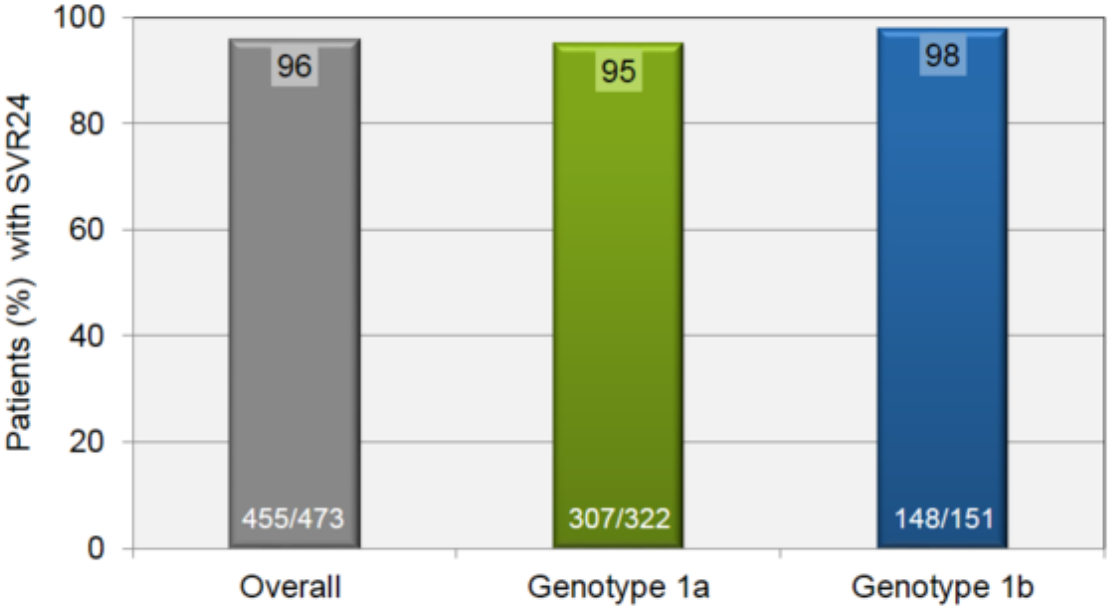
AVIATOR Study
SVR24 by Baseline Subgroups – Null Responders



Source: Kowdley K, et al. 48th EASL; Amsterdam, Netherlands. 2013. Abstract 3.

SAPPHIRE-I Phase 3 Top Line results

ABT-450/r + ABT-267 + ABT-333 + Ribavirin for 12 weeks



Source: Abbvie Press release 11/18/13

PEARL-I Study Design

		Planned N	HCV Genotype/Regimen Treatment Experience BL → Week 12 → Week 24	
Substudy 1: Patients without Cirrhosis	Group 1	40	GT 4 ABT-450/r + ABT-267 Treatment naïve	*Actual N = 44*
	Group 2	40	GT1b ABT-450/r + ABT-267 Treatment naïve	*Actual N = 42*
	Group 3	40	GT1b ABT-450/r + ABT-267 Null Responders	*Actual N = 40*
	Group 4	40	GT4 ABT-450/r + ABT-267+ *RBV* Null Responders	*Actual N = 42*
	Group 5	40	GT4 ABT-450/r + ABT-267+ *RBV* Treatment naïve	
	Group 6	40	GT4 ABT-450/r + ABT-267 + *RBV* Partial/Null Responders & Relapsers	

ABT-450/r 150/100 mg QD; ABT-267 25 mg QD
RBV weight based, 1000 mg or 1200 mg daily divided BID
Patients followed through 48 weeks post-treatment.

PEARL-I Study Design

		Planned N	HCV Genotype/Regimen Treatment Experience	
	BL → Week 12 → Week 24			
Substudy 2: Patients with compensated Cirrhosis	Group 7	40	GT 4 ABT-450/r + ABT-267 Treatment naïve	*Actual N = 47*
	Group 8	40	GT1b ABT-450/r + ABT-267 Partial/Null Responders & Relapsers	*Actual N = 52*

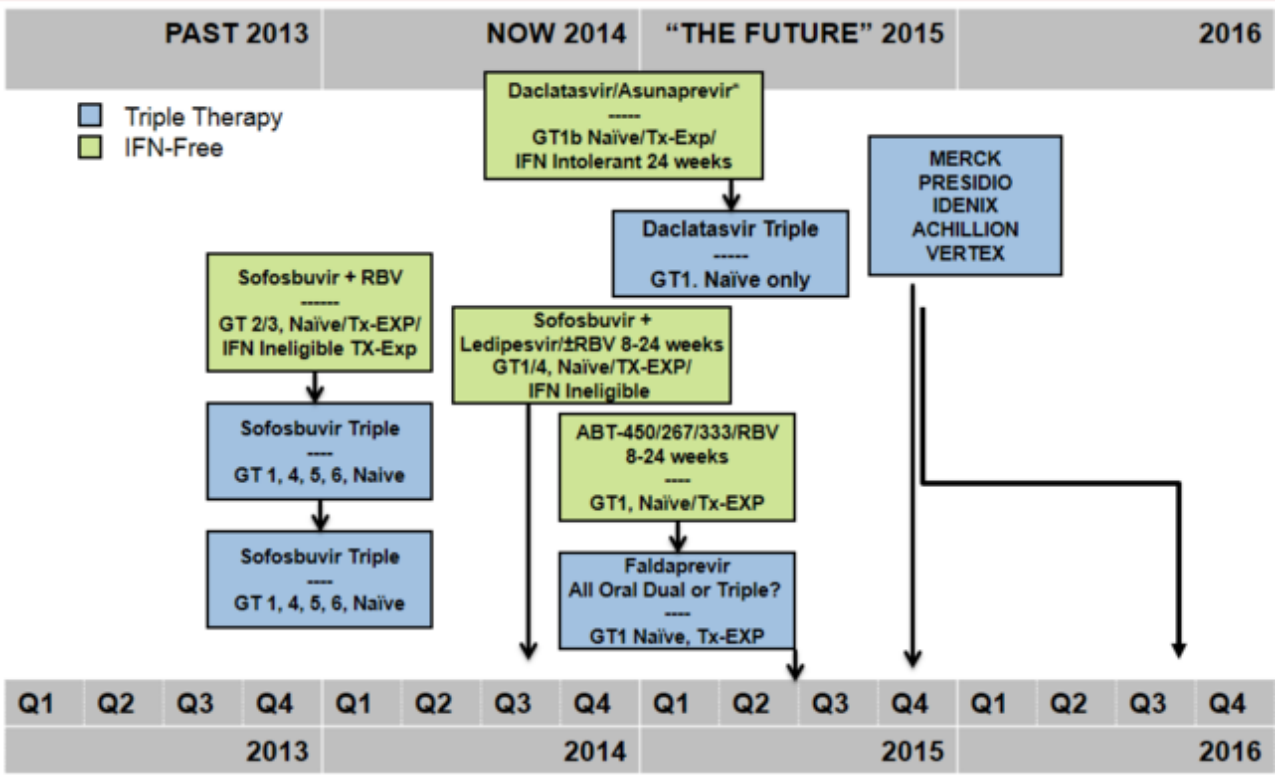
ABT-450/r 150/100 mg QD; ABT-267 25 mg QD; RBV weight based, 1000 mg or 1200 mg daily divided BID. Patients followed through 48 weeks post-treatment.

AbbVie Phase 3 Clinical Development Program

Study	Patients	Treatment Regimen	SVR_{12}
PEARL-II (12 weeks)	GT1b treatment-experienced (N=179)	AbbVie regimen* + RBV (n=88)	97% (85/88)
		AbbVie regimen* only (n=91)	100% (91/91)
PEARL-III (12 weeks)	GT1b treatment-naive (N=419)	AbbVie regimen* + RBV (n=210)	99% (209/210)
		AbbVie regimen* only (n=209)	99% (207/209)
PEARL-IV (12 weeks)	GT1a treatment-naive (N=305)	AbbVie regimen* + RBV (n=100)	97% (97/100)
		AbbVie regimen* only (n=205)	90% (185/205)
TURQUOISE-II (12 & 24 weeks)	GT1 treatment-naive and treatment-experienced w/ compensated cirrhosis (N=380)	AbbVie regimen* + RBV, 12 weeks (n=208)	92% (191/208)
		AbbVie regimen* + RBV, 24 weeks (n=172)	96% (165/172)
SAPPHIRE-I (12 weeks)	GT1 treatment-naive (N=631)	AbbVie regimen* + RBV (n=473)	96% (455/473)
SAPPHIRE-II (12 weeks)	GT1 treatment-experienced (N=394)	AbbVie regimen* + RBV (n=297)	96% (286/297)

* AbbVie Regimen = ABT-450/r/ABT-267(150/100/25 mg QD) plus ABT-333 (250 mg BID)

Projected Timing for New Regimen Launches

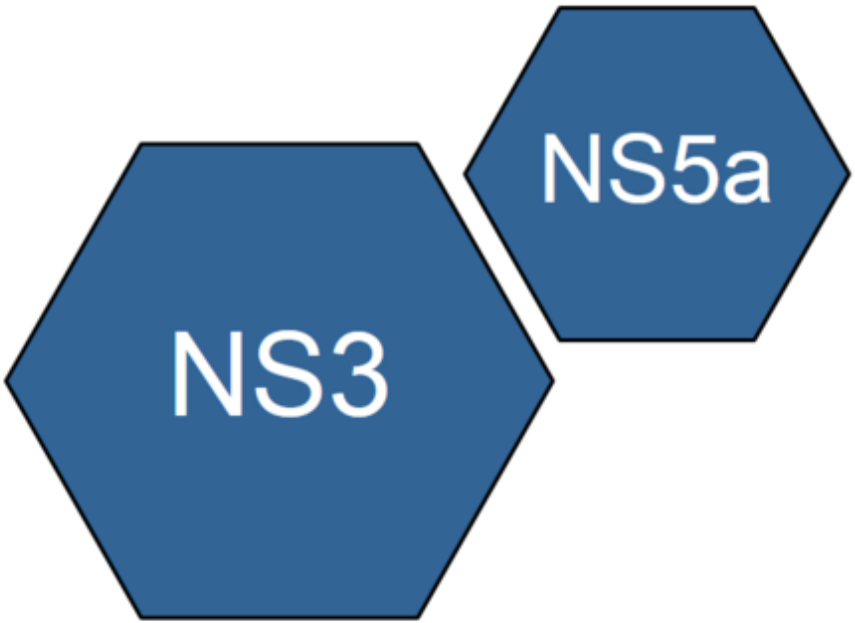


AbbVie HCV Clinical Development Program

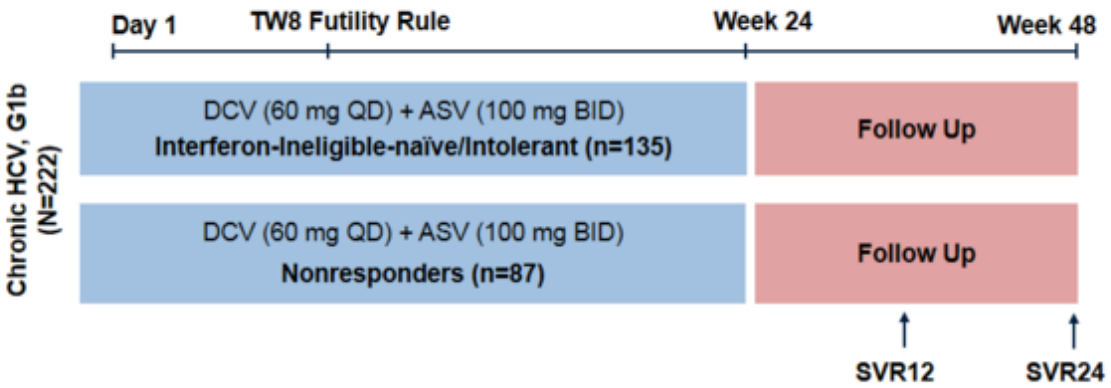
Phase 2a	Phase 3	Special Patient Populations
PILOT GT1 naïve N=11 ABT-450/r + ABT 072 + RBV	**SAPPHIRE– I** GT1 naïve, N= 631 ABT-450/r/ABT-267 + ABT-333 + RBV	**TURQUOISE – I** (HIV/HCV) GT1 naïve/experienced, N= 300 ABT-450/r/ABT-267 + ABT-333 + RBV
CO-PILOT GT1 naïve/experienced, N=50 ABT-450/r + ABT-333 + RBV	**SAPPHIRE–II** GT1b experienced, N=394 ABT/450/r/ABT-267 + ABT-333 + RBV	**TURQUOISE – II** (Compensated Cirrhosis) GT1 naïve/experienced, N= 380 ABT-450/r/ABT-267 + ABT-333 + RBV
Phase 2b		**M12-999** (Liver Transplant Recipients) GT1 naïve/experienced, N= 30 ABT-450/r/ABT-267 + ABT-333 + RBV
AVIATOR GT1 naïve/experienced, N=571 ABT-450/r ABT-267 +/- ABT-333 +/- RBV	**PEARL-II** GT1b experienced, N= 179 ABT-450/r/ABT-267 + ABT-333 +/- RBV	**Comparative Trials**
NAVIGATOR GT1, 2, 3 naïve, N=60 ABT-450/r + ABT-267 +/- RBV	**PEARL-III** GT1b naïve, N=419 ABT-450/r/ABT-267 + ABT-333 +/- RBV	**MALACHITE– I** GT1 naïve, N= 314 ABT-450/r/ABT-267 + ABT-333 + RBV Compared to TPV+ PegIFN + RBV
PEARL–I GT1b, 4 naïve/experienced N=320 ABT-450/r +ABT-267 +/- RBV	**PEARL-IV** GT1a naïve, N=305 ABT-450/r/ABT-267 + ABT-333 +/- RBV	**MALACHITE– II** GT1 experienced, N= 150 ABT-450/r/ABT-267 + ABT-333 + RBV TPV + PegIFN + RBV

Source: www.clinicaltrails .gov; Data on File, AbbVie.

The components of SVR in HCV: Genotype 1b



All-Oral Combination of Daclatasvir plus Asunaprevir in Interferon-Ineligible Naïve/Intolerant and Nonresponder Japanese Patients Chronically Infected with HCV Genotype 1b

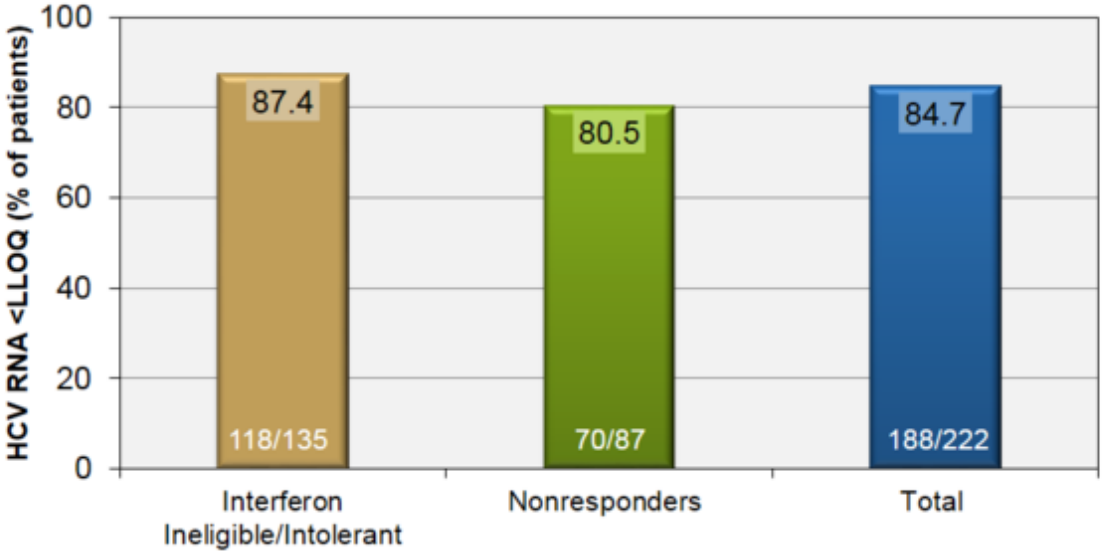


Abbreviations: DCV = daclatasvir; ASV = asunaprevir

Primary efficacy endpoint was SVR_{24}: the proportion of patients with HCV RNA <15 IU/mL (target detected [TD] or target not detected [TND]) at 24 weeks after completion of daclatasvir and asunaprevir treatment, including patients who discontinued treatment early

Source: Chayama K et al. 64th AASLD. 2013; Washington, DC. Oral 211.

Daclatasvir plus Asunaprevir for 24 weeks in HCV Genotype 1b: SVR_{24} (%)

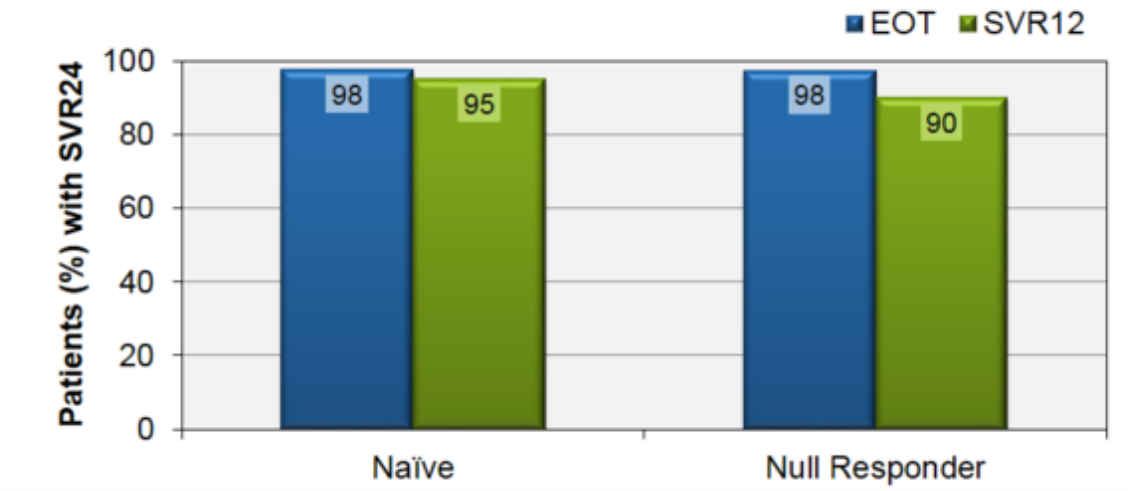


High rates of SVR24 were achieved in patient populations typically associated with poor responses to other therapies or with limited therapeutic options

Source: Chayama K et al. 64th AASLD. 2013; Washington, DC. Oral 211.

PEARL-I Study: ABT-450/r + ABT-267, 12 weeks in GT 1b, Treatment-naïve, Null Responders

PEARL-1 Results: EOT Response and SVR12

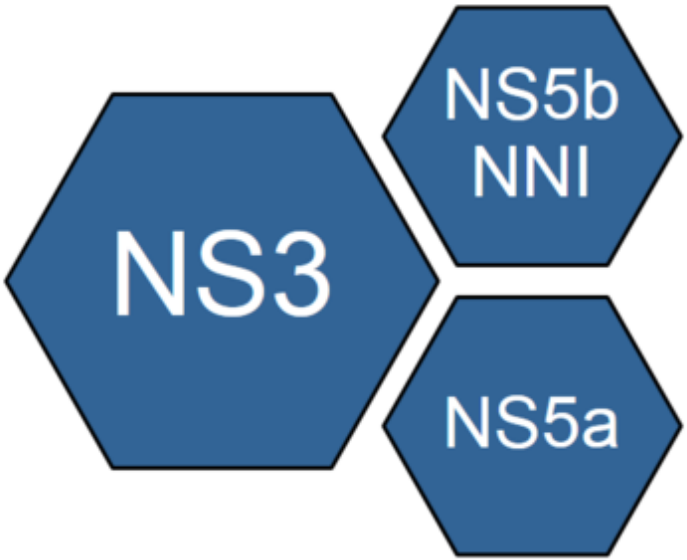


Non-SVR Patients

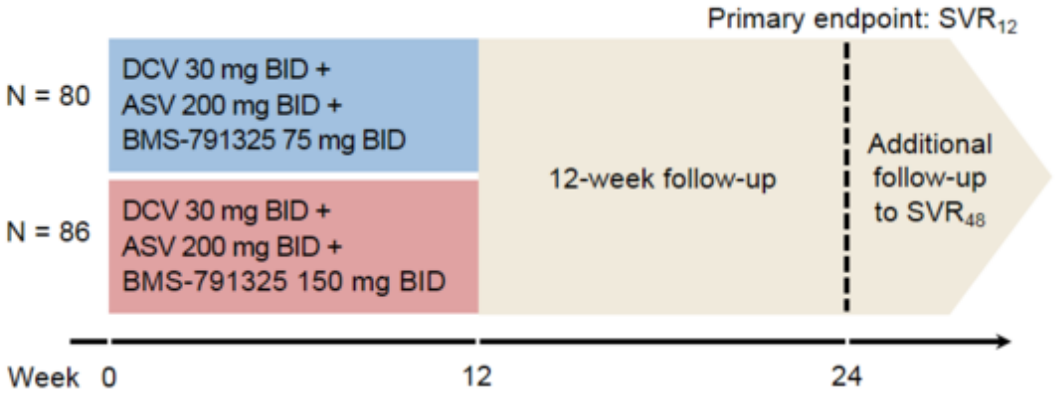
- Naïve: Lost to follow-up, n=2
- Null responders: Viral breakthrough, n=1; Relapse, n=3
- No discontinuations due to AE; Drug interruption due to grade 3 ALT increase, n=1

Source: Lawitz E, et al. 64th AASLD; Washington, DC. 2013. Abstract 75.

Components of SVR in HCV: High SVR rates without RBV



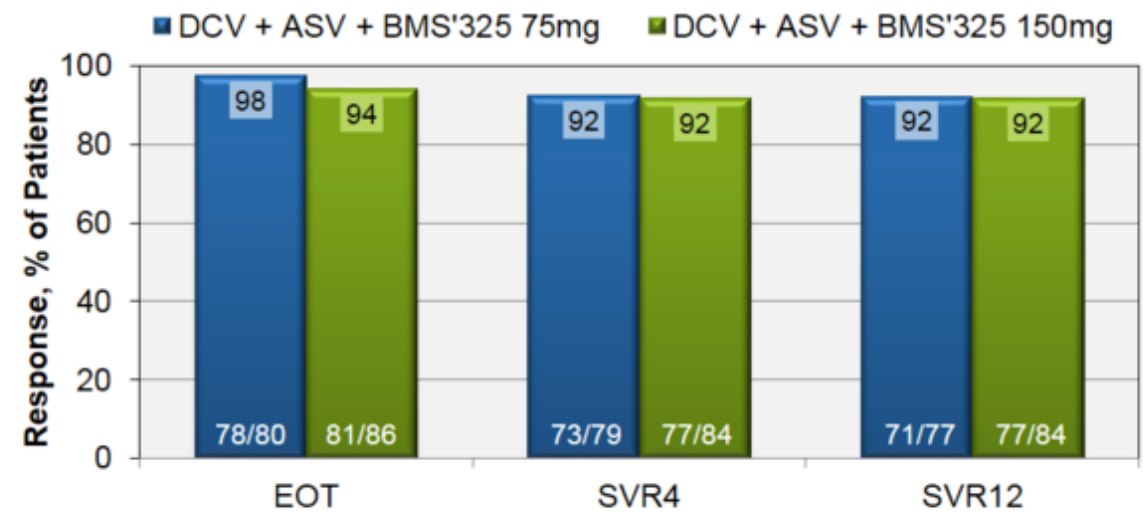
Interferon-Free and Ribavirin-Free Combination of Daclatasvir, Asunaprevir, BMS-791325 for 12 Weeks



- **Patients:** treatment-naive, stratified by GT 1a/1b and presence of biopsy-confirmed cirrhosis (≈ 10% cirrhotics per group)
- **HCV RNA end points:** lower limit of assay quantitation, target detected ($LLOQ_{TD}$; 25 IU/mL), and below LLOQ and target not detected ($LLOQ_{TND}$; ≈ 10 IU/mL)
- **Primary end point:** HCV RNA < LLOQ 12 weeks post-treatment (SVR_{12})
  - Observed analysis: breakthrough, relapse, addition of P/R = failure
  - Modified intent-to-treat analysis: missing, breakthrough, relapse or addition of P/R = failure

Source: Everson GT, et al. 64th AASLD. 2013; Washington, DC. Presentation LB-1.

Efficacy Through SVR12 (Observed)
Study AI443-014

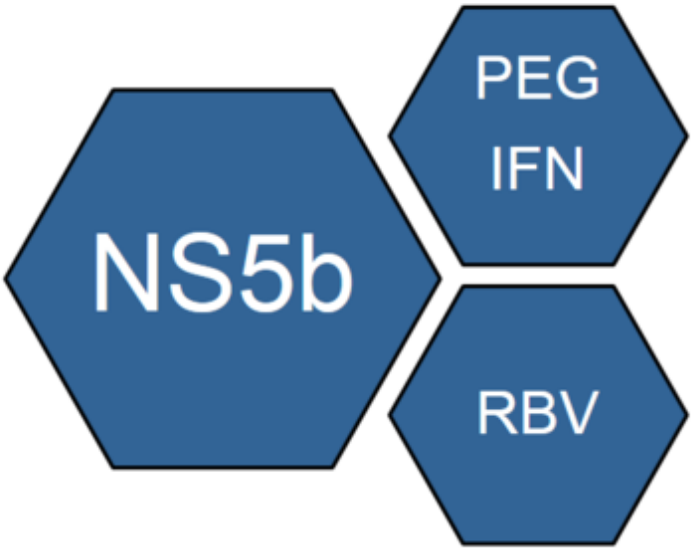


Missing Data at Post Treatment Week 12	
DCV + ASV + BMS'325 75mg	3 patients, mITT SVR12= 88.8%
DCV + ASV + BMS'325 150mg	2 patients, mITT SVR12= 89.5%

Source: Everson GT, et al. 64th AASLD. 2013; Washington, DC. Presentation LB-1.

Genotypes 2/3 has broken the ground with the first approved all-oral regimen with a few caveats

Perhaps the best solution for genotype 3 cirrhotic patients with albumin over 3.5 and platelets over 100k?

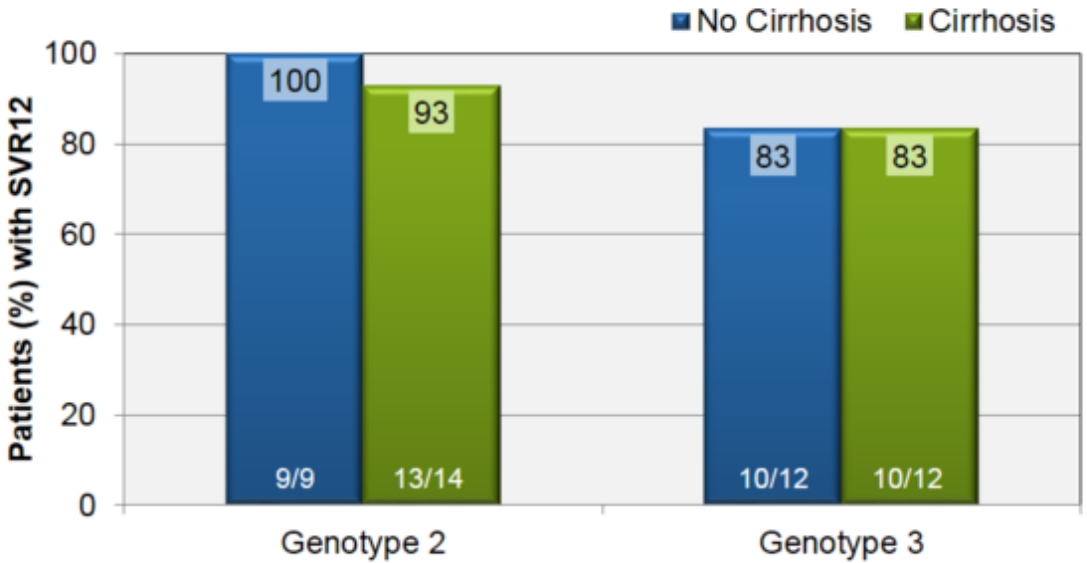


Many Direct Acting Antivirals in Development

- **Protease inhibitors**
  - Faldaprevir
  - Asunaprevir
  - ABT-450
  - MK-5172
  - Sovaprevir
  - ACH-2684
  - GS-9451 NAIAD Synergy trial
- **NS5A Inhibitors**
  - Daclatasvir
  - Ledipasvir
  - ABT-267
  - GS-5816 pangenotypic
  - ACH-3102
  - PPI-668
  - GSK 2336805
  - Samatasvir
  - MK-8742

Role of Peginterferon in Reducing Treatment Costs in GT 2,3
LONESTAR-2: 12 Weeks PR/Sofosbuvir

SVR12 by Cirrhosis Status

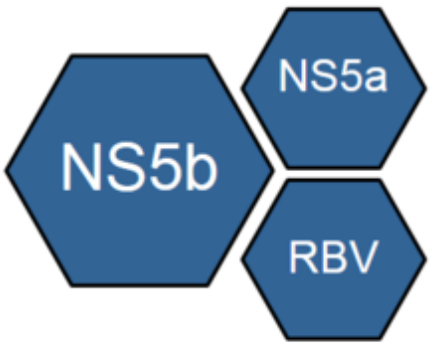


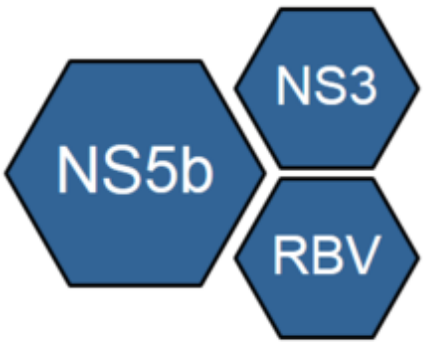
Source: Lawitz E, et al. 64th AASLD; Washington, DC. 2013. Abst. LB-4.

What about those who fail PR ± Telaprevir or Boceprevir

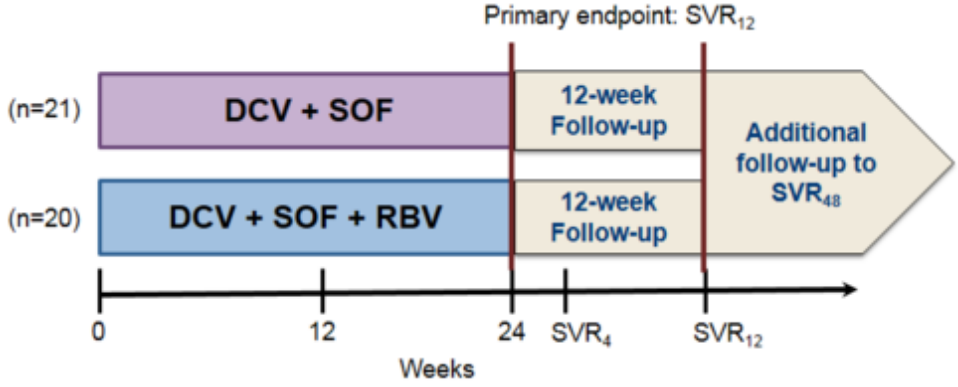
Especially those who need treatment now

- Mixing and Matching DAAs ± RBV
- Will this be allowed?
- Many ongoing and future collaborations





Daclatasvir Plus Sofosbuvir ± RBV in GT1 Who Previously Failed Telaprevir or Boceprevir



Key Demographics:

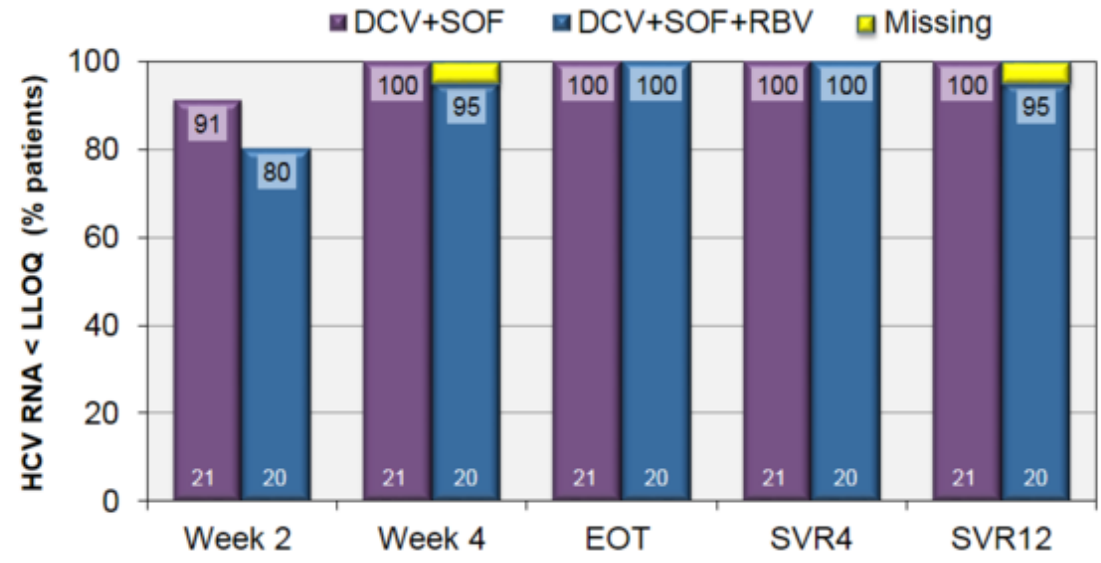
- 83% (34/41) GT1a
- Mean baseline HCV RNA
- 6.3 $\log_{10}$ IU/mL
- 98% (40/41) IL28B "non-CC"

Key Safety Findings:

- No patients discontinued due to adverse events (AEs)
- Most common AEs (≥30% total) were fatigue and headache
- No Grade 3/4 hematologic or hepatic laboratory abnormalities

Source: Sulkowski M, et al. 48th EASL; Amsterdam, Netherlands. 2013. Abstract 1417.

Daclatasvir Plus Sofosbuvir ± RBV in GT1
Virologic Response During and After Treatment (mITT)

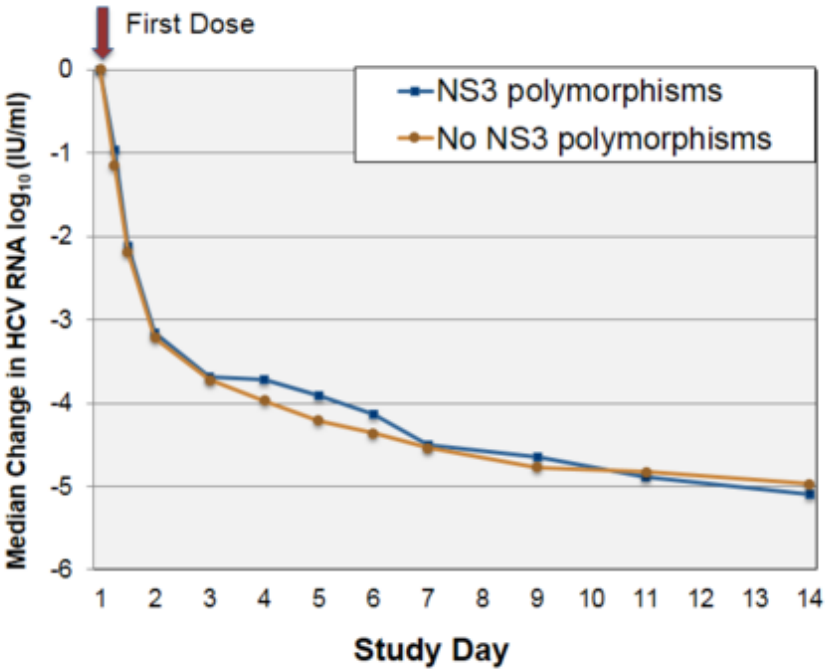


- 1 patient missing at post-treatment (PT) Week 12: HCV RNA was undetectable at PT Week 4 and at PT Week 24 (preliminary)
- 21/41 patients have reached PT Week 24; all have achieved SVR24

Source: Sulkowski M, et al. 48th EASL; Amsterdam, Netherlands. 2013. Abstract 1417.

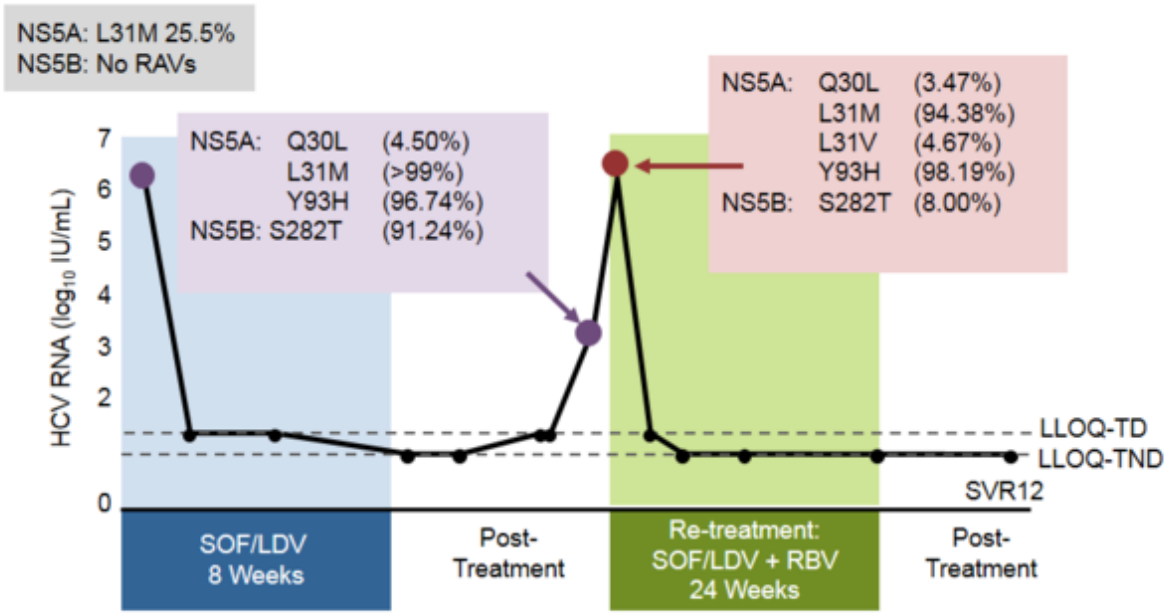
Virologic Response by Presence or Absence of Baseline NS3 Polymorphisms

Patients with NS3 polymorphisms, n	
V36M-R155K	6
R155K	3
V36L-R155K	1
T54S-R155K	1
T54S-V55I-R155K	1
V36M	1
V36M-V55I	1
V36M-V55A-R155K	1
V36M-R155K-I170T	1
V36A	1
V55A	1
V170T	1



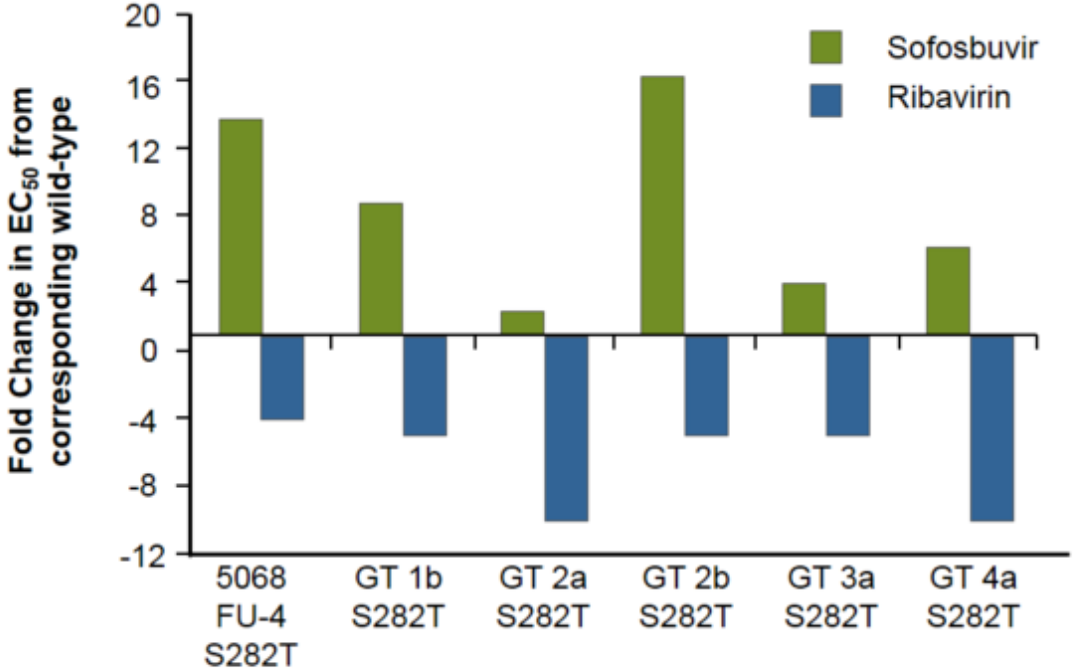
Source: Sulkowski M, et al. 48th EASL; Amsterdam, Netherlands. 2013. Abstract 1417.

Retreatment of a Patient Who Had Relapse with Multi-DAA Resistant Virus Following 8 Weeks of SOF/LDV



Source: Lawitz E, et al. 64th AASLD; Washington, DC. 2013. Abstract 215/1844.

Susceptibility of *S282T to Sofosbuvir and Ribavirin



*S282T demonstrates hyper-susceptibility to RBV

Source: Svarovskaia ES, et al. AASLD. 2012: Poster 753.

Presidio Collaboration Study Design and Methods

Presidio is a company based in San Francisco that has a library of NS5a inhibitors that is moving forward with collaborations in the HCV treatment space for all oral combination therapy

Achillion
Hepatitis C Therapy Drug Development Plans

- **ACH-3422 (Nucleotide NS5B Polymerase Inhibitor)**
  - Phase 1 Trial: in Q2 2014

- **ACH-3102 (second-generation NS5A inhibitor) + Sofosbuvir**
  - Pilot Phase 2 Study: ACH-3102 + sofosbuvir in treatment-naïve in early Q2 2014

- **ACH-3422 + ACH-3102 ± NS3/4A Protease Inhibitor**
  - Phase 2: all-oral combination study by year-end 2014
  - Phase 2: ACH-3422 + ACH-3102 +/- Achillion NS3/4A protease inhibitor, in treatment-naïve over treatment durations of 8 weeks or less in early 2015.

- **ACH-3102 (NS5A inhibitor) + ACH-2684 (next-generation NS3/4A protease inhibitor)**
  - Phase 1: ACH-3102 + ACH-2684 in drug-drug interaction study begin Q1 of 2014.

- **Sovaprevir (NS3/4A Protease Inhibitor)**
  - Ongoing Phase 2 -007 trial: 12-week Rx with sovaprevir + ACH-3102, + ribavirin
  - GT 1b: to date all patients with chronic genotype 1b HCV infection have maintained 100% virologic response despite the presence of multiple baseline NS5A resistance mutations
  - GT 1a: viral breakthroughs previously reported in genotype 1a patients; combination of sovaprevir and ACH-is not being pursued as treatment for genotype 1a HCV infection.

Source: HEPDART 2013.

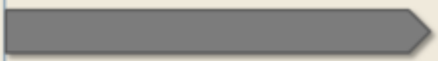
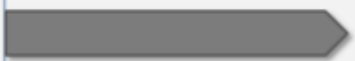
MERCK: Phase 2b MK-5172/MK-8742 and MK-5172/RBV: Covering Key Segments of HCV Disease

C·WORTHY	MK-5172 + MK-8742 ± Ribavirin	✓ G1 treatment-naïve, non-cirrhotic: 8 vs. 12 weeks ✓ G1 treatment-naïve cirrhotic: 12 vs. 18 weeks ✓ G1 prior PR null responder: 12 vs. 18 weeks ✓ G1 treatment-naïve HIV co-infected: 12 weeks
C·SCAPE	MK-5172 + MK-8742 ± Ribavirin	✓ G2: 12 weeks ✓ G4: 12 weeks ✓ G5: 12 weeks ✓ G6: 12 week
C·SPIRIT	MK-5172 ± Ribavirin	✓ G1b treatment-naïve, non-cirrhotic: 12 weeks ✓ G1a/b treatment-naïve, non-cirrhotic: 18 weeks ✓ All IL28 genotypes included
C·SALVAGE	MK-5172 + MK-8742 ± Ribavirin	✓ G1 patients ✓ Failed prior DAA/PR regimens ✓ 12 vs. 18 weeks of therapy

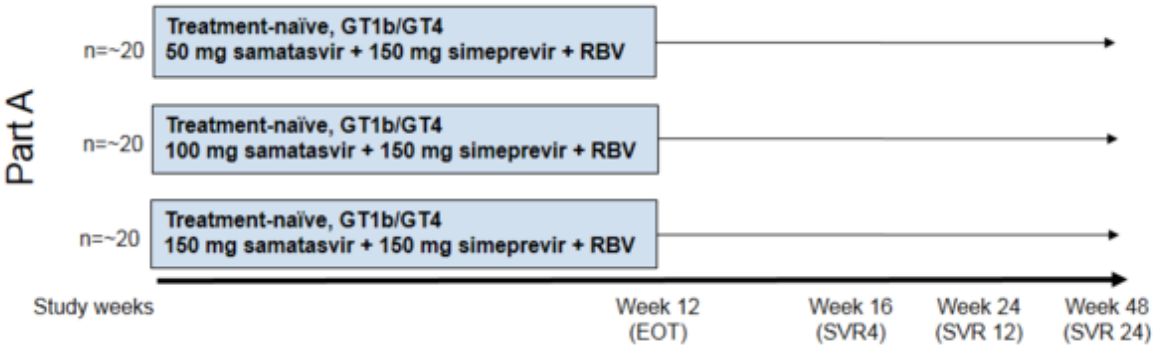
Many Direct Acting Antivirals in Development

- **NS5B Nucleosides**
  - VX 135
  - IDX 20963
  - ACH 3422
- **NS5B Non-nucleosides**
  - ABT 333
  - BMS 791325
  - PPI 383
  - GS 9669
  - TMC 647055

IDENIX HCV Pipeline Overview

Product Candidate	Indication	Preclinical	Phase I	Phase II	Phase III	Market
Independent Development Programs						
Samatasvir (NS5A Inhibitor)	HCV					
IDX21437 (Uridine nucleotide analog)	HCV					
IDX20963 (Uridine nucleotide analog)	HCV					
Additional Nucleotide Inhibitors	HCV					

HELIX-1 Phase II Clinical Trial Design



- Part B is currently enrolling exploratory arms designed to evaluate safety and antiviral activity of simeprevir and ribavirin combined with:
  - 25 mg dose of samatasvir in GT 1b-infected patients
  - 100 mg dose of samatasvir in GT 6-infected patients
  - 100 mg dose of samatasvir in additional GT 1b-infected patients
- Objectives: safety and tolerability, efficacy (primary SVR_4 with supportive SVR_{12} and SVR_{24}), pharmacokinetics and pharmacodynamics, emergence of resistance

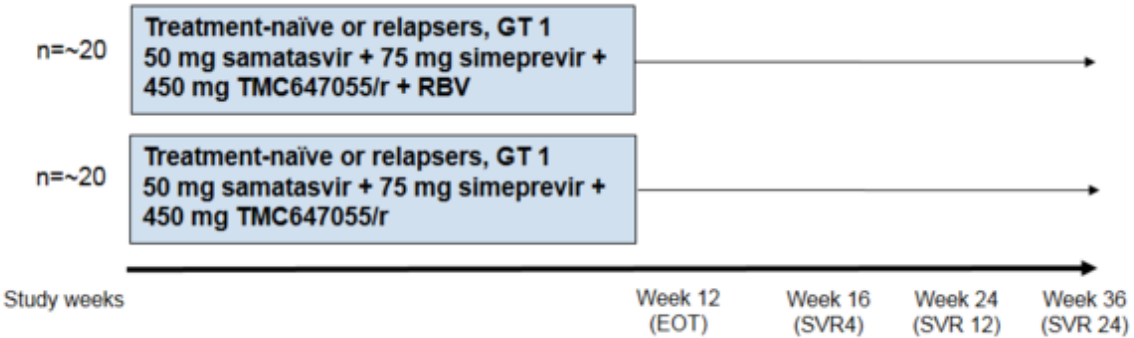
HELIX-1 Phase II Clinical Trial
Part A Results

- Safety: well-tolerated with no treatment-related serious adverse events in the clinical trial to date

Antiviral activity	Samatasvir/Simeprevir Treatment Groups		
	50 mg/150 mg	100 mg/150 mg	150 mg/150 mg
n	20	21	22*
Rapid Virologic Response (RVR); Measured after 4 weeks of treatment (LOQ)	20/20 (100%)	20/21 (95%)	18/19 (95%)
End Of Treatment Response (EOT); Measured at end of 12-week treatment period (LOD)	18/20 (90%)	19/21 (90%)	11/19 (58%)

•Three subjects prematurely discontinued treatment within the first 3 weeks (1 lost to follow-up, 2 non-compliance)
•LOQ = limit of quantitation (< 25 IU/mL); LOD=limit of detection (<10 IU/mL)

HELIX-2 Phase II Clinical Trial Design
All-oral 12-week 3-DAA Combination Regime



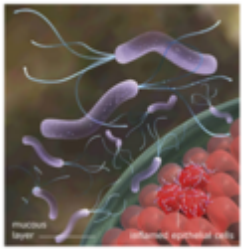
- Ongoing clinical trial initiated in December 2013
- Objectives: safety and tolerability, efficacy (primary SVR_4 with supportive SVR_{12} and SVR_{24}), pharmacokinetics and pharmacodynamics, emergence of resistance
- SVR_4 data anticipated 2H 2014
- Additional exploratory arms may be included

Addition Therapies for Hepatitis C

- Uptake inhibitors: human data pending
- Anti-Sense Linked nucleic acids: animal studies
- Adenovirus delivered anti-Sense
- iRNA: animal studies
- P7 inhibitors: in the test tube
- Lambda interferon: use is pending defining the role of interferon globally
- NS4 inhibitors: in the test tube
- Cyclophilin inhibitors: Failed

Hepatitis C Therapy Will Parallel Helicobacter pylori Therapy

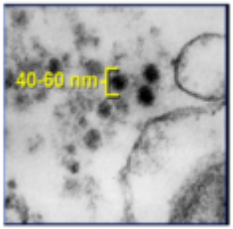
H pylori



Treatment regimen	Duration	Eradication rate (%)
Omeprazole (Prilosec) 20mg daily, plus amoxicillin (Biaxin), 500mg daily	14 days	80 to 86
Lansoprazole (Prevacid), 30mg twice daily, plus amoxicillin, 1g twice daily, 500mg twice daily	10 to 14 days	86
Bismuth subsalicylate (Pepto-Bismol) 525mg four time daily, plus metronidazole (Flagyl), 250mg four times daily, plus tetracycline, 500mg four time daily, plus histamine H_2 blocker	14 days (H_2 blocker alone for an additional 14 days taken once or twice daily	80

Source: Paul Kwo MD

HCV



All Oral Therapy

Duration 8-24 weeks

Polymerase Inhibitor

±

±

Protease Inhibitor

NS5a

±

Non-nucleoside Inhibitor

±

All Oral Therapy, single tablet

Hepatitis web study

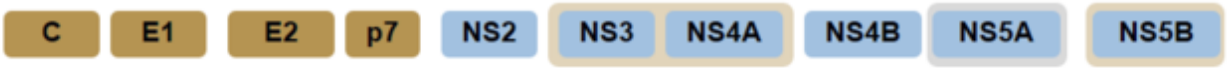
Special Thanks

Paul Kwo
Ira Jacobson

Current standards and future directions

- Genotype 1: PEG/RBV/SOF 12 weeks or Sofosbuvir + Simprevir for 12 weeks
- This is the last phase of major use for Peginterferon/RBV in the US
  - INF can shorten therapy with SOF for HIV/HCV co-infected patients and genotype 3 patients by using a 12 week triple protocol and save substantial money by cutting treatment duration by one-half
  - Continues to be used with genotype 4, 5, 6 for triple 12 week SOF based therapy
- All oral agents is the standard of care for genotype 2 and 3 and evolving to primary treatment with all oral therapy <18 months for all patients with genotypes 1, 4, 5,6
- Ribavirin: rescue therapy and treatment of drug resistance

Direct-Acting Antiviral Agents (DAAs) - Key Characteristics



NS3 /4A Inhibitors (Protease inhibitor PI)

- High potency
- Limited genotypic coverage
- Low barrier to resistance

NS5B Nucleos(t)ide Inhibitors (NI)

- Intermediate potency
- Pan genotypic coverage
- High barrier to resistance

NS5A Inhibitors

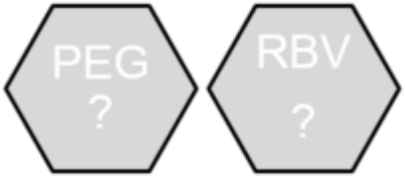
- High potency
- Multi-genotypic coverage
- Low barrier to resistance

NS5B Non Nucleoside Inhibitors (NNI)

- Intermediate potency
- Limited genotypic coverage
- Low barrier to resistance

Components for Achieving SVR in HCV: February 2014

Components for Achieving SVR in HCV: September 2014



Shorter therapy
Treat/prevent resistance

or